

BENEFITS AND COSTS OF INNOVATIVE ONCOLOGY DRUGS IN BELGIUM

SUPPLEMENT



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■ APPENDICES CANCER INDICATIONS

APPENDIX 1. BREAST CANCER

Appendix 1.1. BCR data

Appendix 1.1.1. Descriptive statistics

Appendix 1.1.1.1. Female Breast cancer, exploration

Table 1 – Female Breast cancer (2004-2017): Frequency table of patient and tumour characteristics

Characteristic	Total	Incidence period		
		2004-2008	2009-2013	2014-2017
Overall	149,529	49,829	54,436	45,264
Gender				
Female	149,529 (100.0)	49,829 (100.0)	54,436 (100.0)	45,264 (100.0)
Age at diagnosis (year)				
<50 years	30,658 (20.5)	11,208 (22.5)	11,038 (20.3)	8,412 (18.6)
50-59 years	35,078 (23.5)	12,241 (24.6)	12,724 (23.4)	10,113 (22.3)
60-69 years	36,056 (24.1)	11,161 (22.4)	13,337 (24.5)	11,558 (25.5)
70-79 years	27,918 (18.7)	9,350 (18.8)	9,986 (18.3)	8,582 (19.0)
80+ years	19,819 (13.3)	5,869 (11.8)	7,351 (13.5)	6,599 (14.6)
WHO - Performance Status				
0 – Asymptomatic	71,230 (47.6)	21,274 (42.7)	25,851 (47.5)	24,105 (53.3)
1 – Symptomatic but completely ambulatory	48,557 (32.5)	13,046 (26.2)	19,849 (36.5)	15,662 (34.6)
2 – Symptomatic, <50% in bed during the day	2,843 (1.9)	1,311 (2.6)	740 (1.4)	792 (1.7)
3 – Symptomatic, >50% in bed, but not bedbound	813 (0.5)	250 (0.5)	263 (0.5)	300 (0.7)



4 – Bedbound	339 (0.2)	95 (0.2)	133 (0.2)	111 (0.2)
Not reported	25,747 (17.2)	13,853 (27.8)	7,600 (14.0)	4,294 (9.5)
Combined stage				
0	1,219 (0.8)	20 (0.0)	315 (0.6)	884 (2.0)
is	451 (0.3)	9 (0.0)	152 (0.3)	290 (0.6)
I	61,632 (41.2)	18,634 (37.4)	23,000 (42.3)	19,998 (44.2)
II	50,579 (33.8)	17,289 (34.7)	18,322 (33.7)	14,968 (33.1)
III	17,285 (11.6)	6,038 (12.1)	6,449 (11.8)	4,798 (10.6)
IV	8,689 (5.8)	2,562 (5.1)	3,247 (6.0)	2,880 (6.4)
X	9,101 (6.1)	5,064 (10.2)	2,736 (5.0)	1,301 (2.9)
NA	573 (0.4)	213 (0.4)	215 (0.4)	145 (0.3)

Note: the values between parentheses are column percentages.

Table 2 – Female Breast cancer (2004-2017), Combined stage I, Frequency table of patient and tumour characteristics

Characteristic	Total	Incidence period		
		2004-2008	2009-2013	2014-2017
Overall	61,632	18,634	23,000	19,998
Gender				
Female	61,632 (100.0)	18,634 (100.0)	23,000 (100.0)	19,998 (100.0)
Age at diagnosis (year)				
<50 years	12,559 (20.4)	4,323 (23.2)	4,662 (20.3)	3,574 (17.9)
50-59 years	17,045 (27.7)	5,406 (29.0)	6,377 (27.7)	5,262 (26.3)
60-69 years	17,634 (28.6)	4,916 (26.4)	6,652 (28.9)	6,066 (30.3)
70-79 years	10,058 (16.3)	2,876 (15.4)	3,702 (16.1)	3,480 (17.4)
80+ years	4,336 (7.0)	1,113 (6.0)	1,607 (7.0)	1,616 (8.1)
WHO - Performance Status				
0 – Asymptomatic	36,482 (59.2)	10,168 (54.6)	13,418 (58.3)	12,896 (64.5)
1 – Symptomatic but completely ambulatory	16,257 (26.4)	4,102 (22.0)	6,868 (29.9)	5,287 (26.4)



2 – Symptomatic, <50% in bed during the day	521 (0.8)	279 (1.5)	105 (0.5)	137 (0.7)
3 – Symptomatic, >50% in bed, but not bedbound	97 (0.2)	19 (0.1)	29 (0.1)	49 (0.2)
4 – Bedbound	43 (0.1)	6 (0.0)	11 (0.0)	26 (0.1)
Not reported	8,232 (13.4)	4,060 (21.8)	2,569 (11.2)	1,603 (8.0)

Note: the values between parentheses are column percentages.

Table 3 – Female Breast cancer (2004-2017), Combined stage II, Frequency table of patient and tumour characteristics

Characteristic	Total	Incidence period		
		2004-2008	2009-2013	2014-2017
Overall	50,579	17,289	18,322	14,968
Gender				
Female	50,579 (100.0)	17,289 (100.0)	18,322 (100.0)	14,968 (100.0)
Age at diagnosis (year)				
<50 years	10,975 (21.7)	4,180 (24.2)	3,923 (21.4)	2,872 (19.2)
50-59 years	10,857 (21.5)	3,978 (23.0)	3,911 (21.3)	2,968 (19.8)
60-69 years	10,887 (21.5)	3,537 (20.5)	4,017 (21.9)	3,333 (22.3)
70-79 years	9,983 (19.7)	3,450 (20.0)	3,532 (19.3)	3,001 (20.0)
80+ years	7,877 (15.6)	2,144 (12.4)	2,939 (16.0)	2,794 (18.7)
WHO - Performance Status				
0 – Asymptomatic	24,088 (47.6)	7,959 (46.0)	8,538 (46.6)	7,591 (50.7)
1 – Symptomatic but completely ambulatory	18,675 (36.9)	5,215 (30.2)	7,553 (41.2)	5,907 (39.5)
2 – Symptomatic, <50% in bed during the day	939 (1.9)	464 (2.7)	232 (1.3)	243 (1.6)
3 – Symptomatic, >50% in bed, but not bedbound	201 (0.4)	64 (0.4)	61 (0.3)	76 (0.5)
4 – Bedbound	97 (0.2)	28 (0.2)	40 (0.2)	29 (0.2)
Not reported	6,579 (13.0)	3,559 (20.6)	1,898 (10.4)	1,122 (7.5)

Note: the values between parentheses are column percentages.


Table 4 – Female Breast cancer (2004-2017), Combined stage III, Frequency table of patient and tumour characteristics

Characteristic	Total	Incidence period		
		2004-2008	2009-2013	2014-2017
Overall	17,285	6,038	6,449	4,798
Gender				
Female	17,285 (100.0)	6,038 (100.0)	6,449 (100.0)	4,798 (100.0)
Age at diagnosis (year)				
<50 years	3,563 (20.6)	1,354 (22.4)	1,327 (20.6)	882 (18.4)
50-59 years	3,464 (20.0)	1,254 (20.8)	1,298 (20.1)	912 (19.0)
60-69 years	3,500 (20.2)	1,174 (19.4)	1,318 (20.4)	1,008 (21.0)
70-79 years	3,655 (21.1)	1,317 (21.8)	1,346 (20.9)	992 (20.7)
80+ years	3,103 (18.0)	939 (15.6)	1,160 (18.0)	1,004 (20.9)
WHO - Performance Status				
0 – Asymptomatic	6,843 (39.6)	2,292 (38.0)	2,533 (39.3)	2,018 (42.1)
1 – Symptomatic but completely ambulatory	7,543 (43.6)	2,250 (37.3)	3,089 (47.9)	2,204 (45.9)
2 – Symptomatic, <50% in bed during the day	493 (2.9)	242 (4.0)	114 (1.8)	137 (2.9)
3 – Symptomatic, >50% in bed, but not bedbound	128 (0.7)	42 (0.7)	39 (0.6)	47 (1.0)
4 – Bedbound	51 (0.3)	11 (0.2)	21 (0.3)	19 (0.4)
Not reported	2,227 (12.9)	1,201 (19.9)	653 (10.1)	373 (7.8)

Note: the values between parentheses are column percentages.

**Table 5 – Female Breast cancer (2004-2017), Combined stage IV, Frequency table of patient and tumour characteristics**

Characteristic	Total	Incidence period		
		2004-2008	2009-2013	2014-2017
Overall	8,689	2,562	3,247	2,880
Gender				
Female	8,689 (100.0)	2,562 (100.0)	3,247 (100.0)	2,880 (100.0)
Age at diagnosis (year)				
<50 years	1,211 (13.9)	378 (14.8)	476 (14.7)	357 (12.4)
50-59 years	1,515 (17.4)	497 (19.4)	537 (16.5)	481 (16.7)
60-69 years	1,938 (22.3)	541 (21.1)	740 (22.8)	657 (22.8)
70-79 years	2,236 (25.7)	701 (27.4)	787 (24.2)	748 (26.0)
80+ years	1,789 (20.6)	445 (17.4)	707 (21.8)	637 (22.1)
WHO - Performance Status				
0 – Asymptomatic	2,052 (23.6)	540 (21.1)	788 (24.3)	724 (25.1)
1 – Symptomatic but completely ambulatory	4,462 (51.4)	1,183 (46.2)	1,724 (53.1)	1,555 (54.0)
2 – Symptomatic, <50% in bed during the day	759 (8.7)	277 (10.8)	249 (7.7)	233 (8.1)
3 – Symptomatic, >50% in bed, but not bedbound	338 (3.9)	113 (4.4)	119 (3.7)	106 (3.7)
4 – Bedbound	123 (1.4)	42 (1.6)	48 (1.5)	33 (1.1)
Not reported	955 (11.0)	407 (15.9)	319 (9.8)	229 (8.0)

Note: the values between parentheses are column percentages.



Appendix 1.1.1.2. Female Breast cancer, Observed and Relative Survival graphs

Female Breast cancer (2004-2017)

Figure 1 – Female Breast cancer (2004-2017), Kaplan-Meier graphs observed survival by incidence period

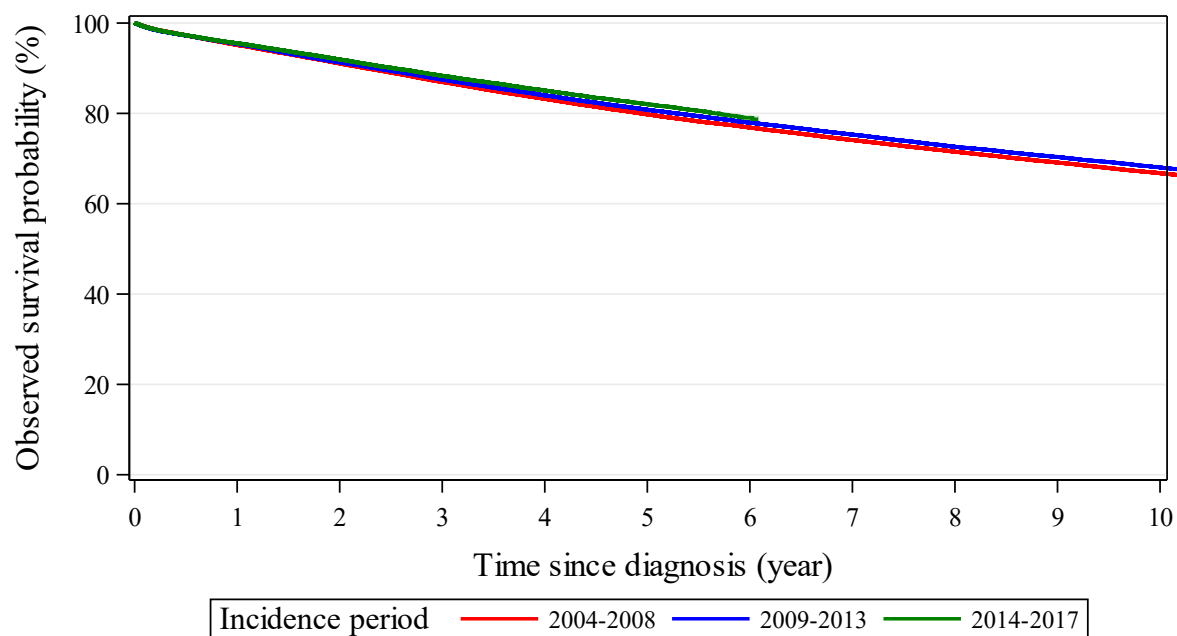
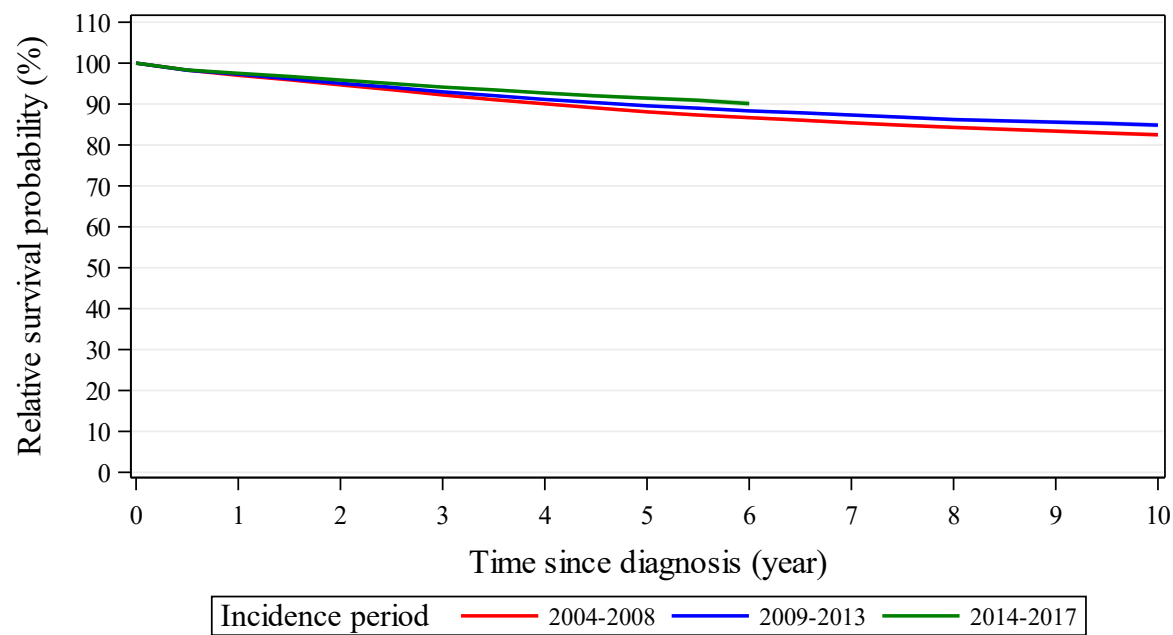




Figure 2 – Female Breast cancer (2004-2017), relative survival graphs by incidence period



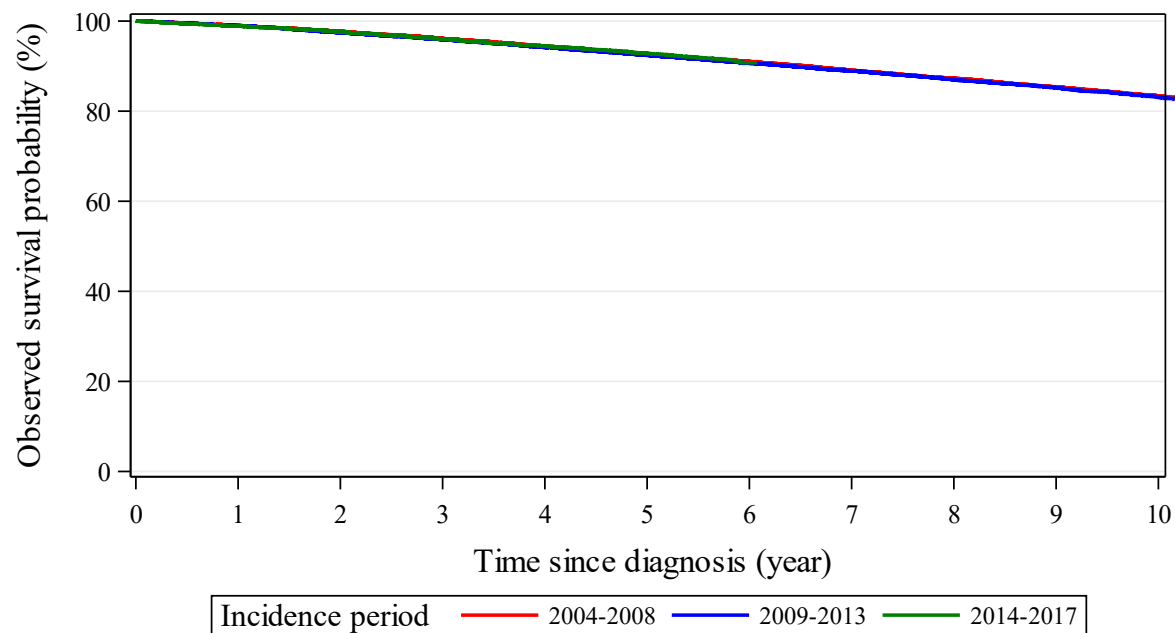
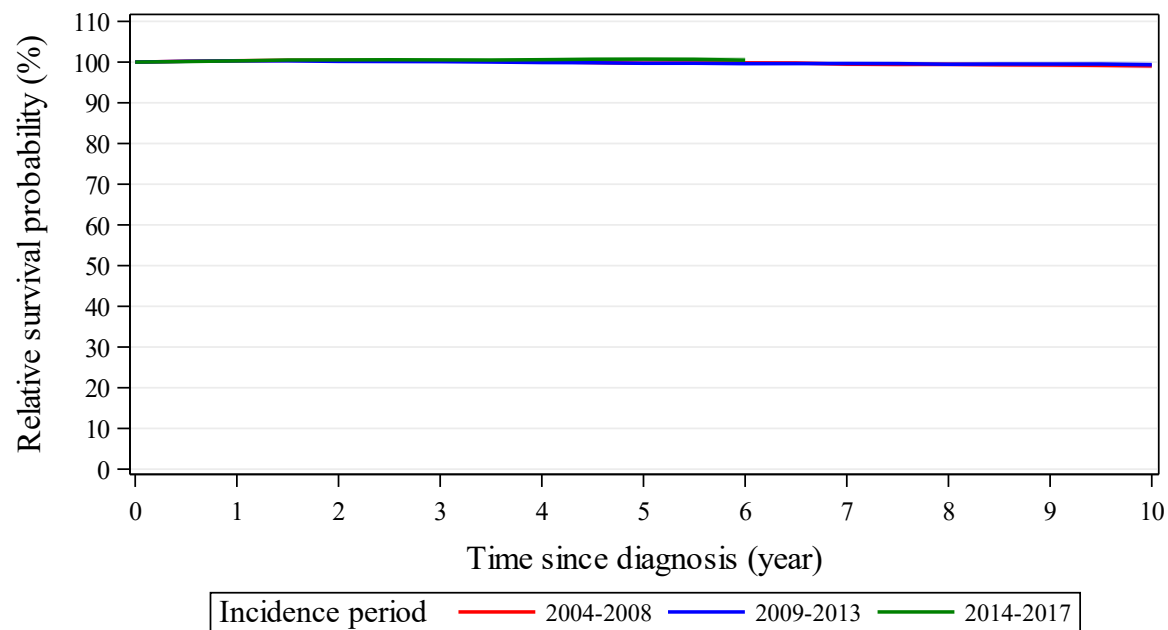
**Female Breast cancer, combined stage I (2004-2017)****Figure 3 – Female Breast cancer (2004-2017), combined stage I, Kaplan-Meier graphs observed survival by incidence period**



Figure 4 – Female Breast cancer (2004-2017), combined stage I, relative survival graphs by incidence period



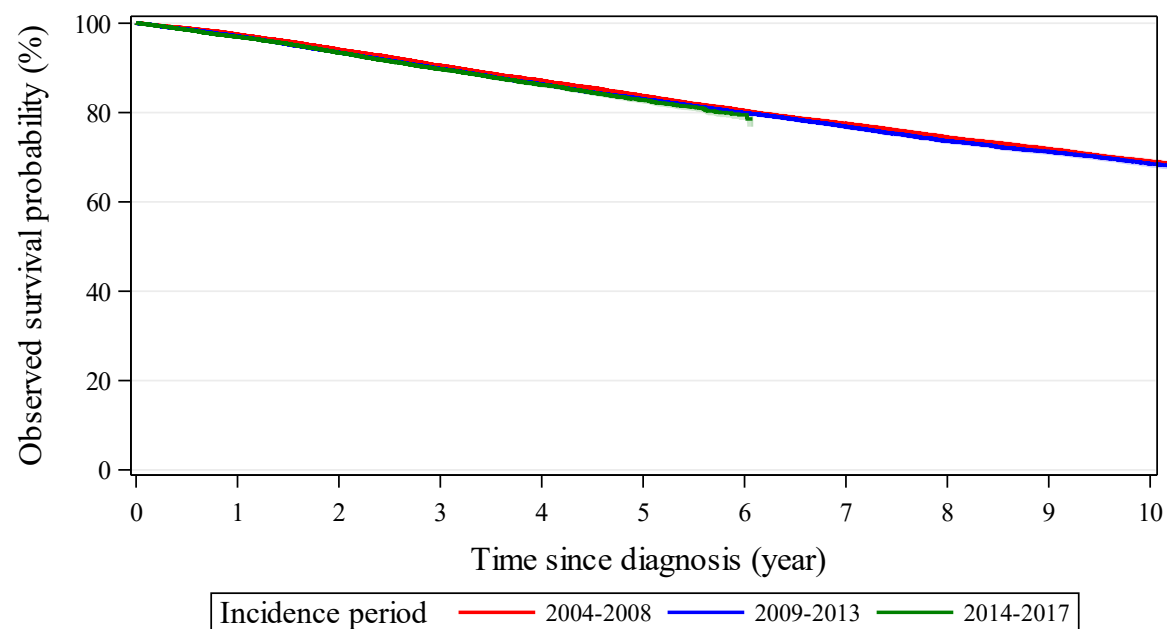
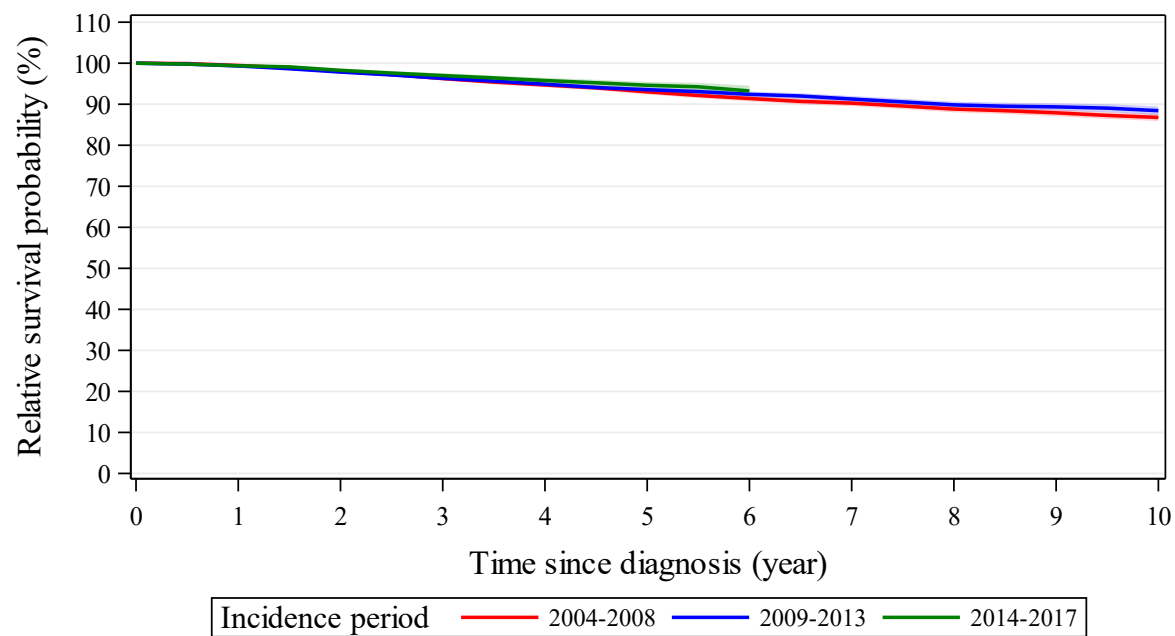
**Female Breast cancer, combined stage II (2004-2017)****Figure 5 – Female Breast cancer (2004-2017), combined stage II, Kaplan-Meier graphs observed survival by incidence period**



Figure 6 – Female Breast cancer (2004-2017), combined stage II, relative survival graphs by incidence period



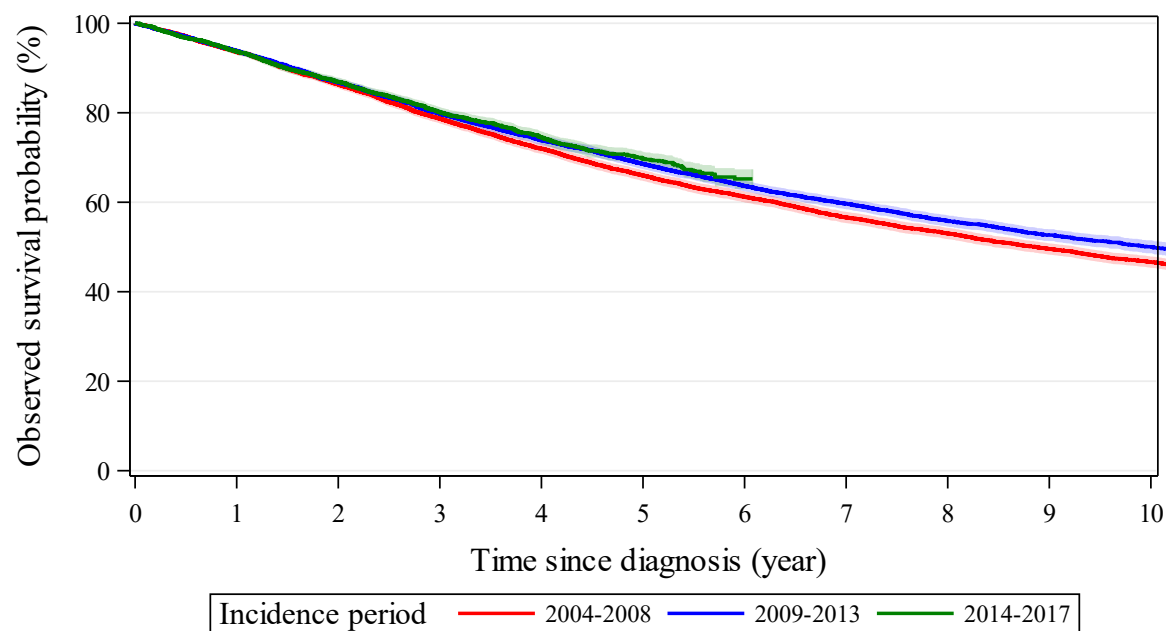
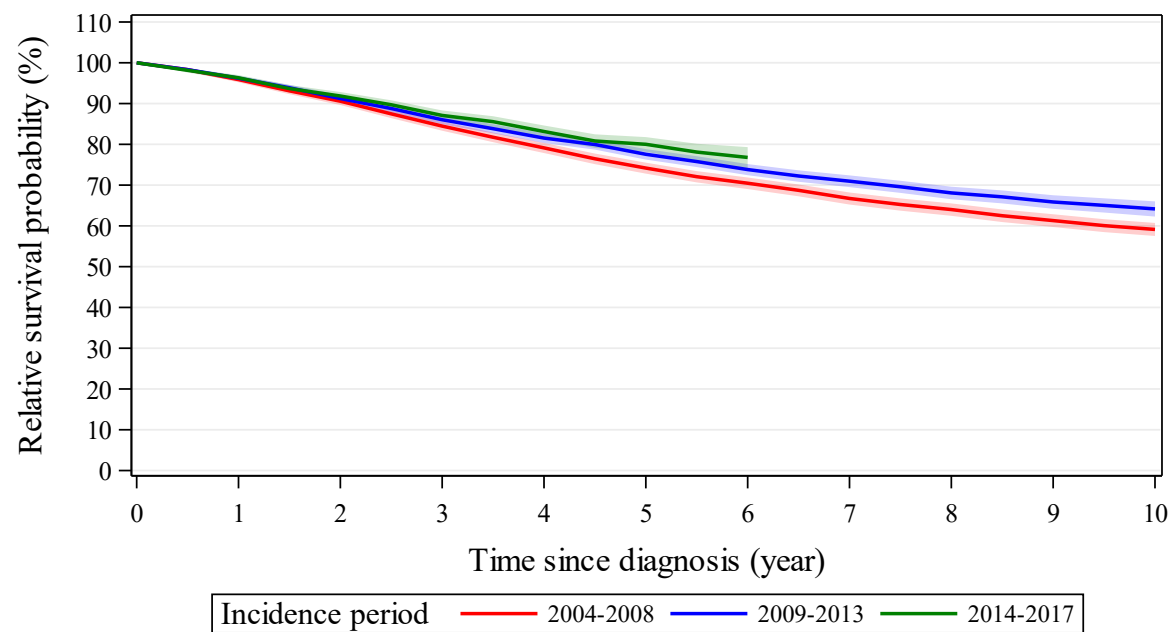
**Female Breast cancer, combined stage III (2004-2017)****Figure 7 – Female Breast cancer (2004-2017), combined stage III, Kaplan-Meier graphs observed survival by incidence period**



Figure 8 – Female Breast cancer (2004-2017), combined stage III, relative survival graphs by incidence period



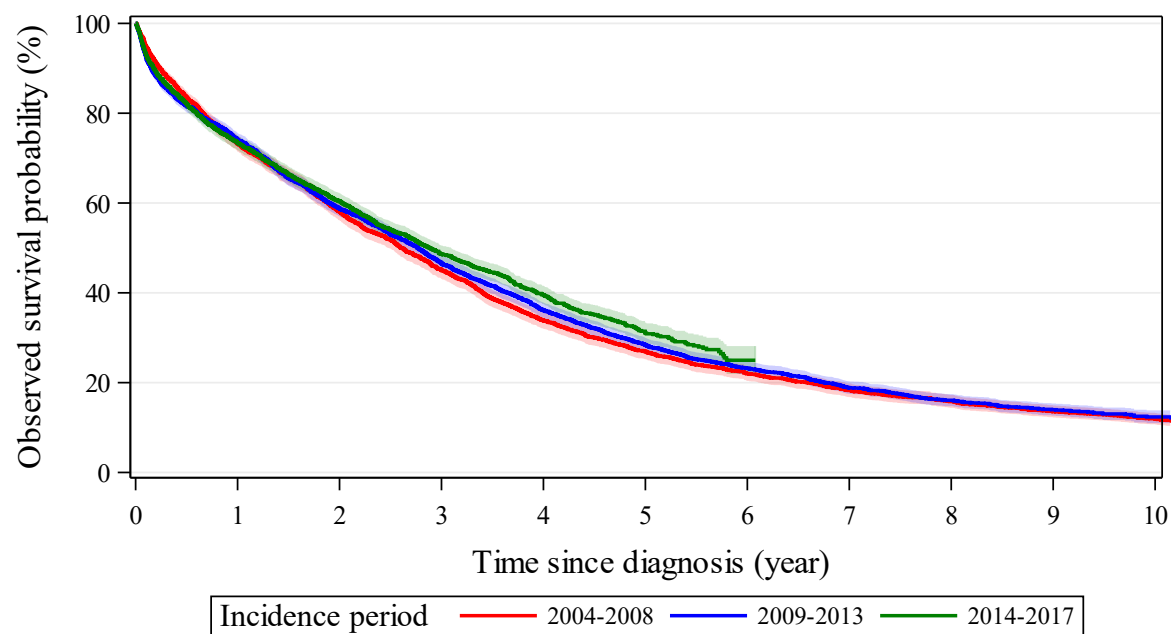
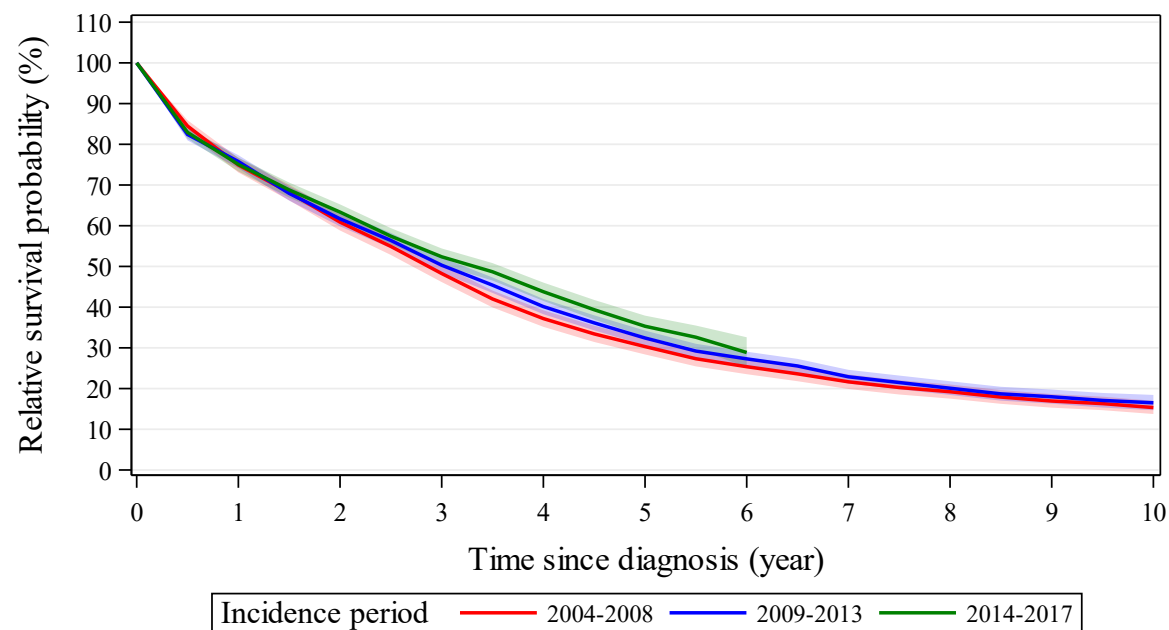
**Female Breast cancer, combined stage IV (2004-2017)****Figure 9 – Female Breast cancer (2004-2017), combined stage IV, Kaplan-Meier graphs observed survival by incidence period**



Figure 10 – Female Breast cancer (2004-2017), combined stage IV, relative survival graphs by incidence period

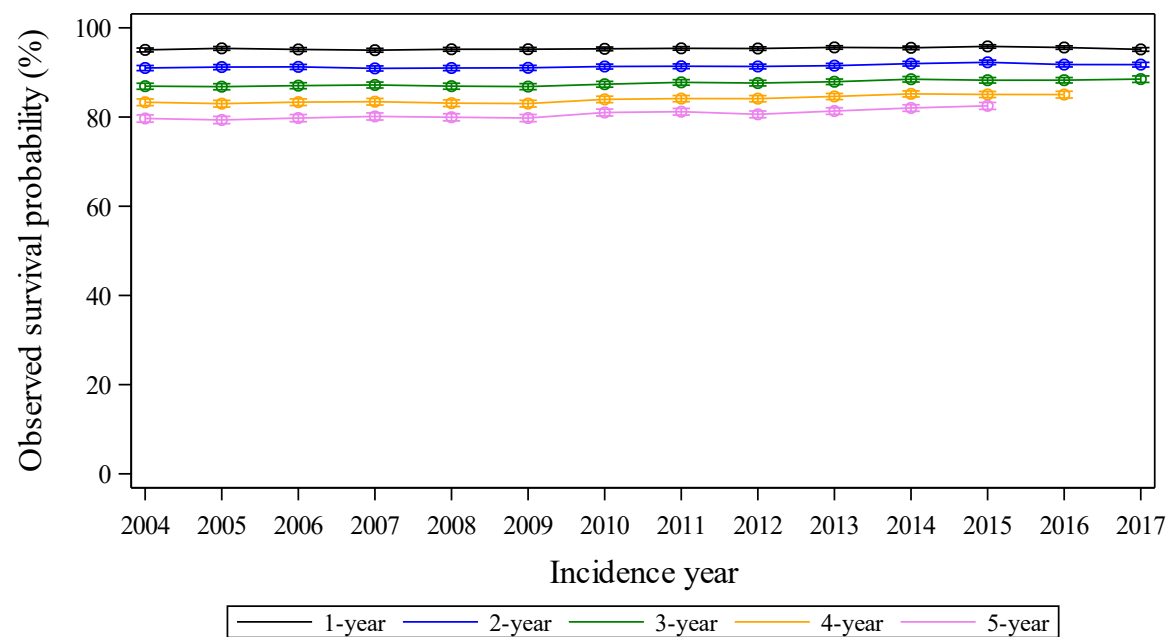




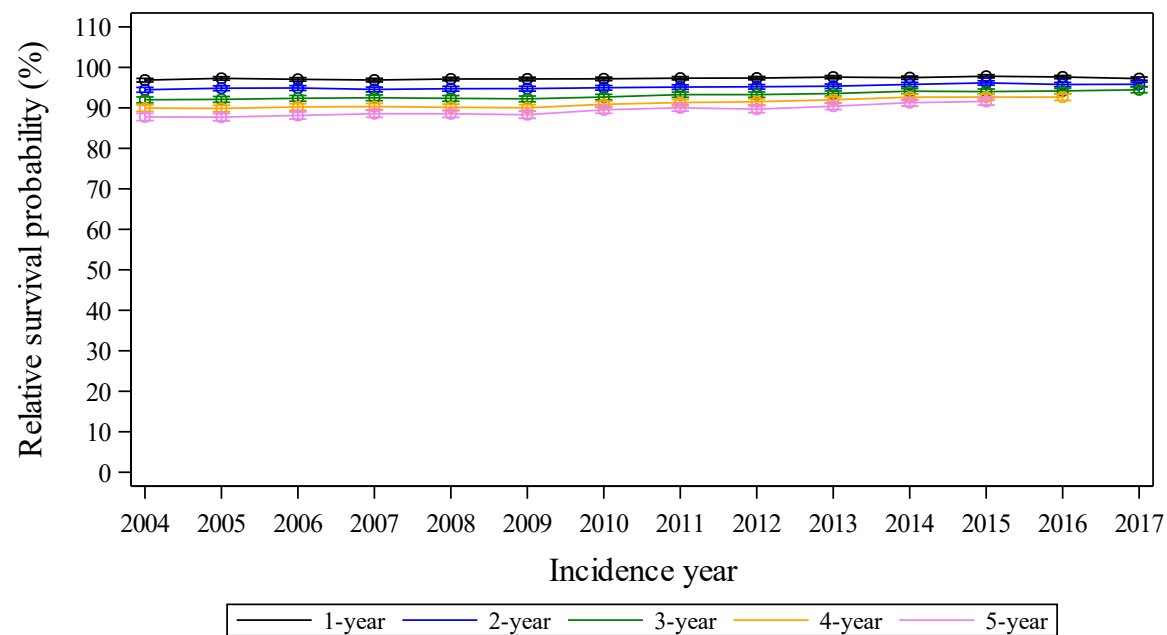
Appendix 1.1.1.3. Female Breast cancer, time trend Observed and Relative Survival

Female Breast cancer (2004-2017)

Figure 11 – Female Breast cancer (2004-2017), time trend observed survival with incidence year



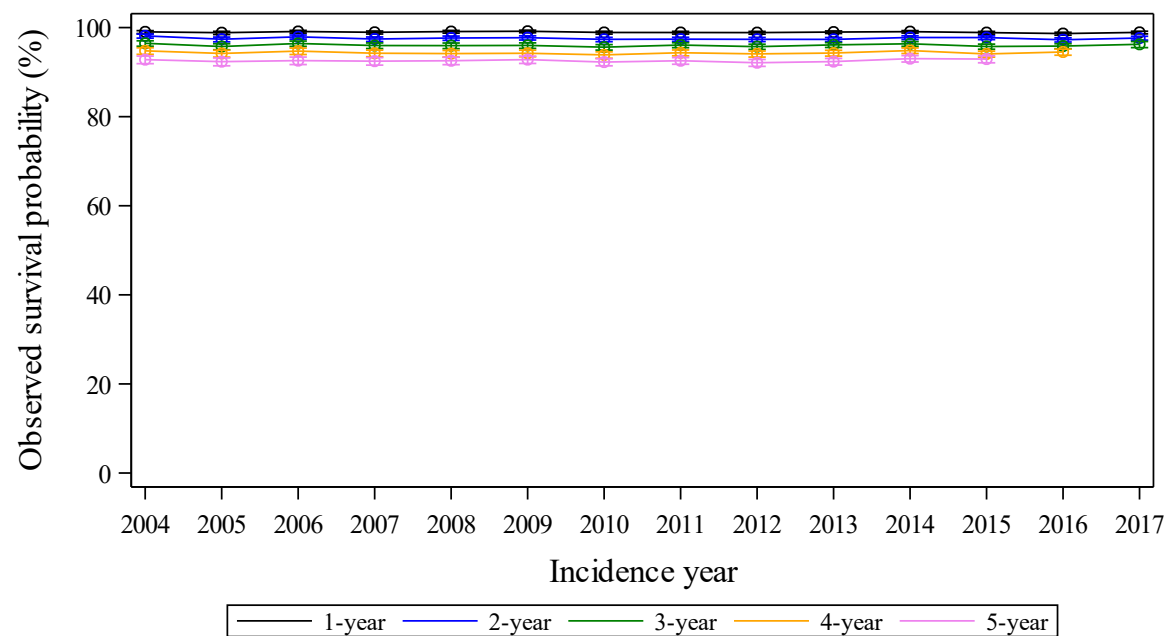
Note: the error bars represent the 95% CI.

**Figure 12 – Female Breast cancer (2004-2017), time trend relative survival with incidence year**

Note: the error bars represent the 95% CI.

**Figure 13 – Female Breast cancer (2004-2017), Median time observed survival**

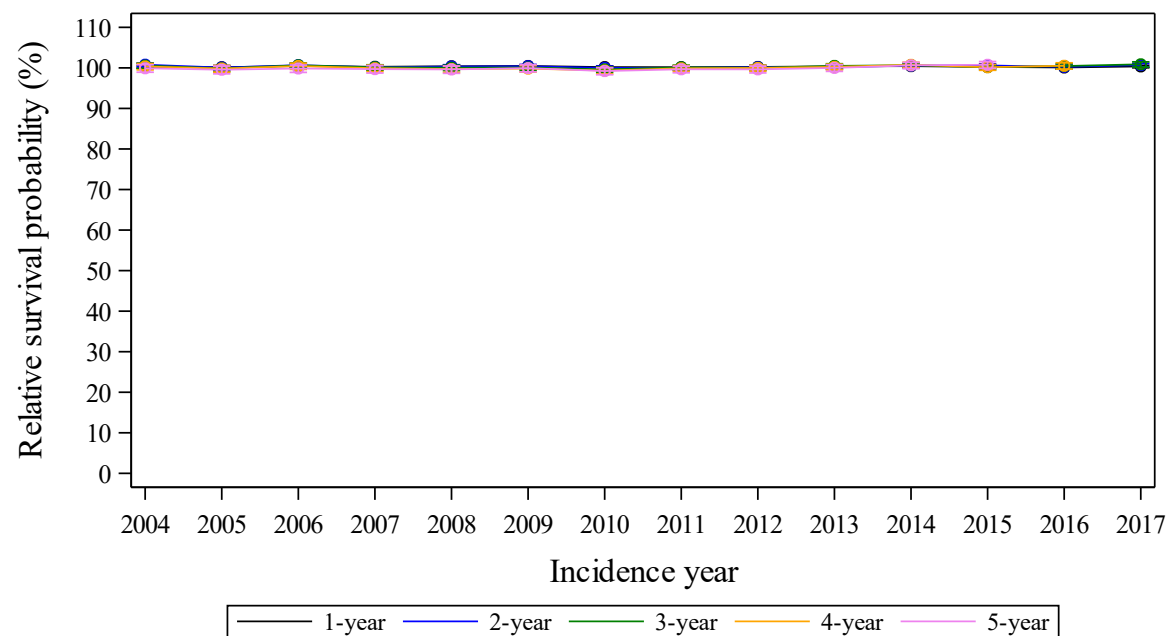
No data points to plot, as survival curves remain above 50% and the median survival time can therefore not be determined.

**Female Breast cancer, combined stage I (2004-2017)****Figure 14 – Female Breast cancer (2004-2017), combined stage I, time trend observed survival with incidence year**

Note: the error bars represent the 95% CI.



Figure 15 – Female Breast cancer (2004-2017), combined stage I, time trend relative survival with incidence year



Note: the error bars represent the 95% CI.

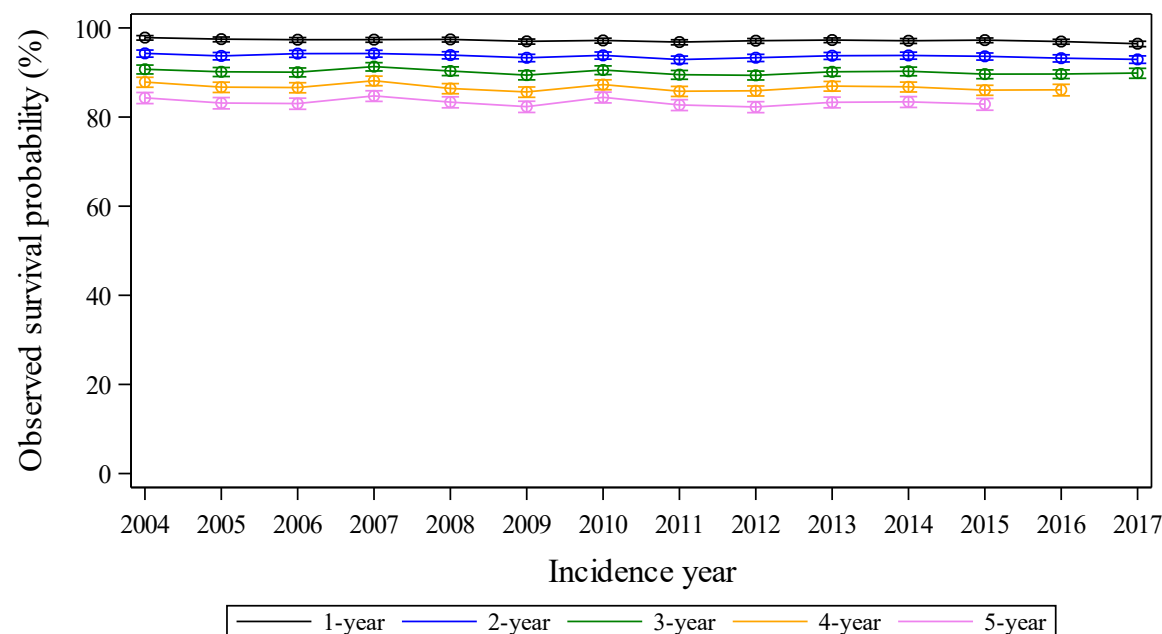


Figure 16 – Female Breast cancer (2004-2017), combined stage I, median time observed survival

No data points to plot, as survival curves remain above 50% and the median survival time can therefore not be determined.

Female Breast cancer, combined stage II (2004-2017)

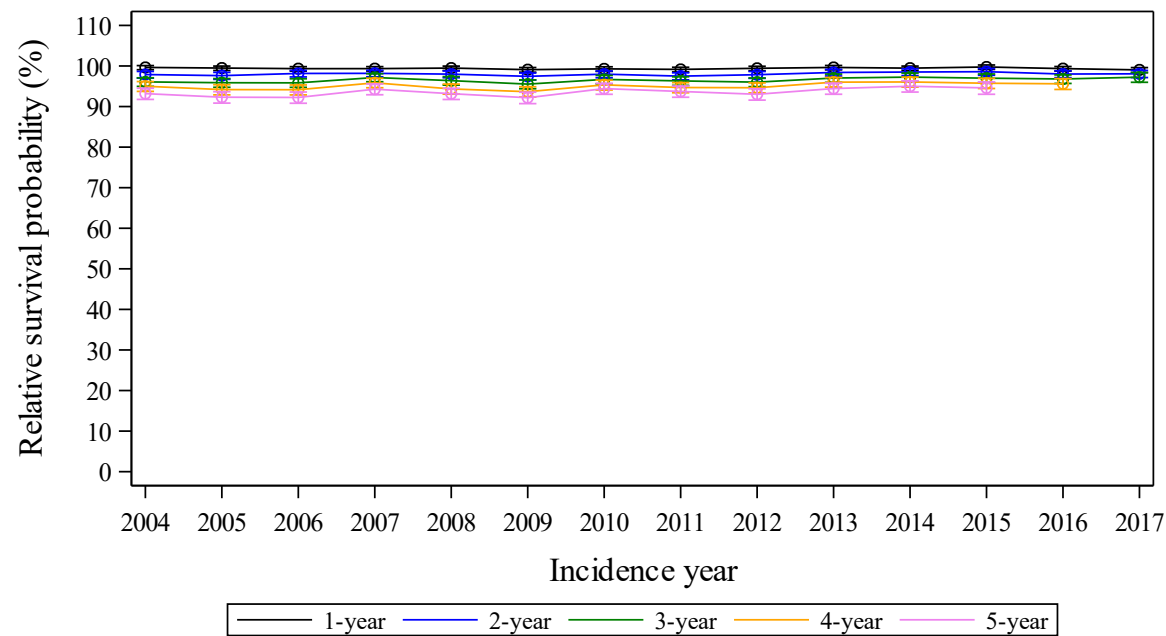
Figure 17 – Female Breast cancer (2004-2017), combined stage II, time trend observed survival with incidence year



Note: the error bars represent the 95% CI.



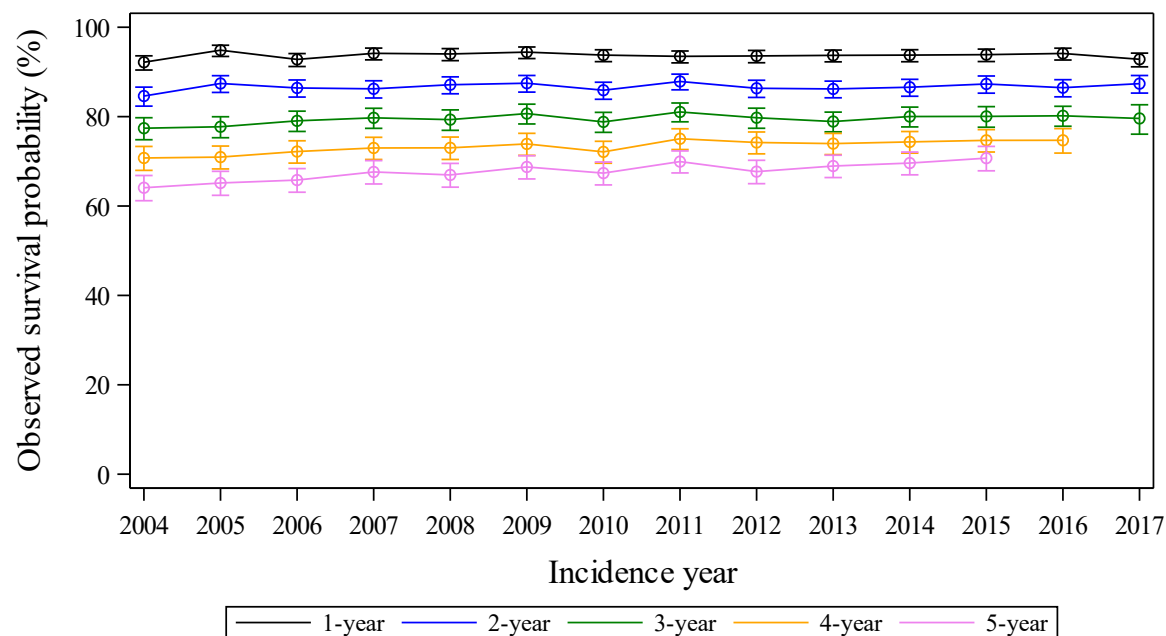
Figure 18 – Female Breast cancer (2004-2017), combined stage II, time trend relative survival with incidence year



Note: the error bars represent the 95% CI.

**Figure 19 – Female Breast cancer (2004-2017), combined stage II, median time observed survival**

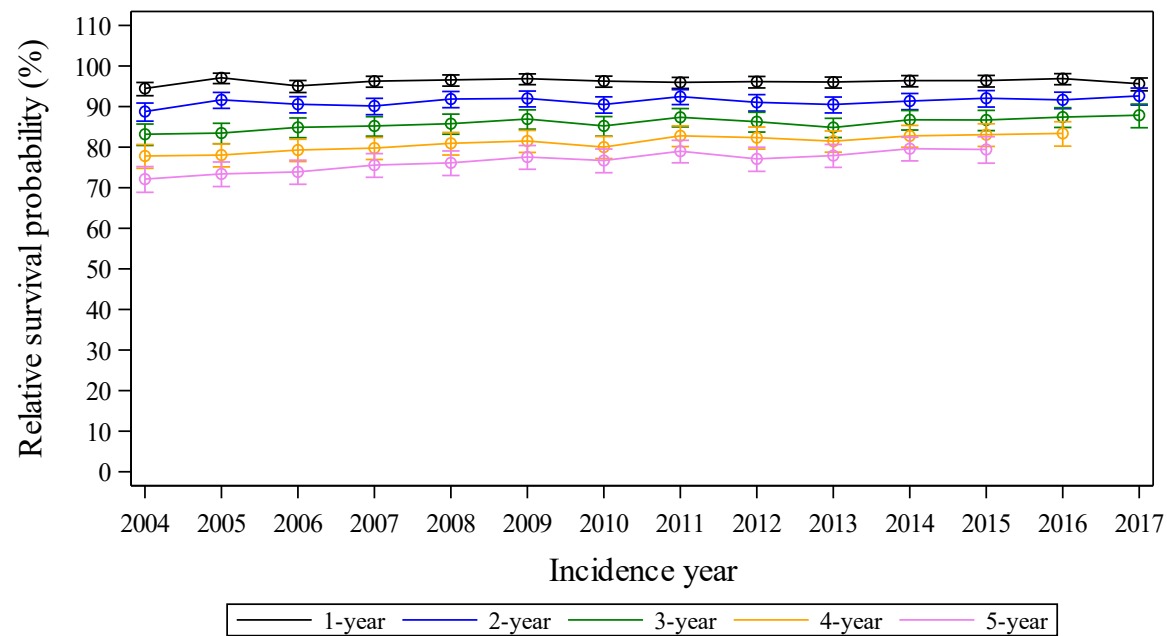
No data points to plot, as survival curves remain above 50% and the median survival time can therefore not be determined.

Female Breast cancer, combined stage III (2004-2017)**Figure 20 – Female Breast cancer (2004-2017), combined stage III, time trend observed survival with incidence year**

Note: the error bars represent the 95% CI.



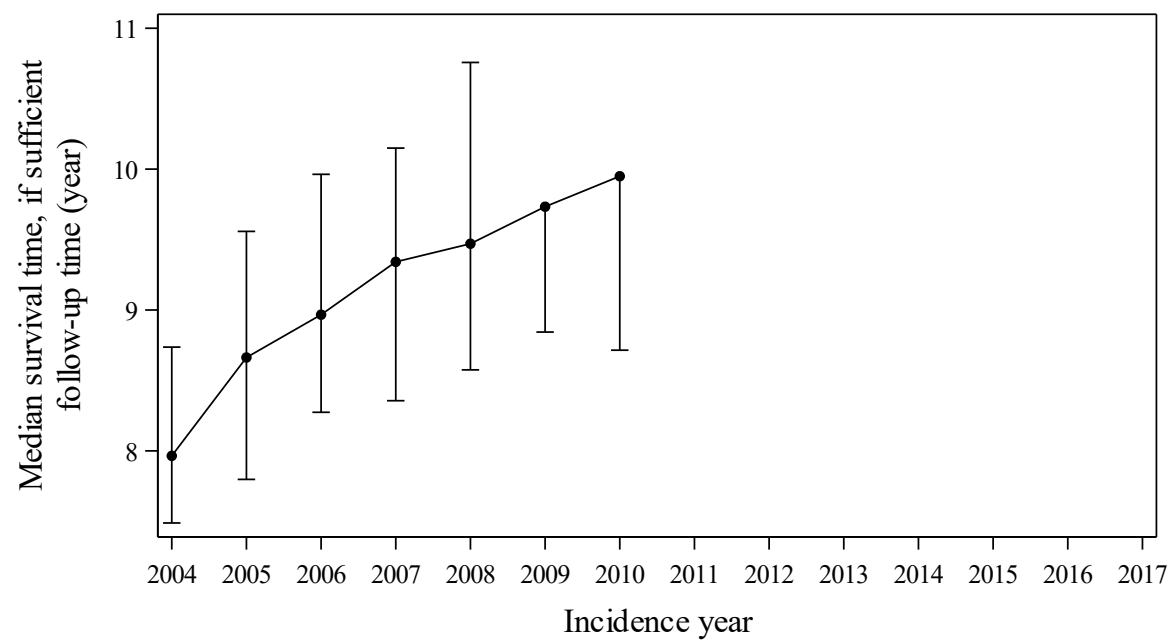
Figure 21 – Female Breast cancer (2004-2017), combined stage III, time trend relative survival with incidence year



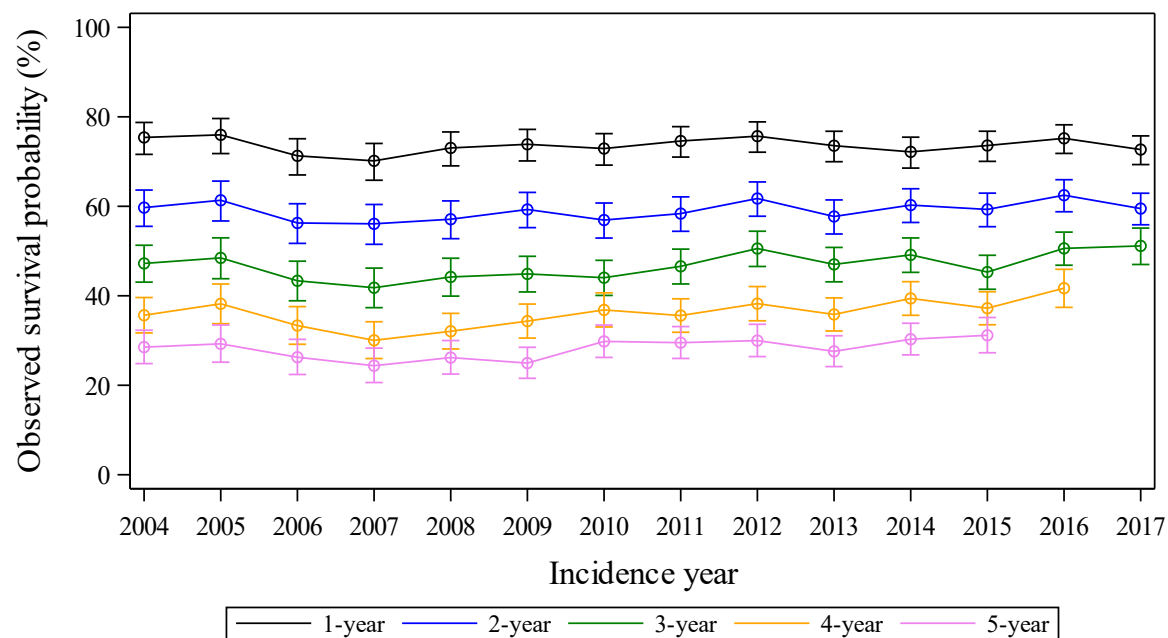
Note: the error bars represent the 95% CI.



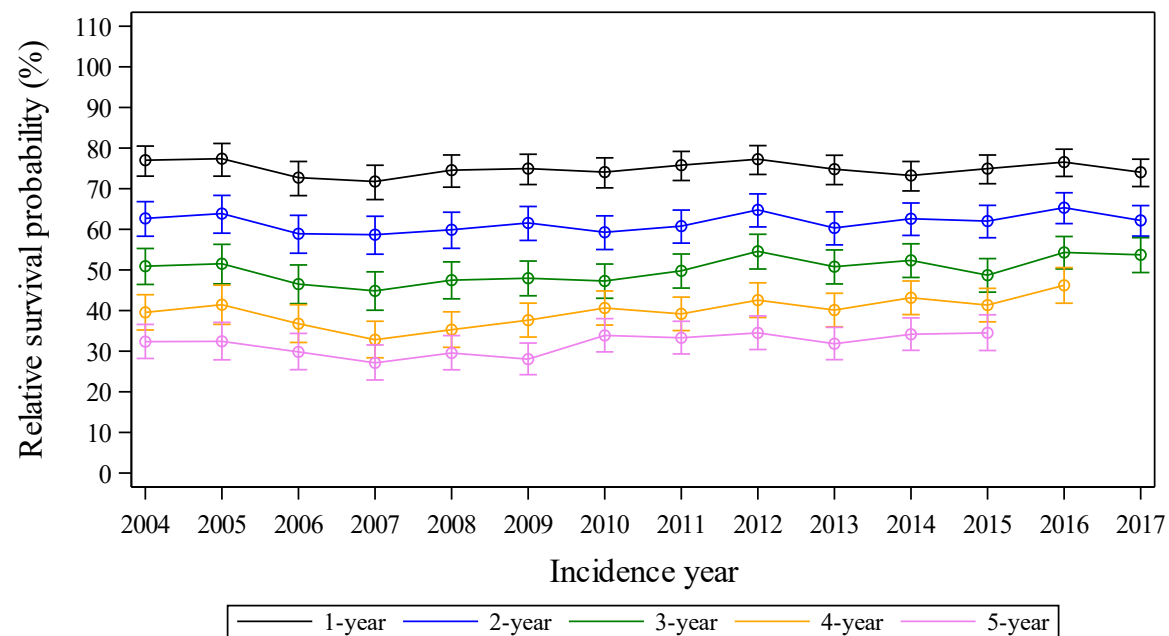
Figure 22 – Female Breast cancer (2004-2017), combined stage III, median time observed survival



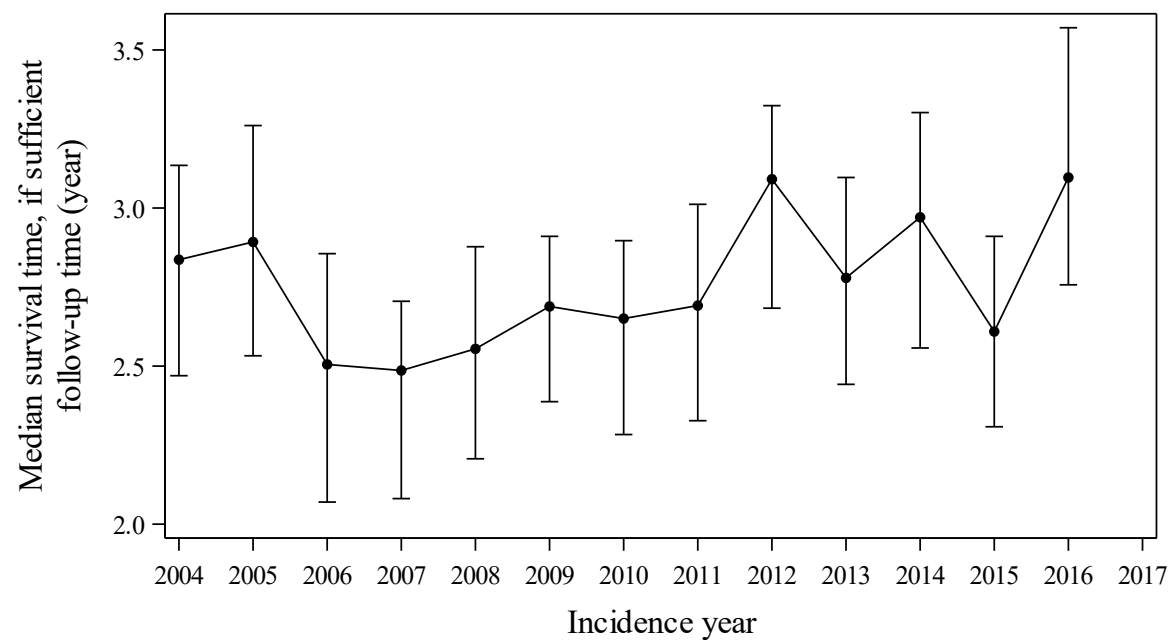
Note: the error bars represent the 95% CI. When the upper error is not plotted, the upper limit could not be determined with the follow-up available.

**Female Breast cancer, combined stage IV (2004-2017)****Figure 23 – Female Breast cancer (2004-2017), combined stage IV, time trend observed survival with incidence year**

Note: the error bars represent the 95% CI.

**Figure 24 – Female Breast cancer (2004-2017), combined stage IV, time trend relative survival with incidence year**

Note: the error bars represent the 95% CI.

**Figure 25 – Female Breast cancer (2004-2017), combined stage IV, median time observed survival**

Note: the error bars represent the 95% CI. When the upper error is not plotted, the upper limit could not be determined with the follow-up available.



Appendix 1.1.1.4. Female Breast cancer, time trend tables Observed and Relative Survival

Table 6 – Female Breast cancer (2004-2017), time trend observed survival with incidence year

Unadjusted observed survival, %													
Characteristic	N at risk	1 year		2 year		3 year		4 year		5 year		Median survival time (year)	
		%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI	T	95% CI
All													
2004	9,544	95.1	[94.6, 95.5]	91.0	[90.4, 91.6]	86.9	[86.2, 87.6]	83.3	[82.6, 84.1]	79.7	[78.9, 80.5]	>16	
2005	9,568	95.4	[95.0, 95.8]	91.2	[90.6, 91.8]	86.8	[86.1, 87.5]	83.0	[82.2, 83.7]	79.3	[78.5, 80.1]	>15	
2006	9,705	95.2	[94.7, 95.6]	91.2	[90.7, 91.8]	87.0	[86.4, 87.7]	83.3	[82.6, 84.1]	79.8	[79.0, 80.6]	>14	
2007	9,836	95.0	[94.5, 95.4]	90.9	[90.3, 91.5]	87.2	[86.5, 87.8]	83.4	[82.7, 84.2]	80.1	[79.3, 80.9]	>13	
2008	9,765	95.2	[94.8, 95.6]	91.0	[90.4, 91.5]	86.9	[86.2, 87.6]	83.1	[82.4, 83.8]	80.0	[79.1, 80.7]	>12	
2009	9,761	95.2	[94.8, 95.6]	91.0	[90.5, 91.6]	86.8	[86.1, 87.5]	83.0	[82.3, 83.7]	79.8	[79.0, 80.6]	>11	
2010	10,078	95.3	[94.9, 95.7]	91.3	[90.8, 91.9]	87.4	[86.7, 88.0]	84.0	[83.2, 84.7]	81.0	[80.2, 81.8]	>10	
2011	10,731	95.4	[95.0, 95.8]	91.4	[90.8, 91.9]	87.8	[87.1, 88.4]	84.1	[83.4, 84.8]	81.2	[80.4, 81.9]	>9	
2012	10,680	95.4	[94.9, 95.7]	91.3	[90.8, 91.9]	87.6	[87.0, 88.2]	84.1	[83.4, 84.8]	80.6	[79.8, 81.3]	>8	
2013	10,848	95.6	[95.2, 96.0]	91.5	[91.0, 92.0]	87.9	[87.3, 88.5]	84.6	[83.9, 85.3]	81.3	[80.6, 82.1]	>7	
2014	10,583	95.5	[95.1, 95.9]	92.0	[91.4, 92.5]	88.5	[87.9, 89.1]	85.2	[84.5, 85.9]	82.0	[81.3, 82.8]	>6	
2015	10,500	95.8	[95.4, 96.2]	92.3	[91.7, 92.8]	88.3	[87.6, 88.9]	85.1	[84.4, 85.7]	82.5	[81.7, 83.3]	>5	
2016	10,872	95.6	[95.2, 96.0]	91.8	[91.2, 92.3]	88.3	[87.6, 88.9]	85.0	[84.3, 85.8]	no FU	—	>4	
2017	10,710	95.2	[94.7, 95.6]	91.8	[91.2, 92.3]	88.5	[87.8, 89.2]	no FU	—	no FU	—	>3	
Combined Stage I													
2004	3,544	99.0	[98.7, 99.3]	98.1	[97.6, 98.5]	96.5	[95.8, 97.0]	94.8	[94.0, 95.5]	92.8	[91.9, 93.6]	>16	
2005	3,485	98.9	[98.4, 99.2]	97.4	[96.8, 97.9]	95.7	[95.0, 96.4]	94.2	[93.4, 94.9]	92.4	[91.4, 93.2]	>15	
2006	3,755	99.1	[98.8, 99.4]	97.9	[97.4, 98.3]	96.4	[95.8, 97.0]	94.7	[94.0, 95.4]	92.6	[91.7, 93.4]	>14	
2007	3,774	98.9	[98.6, 99.2]	97.4	[96.9, 97.9]	96.0	[95.3, 96.6]	94.2	[93.4, 94.9]	92.5	[91.6, 93.3]	>13	
2008	3,807	99.1	[98.8, 99.4]	97.7	[97.1, 98.1]	96.0	[95.3, 96.5]	94.2	[93.4, 94.9]	92.6	[91.7, 93.3]	>12	
2009	3,877	99.2	[98.8, 99.4]	97.7	[97.2, 98.2]	96.0	[95.3, 96.6]	94.2	[93.5, 94.9]	92.8	[91.9, 93.6]	>11	



Unadjusted observed survival, %													
		1 year		2 year		3 year		4 year		5 year		Median survival time (year)	
Characteristic	N at risk	%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI	T	95% CI
2004	1,112	92.2	[90.4, 93.6]	84.6	[82.4, 86.6]	77.4	[74.8, 79.8]	70.7	[68.0, 73.3]	64.1	[61.2, 66.8]	8.0	[7.5, 8.7]
2005	1,209	94.9	[93.5, 96.0]	87.4	[85.4, 89.2]	77.7	[75.3, 80.0]	70.9	[68.3, 73.4]	65.2	[62.4, 67.8]	8.7	[7.8, 9.6]
2006	1,237	92.8	[91.2, 94.1]	86.4	[84.4, 88.2]	79.1	[76.7, 81.2]	72.2	[69.6, 74.6]	65.8	[63.1, 68.4]	9.0	[8.3, 10.0]
2007	1,234	94.2	[92.7, 95.3]	86.2	[84.2, 88.0]	79.7	[77.4, 81.9]	73.0	[70.4, 75.4]	67.6	[64.9, 70.2]	9.3	[8.4, 10.1]
2008	1,206	94.0	[92.5, 95.2]	87.1	[85.1, 88.9]	79.3	[76.9, 81.5]	73.0	[70.4, 75.4]	67.0	[64.2, 69.5]	9.5	[8.6, 10.8]
2009	1,223	94.4	[93.0, 95.6]	87.5	[85.5, 89.2]	80.7	[78.4, 82.8]	73.9	[71.3, 76.3]	68.7	[66.1, 71.3]	9.7	[8.8, .]
2010	1,285	93.8	[92.3, 95.0]	85.9	[83.9, 87.7]	78.8	[76.5, 81.0]	72.1	[69.6, 74.5]	67.4	[64.7, 69.9]	9.9	[8.7, .]
2011	1,337	93.5	[92.0, 94.7]	87.9	[86.0, 89.5]	81.1	[78.8, 83.1]	75.1	[72.6, 77.3]	69.9	[67.4, 72.3]	>9	
2012	1,232	93.6	[92.1, 94.8]	86.3	[84.3, 88.1]	79.8	[77.4, 81.9]	74.2	[71.7, 76.6]	67.7	[65.0, 70.2]	>8	
2013	1,321	93.7	[92.3, 94.9]	86.2	[84.2, 87.9]	78.9	[76.6, 81.0]	74.0	[71.5, 76.2]	68.9	[66.4, 71.4]	>7	
2014	1,254	93.8	[92.3, 95.0]	86.6	[84.6, 88.4]	80.0	[77.7, 82.1]	74.3	[71.8, 76.7]	69.6	[67.0, 72.1]	>6	
2015	1,160	93.9	[92.3, 95.1]	87.3	[85.3, 89.1]	80.1	[77.6, 82.2]	74.7	[72.1, 77.1]	70.7	[67.9, 73.3]	>5	
2016	1,229	94.1	[92.7, 95.3]	86.5	[84.4, 88.3]	80.2	[77.8, 82.3]	74.7	[71.8, 77.3]	no FU	—	>4	
2017	1,103	92.8	[91.1, 94.2]	87.4	[85.3, 89.2]	79.6	[76.1, 82.7]	no FU	—	no FU	—	>3	
Combined Stage IV													
2004	561	75.4	[71.6, 78.8]	59.7	[55.5, 63.6]	47.2	[43.1, 51.3]	35.7	[31.7, 39.6]	28.5	[24.8, 32.3]	2.8	[2.5, 3.1]
2005	458	76.0	[71.8, 79.6]	61.4	[56.7, 65.6]	48.5	[43.8, 53.0]	38.2	[33.8, 42.6]	29.3	[25.2, 33.5]	2.9	[2.5, 3.3]
2006	482	71.3	[67.0, 75.1]	56.3	[51.7, 60.6]	43.4	[38.9, 47.7]	33.4	[29.2, 37.6]	26.3	[22.4, 30.3]	2.5	[2.1, 2.9]
2007	476	70.2	[65.8, 74.1]	56.1	[51.5, 60.4]	41.8	[37.4, 46.2]	30.0	[26.0, 34.2]	24.4	[20.6, 28.3]	2.5	[2.1, 2.7]
2008	527	73.1	[69.1, 76.6]	57.1	[52.8, 61.2]	44.2	[39.9, 48.4]	32.1	[28.1, 36.1]	26.2	[22.5, 30.0]	2.6	[2.2, 2.9]
2009	598	73.9	[70.1, 77.2]	59.3	[55.2, 63.1]	44.9	[40.9, 48.8]	34.3	[30.6, 38.2]	25.0	[21.6, 28.5]	2.7	[2.4, 2.9]
2010	613	72.9	[69.2, 76.3]	56.9	[52.9, 60.7]	44.0	[40.1, 47.9]	36.8	[33.0, 40.7]	29.8	[26.2, 33.5]	2.7	[2.3, 2.9]
2011	630	74.6	[71.0, 77.8]	58.4	[54.4, 62.1]	46.6	[42.6, 50.4]	35.6	[31.9, 39.3]	29.5	[26.0, 33.1]	2.7	[2.3, 3.0]
2012	617	75.7	[72.1, 78.9]	61.8	[57.8, 65.5]	50.6	[46.6, 54.4]	38.2	[34.4, 42.1]	30.0	[26.4, 33.6]	3.1	[2.7, 3.3]



Unadjusted observed survival, %													
		1 year		2 year		3 year		4 year		5 year		Median survival time (year)	
Characteristic	N at risk	%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI	T	95% CI
2013	647	73.6	[70.0, 76.8]	57.7	[53.8, 61.4]	47.0	[43.1, 50.8]	35.8	[32.1, 39.5]	27.6	[24.2, 31.1]	2.8	[2.4, 3.1]
2014	647	72.2	[68.6, 75.5]	60.3	[56.4, 63.9]	49.1	[45.2, 52.9]	39.4	[35.6, 43.2]	30.3	[26.8, 33.9]	3.0	[2.6, 3.3]
2015	659	73.6	[70.1, 76.8]	59.3	[55.5, 62.9]	45.3	[41.5, 49.1]	37.2	[33.5, 40.9]	31.2	[27.3, 35.1]	2.6	[2.3, 2.9]
2016	703	75.2	[71.8, 78.2]	62.5	[58.8, 66.0]	50.6	[46.8, 54.2]	41.7	[37.4, 45.9]	no FU	—	3.1	[2.8, 3.6]
2017	744	72.7	[69.3, 75.7]	59.5	[55.9, 62.9]	51.2	[47.0, 55.1]	no FU	—	no FU	—	>3	



Table 7 – Female Breast cancer (2004-2017), time trend relative survival with incidence year

Unadjusted relative survival, %												
Characteristic	N at risk	1 year			2 year		3 year		4 year		5 year	
		%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI	
All												
2004	9,544	96.9	[96.4, 97.3]	94.5	[93.9, 95.1]	92.0	[91.3, 92.7]	89.9	[89.1, 90.7]	87.8	[86.9, 88.6]	
2005	9,568	97.3	[96.8, 97.7]	94.9	[94.2, 95.4]	92.1	[91.4, 92.8]	89.9	[89.0, 90.7]	87.7	[86.8, 88.6]	
2006	9,705	97.1	[96.6, 97.5]	94.9	[94.3, 95.5]	92.4	[91.6, 93.1]	90.2	[89.4, 91.0]	88.1	[87.2, 89.0]	
2007	9,836	96.9	[96.4, 97.3]	94.6	[93.9, 95.1]	92.5	[91.8, 93.2]	90.3	[89.5, 91.1]	88.6	[87.7, 89.4]	
2008	9,765	97.1	[96.7, 97.6]	94.7	[94.1, 95.3]	92.3	[91.6, 93.0]	90.1	[89.3, 90.9]	88.5	[87.6, 89.4]	
2009	9,761	97.1	[96.7, 97.6]	94.8	[94.1, 95.3]	92.2	[91.5, 92.9]	90.0	[89.2, 90.8]	88.3	[87.4, 89.2]	
2010	10,078	97.2	[96.7, 97.6]	95.0	[94.4, 95.5]	92.7	[92.0, 93.3]	90.9	[90.1, 91.6]	89.5	[88.7, 90.3]	
2011	10,731	97.3	[96.9, 97.7]	95.1	[94.6, 95.7]	93.3	[92.6, 93.9]	91.3	[90.5, 92.0]	90.0	[89.2, 90.8]	
2012	10,680	97.4	[96.9, 97.8]	95.2	[94.6, 95.8]	93.3	[92.6, 93.9]	91.5	[90.7, 92.3]	89.7	[88.8, 90.5]	
2013	10,848	97.6	[97.2, 98.0]	95.4	[94.8, 95.9]	93.5	[92.9, 94.2]	92.0	[91.2, 92.7]	90.4	[89.6, 91.2]	
2014	10,583	97.5	[97.0, 97.8]	95.8	[95.2, 96.3]	94.1	[93.5, 94.8]	92.6	[91.9, 93.4]	91.3	[90.4, 92.1]	
2015	10,500	97.8	[97.4, 98.2]	96.2	[95.6, 96.7]	94.0	[93.3, 94.7]	92.7	[91.9, 93.4]	91.6	[90.7, 92.4]	
2016	10,872	97.6	[97.2, 98.0]	95.8	[95.2, 96.3]	94.2	[93.5, 94.8]	92.6	[91.8, 93.4]	no FU	—	
2017	10,710	97.2	[96.8, 97.6]	95.8	[95.3, 96.4]	94.5	[93.7, 95.2]	no FU	—	no FU	—	
Combined Stage I												
2004	3,544	100.3	[99.9, 100.6]	100.8	[100.3, 101.2]	100.6	[99.9, 101.2]	100.4	[99.5, 101.1]	99.9	[98.9, 100.8]	
2005	3,485	100.2	[99.8, 100.5]	100.1	[99.5, 100.6]	99.9	[99.1, 100.5]	99.8	[99.0, 100.6]	99.5	[98.5, 100.4]	
2006	3,755	100.5	[100.1, 100.7]	100.7	[100.2, 101.1]	100.6	[100.0, 101.2]	100.5	[99.6, 101.2]	99.8	[98.9, 100.7]	
2007	3,774	100.3	[99.9, 100.6]	100.2	[99.6, 100.6]	100.2	[99.5, 100.8]	99.9	[99.1, 100.7]	99.7	[98.7, 100.6]	
2008	3,807	100.4	[100.1, 100.7]	100.3	[99.8, 100.8]	100.0	[99.3, 100.7]	99.7	[98.9, 100.5]	99.6	[98.7, 100.5]	
2009	3,877	100.5	[100.1, 100.7]	100.4	[99.9, 100.9]	100.1	[99.4, 100.7]	99.8	[99.0, 100.6]	100.0	[99.0, 100.8]	



Characteristic	N at risk	Unadjusted relative survival, %									
		1 year		2 year		3 year		4 year		5 year	
		%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI
2010	4,281	100.2	[99.8, 100.5]	100.0	[99.5, 100.5]	99.6	[99.0, 100.2]	99.3	[98.5, 100.1]	99.2	[98.3, 100.0]
2011	4,698	100.2	[99.8, 100.4]	100.0	[99.5, 100.5]	100.1	[99.5, 100.7]	99.9	[99.2, 100.6]	99.7	[98.8, 100.4]
2012	4,699	100.2	[99.9, 100.5]	100.2	[99.7, 100.6]	100.0	[99.4, 100.6]	100.0	[99.2, 100.7]	99.6	[98.8, 100.4]
2013	4,873	100.4	[100.1, 100.6]	100.2	[99.7, 100.6]	100.5	[99.9, 101.0]	100.3	[99.5, 100.9]	100.0	[99.1, 100.8]
2014	4,817	100.4	[100.1, 100.7]	100.6	[100.1, 101.0]	100.7	[100.1, 101.2]	100.8	[100.1, 101.4]	100.6	[99.8, 101.4]
2015	4,811	100.2	[99.9, 100.5]	100.6	[100.1, 101.0]	100.2	[99.6, 100.8]	100.2	[99.4, 100.8]	100.8	[99.9, 101.6]
2016	4,833	100.1	[99.7, 100.4]	100.3	[99.7, 100.7]	100.5	[99.8, 101.0]	100.5	[99.7, 101.3]	no FU	—
2017	4,833	100.4	[100.0, 100.6]	100.7	[100.2, 101.1]	100.9	[100.2, 101.5]	no FU	—	no FU	—
Combined Stage II											
2004	3,279	99.6	[99.1, 100.1]	97.9	[97.0, 98.7]	96.1	[95.0, 97.1]	95.0	[93.7, 96.2]	93.2	[91.8, 94.5]
2005	3,344	99.5	[98.9, 100.0]	97.6	[96.7, 98.4]	95.9	[94.7, 96.9]	94.2	[92.9, 95.4]	92.3	[90.8, 93.7]
2006	3,487	99.3	[98.7, 99.8]	98.2	[97.3, 98.9]	95.8	[94.7, 96.8]	94.1	[92.9, 95.3]	92.2	[90.8, 93.6]
2007	3,507	99.3	[98.7, 99.8]	98.2	[97.3, 98.9]	97.2	[96.1, 98.1]	95.8	[94.6, 97.0]	94.3	[92.9, 95.6]
2008	3,500	99.5	[98.9, 100.0]	98.0	[97.1, 98.8]	96.4	[95.3, 97.4]	94.3	[93.1, 95.5]	93.2	[91.7, 94.5]
2009	3,527	99.1	[98.5, 99.6]	97.4	[96.5, 98.3]	95.5	[94.4, 96.6]	93.7	[92.3, 94.9]	92.2	[90.7, 93.5]
2010	3,466	99.3	[98.7, 99.8]	98.0	[97.1, 98.8]	96.7	[95.6, 97.7]	95.3	[94.1, 96.5]	94.4	[93.0, 95.7]
2011	3,698	99.2	[98.5, 99.7]	97.5	[96.6, 98.3]	96.3	[95.2, 97.3]	94.7	[93.4, 95.9]	93.7	[92.3, 95.1]
2012	3,704	99.4	[98.8, 99.9]	97.9	[97.0, 98.6]	96.0	[94.9, 97.0]	94.6	[93.4, 95.8]	93.0	[91.6, 94.4]
2013	3,726	99.6	[99.0, 100.1]	98.4	[97.5, 99.2]	97.0	[95.9, 98.0]	96.0	[94.8, 97.2]	94.4	[93.0, 95.8]
2014	3,618	99.5	[98.9, 100.0]	98.5	[97.6, 99.3]	97.3	[96.2, 98.3]	96.1	[94.8, 97.2]	95.0	[93.6, 96.3]
2015	3,666	99.8	[99.2, 100.2]	98.6	[97.7, 99.4]	97.0	[95.9, 98.0]	95.7	[94.4, 96.9]	94.6	[93.0, 96.1]
2016	3,777	99.4	[98.7, 99.9]	98.0	[97.1, 98.8]	96.8	[95.7, 97.8]	95.6	[94.2, 96.9]	no FU	—
2017	3,652	99.0	[98.4, 99.6]	98.1	[97.1, 98.9]	97.2	[96.0, 98.4]	no FU	—	no FU	—



Unadjusted relative survival, %												
Characteristic	N at risk	1 year			2 year		3 year		4 year		5 year	
		%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI	
Combined Stage III												
2004	1,112	94.5	[92.7, 95.9]	88.8	[86.4, 90.9]	83.2	[80.4, 85.7]	77.8	[74.8, 80.7]	72.1	[68.9, 75.2]	
2005	1,209	97.1	[95.7, 98.2]	91.7	[89.6, 93.5]	83.5	[80.8, 85.9]	78.1	[75.1, 80.8]	73.4	[70.3, 76.3]	
2006	1,237	95.1	[93.5, 96.4]	90.6	[88.4, 92.4]	84.9	[82.3, 87.2]	79.3	[76.5, 81.9]	73.9	[70.8, 76.8]	
2007	1,234	96.3	[94.8, 97.5]	90.1	[88.0, 92.0]	85.2	[82.7, 87.5]	79.8	[77.0, 82.4]	75.6	[72.6, 78.4]	
2008	1,206	96.6	[95.0, 97.8]	91.9	[89.7, 93.7]	85.8	[83.2, 88.1]	80.9	[78.1, 83.6]	76.1	[73.0, 79.1]	
2009	1,223	96.9	[95.4, 98.1]	92.0	[89.9, 93.8]	86.9	[84.4, 89.2]	81.5	[78.7, 84.1]	77.6	[74.5, 80.4]	
2010	1,285	96.3	[94.8, 97.5]	90.5	[88.4, 92.4]	85.2	[82.7, 87.5]	80.0	[77.2, 82.6]	76.7	[73.7, 79.5]	
2011	1,337	96.0	[94.5, 97.2]	92.5	[90.5, 94.2]	87.4	[85.0, 89.5]	82.8	[80.1, 85.2]	79.0	[76.1, 81.7]	
2012	1,232	96.2	[94.6, 97.4]	91.0	[88.9, 92.9]	86.3	[83.7, 88.6]	82.3	[79.5, 85.0]	77.1	[74.0, 80.0]	
2013	1,321	96.1	[94.6, 97.3]	90.5	[88.4, 92.3]	84.8	[82.4, 87.1]	81.5	[78.8, 84.0]	77.9	[75.0, 80.7]	
2014	1,254	96.4	[94.9, 97.6]	91.4	[89.2, 93.2]	86.7	[84.2, 89.0]	82.8	[80.0, 85.4]	79.6	[76.6, 82.4]	
2015	1,160	96.4	[94.8, 97.7]	92.1	[89.9, 93.9]	86.7	[84.1, 89.1]	83.1	[80.2, 85.8]	79.4	[76.0, 82.6]	
2016	1,229	96.9	[95.4, 98.1]	91.6	[89.5, 93.5]	87.4	[84.9, 89.7]	83.4	[80.3, 86.3]	no FU	—	
2017	1,103	95.6	[93.9, 97.0]	92.6	[90.4, 94.6]	87.9	[84.8, 90.6]	no FU	—	no FU	—	
Combined Stage IV												
2004	561	77.0	[73.1, 80.5]	62.7	[58.3, 66.8]	50.9	[46.4, 55.3]	39.6	[35.2, 43.9]	32.3	[28.2, 36.6]	
2005	458	77.4	[73.1, 81.1]	63.9	[59.0, 68.3]	51.5	[46.6, 56.3]	41.4	[36.6, 46.3]	32.4	[27.9, 37.1]	
2006	482	72.7	[68.3, 76.7]	58.9	[54.1, 63.4]	46.5	[41.7, 51.2]	36.8	[32.1, 41.4]	29.8	[25.4, 34.4]	
2007	476	71.8	[67.3, 75.8]	58.7	[53.9, 63.2]	44.8	[40.1, 49.5]	32.8	[28.4, 37.4]	27.1	[22.9, 31.5]	
2008	527	74.6	[70.4, 78.3]	59.9	[55.3, 64.2]	47.5	[42.9, 52.0]	35.3	[31.0, 39.7]	29.6	[25.4, 33.8]	
2009	598	75.0	[71.0, 78.5]	61.6	[57.3, 65.6]	48.0	[43.6, 52.2]	37.6	[33.5, 41.8]	28.0	[24.2, 32.0]	
2010	613	74.1	[70.2, 77.6]	59.3	[55.0, 63.3]	47.3	[43.0, 51.5]	40.6	[36.4, 44.8]	33.9	[29.8, 38.0]	



Characteristic	N at risk	Unadjusted relative survival, %									
		1 year		2 year		3 year		4 year		5 year	
		%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI
2011	630	75.8	[72.0, 79.2]	60.8	[56.6, 64.7]	49.8	[45.5, 53.9]	39.2	[35.1, 43.3]	33.3	[29.3, 37.4]
2012	617	77.3	[73.5, 80.6]	64.8	[60.6, 68.7]	54.6	[50.2, 58.8]	42.6	[38.3, 46.8]	34.5	[30.4, 38.7]
2013	647	74.8	[71.0, 78.2]	60.3	[56.2, 64.3]	50.8	[46.6, 54.9]	40.1	[36.0, 44.3]	31.8	[27.9, 35.9]
2014	647	73.2	[69.5, 76.7]	62.6	[58.5, 66.5]	52.4	[48.1, 56.4]	43.2	[39.0, 47.3]	34.2	[30.2, 38.2]
2015	659	74.9	[71.2, 78.3]	62.0	[57.9, 65.9]	48.7	[44.5, 52.8]	41.3	[37.2, 45.5]	34.5	[30.2, 39.0]
2016	703	76.5	[73.0, 79.7]	65.3	[61.4, 69.0]	54.3	[50.2, 58.2]	46.2	[41.8, 50.6]	no FU	–
2017	744	74.1	[70.5, 77.3]	62.2	[58.3, 65.8]	53.7	[49.4, 57.9]	no FU	–	no FU	–



Appendix 1.1.2. Uptake of selected drugs

Table 8 – Proportion of patients who received at least one dose during 5-year period after diagnosis (breast cancer stage I)

Drug/incidence year (n)	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
	3570	3525	3822	3840	3881	3956	4378	4828	4825	5014	4996	4996	4997	5041
pertuzumab							0.2%	0.2%	0.2%	0.3%	0.2%	0.2%	0.3%	0.1%
trastuzumab emtansine							0.1%	0.1%	0.1%	0.1%	0.1%	0.1%		
palbociclib										0.5%	0.4%	0.4%	0.3%	0.2%
abemaciclib														
ribociclib														

Source: BCR-IMA.

Table 9 – Proportion of patients who received at least one dose during 5-year period after diagnosis (breast cancer stage II)

Drug/incidence year (n)	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
	3299	3379	3520	3553	3539	3558	3502	3743	3756	3766	3689	3724	3849	3709
pertuzumab							0.2%	0.2%	0.9%	0.7%	0.9%	0.6%	0.5%	0.4%
trastuzumab emtansine							0.3%	0.5%	0.4%	0.5%	0.5%	0.4%	0.2%	0.1%
palbociclib										1.2%	1.0%	0.8%	0.9%	0.4%
abemaciclib														
ribociclib													0.1%	

Source: BCR-IMA.

Table 10 – Proportion of patients who received at least one dose during 5-year period after diagnosis (breast cancer stage III)

Drug/incidence year (n)	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
	1118	1224	1245	1243	1209	1234	1295	1347	1239	1335	1273	1170	1242	1113
pertuzumab							0.5%	1.8%	2.0%	2.8%	2.3%	2.9%	1.7%	1.5%



trastuzumab emtansine	0.7%	1.2%	1.4%	1.9%	1.2%	1.3%	0.8%	
palbociclib			0.1%	3.2%	2.4%	3.2%	1.9%	1.9%
abemaciclib								
ribociclib					0.1%			0.1%

Source: BCR-IMA.

Table 11 – Proportion of patients who received at least one dose during 5-year period after diagnosis (breast cancer stage IV)

Drug/incidence year (n)	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
	578	467	487	490	542	618	636	663	655	677	676	696	728	784
pertuzumab							0.3	0.8	0.9	2.5	13.3	16.7	14.4	16.1
trastuzumab emtansine							2.0	3.3	5.3	5.8	7.1	7.0	4.4	2.9
palbociclib										4.7	5.9	7.2	11.5	18.4
abemaciclib														
ribociclib										0.1		0.3	0.3	0.1

* Numbers in yellow indicate the first calendar year of reimbursement. For example, pertuzumab was first reimbursed in 2014. The columns in this table indicate the incidence year. For example, for incidence year 2013, 2.5% of patients received reimbursed pertuzumab during the 5 years after diagnosis. Source: BCR-IMA.



Appendix 1.2. Reimbursement criteria for selected drugs

Table 12 – Targeted drugs in breast

Drug	Trade name	Date start reimbursement	Indication NI	Indication Fr
pertuzumab	Perjeta	1/6/2014	<p>in combinatie met trastuzumab en een taxaan in het kader van de behandeling van bij volwassen patiënten met HER2-positieve gemetastaseerde of lokaal teruggekeerde, niet-reseceerbare borstkanker met viscerale metastasen die geen eerdere anti-HER2-therapie of chemotherapie voor hun gemetastaseerde ziekte hebben gehad.</p> <p>De amplificatie van het gen van de Humane Epidermale groeifactor Receptor-2 (HER2 of Human Epidermal growth factor Receptor-2) moet aangetoond worden door een positieve In Situ Hybridisatie test (ISH).</p>	<p>en association au trastuzumab et un taxane, dans le cadre du traitement de patients adultes atteints d'un cancer du sein métastatique ou localement récidivant non résécable HER2 positif avec atteinte viscérale, n'ayant pas reçu au préalable de traitement anti-HER2 ou de chimiothérapie pour leur maladie métastatique.</p> <p>L'amplification du gène du Récepteur 2 du facteur de croissance Epidermique Humain (HER2 ou Human Epidermal growth factor Receptor-2) doit être prouvée par un test d'Hybridation In Situ (ISH) positif.</p>
		1/6/2014	<p>toegediend in combinatie met trastuzumab en een taxaan in het kader van de behandeling van volwassen patiënten met HER2-positieve gemetastaseerde of lokaal teruggekeerde, niet-reseceerbare borstkanker zonder viscerale metastasen die geen eerdere anti-HER2-therapie of chemotherapie voor hun gemetastaseerde ziekte hebben gehad.</p> <p>De amplificatie van het gen van de Humane Epidermale groeifactor Receptor-2 (HER2 of Human Epidermal growth factor Receptor-2) moet aangetoond worden door een positieve In Situ Hybridisatie test (ISH).</p>	<p>en association au trastuzumab et un taxane, dans le cadre du traitement de patients adultes atteints d'un cancer du sein métastatique ou localement récidivant non résécable HER2 positif sans atteinte viscérale, n'ayant pas reçu au préalable de traitement anti-HER2 ou de chimiothérapie pour leur maladie métastatique.</p> <p>L'amplification du gène du Récepteur 2 du facteur de croissance Epidermique Humain (HER2 ou Human Epidermal growth factor Receptor-2) doit être prouvée par un test d'Hybridation In Situ (ISH) positif.</p>
		1/7/2019	<p>maximaal 6 cycli in neo-adjuvant kader indien het wordt toegediend in combinatie met trastuzumab en chemotherapie voor de behandeling van volwassen patiënten met HER2-positieve vroege borstkanker met lymfeklierpositieve ziekte welke bevestigd is met een FNAC (fine needle aspiration cytology) of histologie. Pertuzumab kan in neo-adjuvant kader vergoed worden in combinatie met trastuzumab en chemotherapie gedurende maximaal 6 cycli of tot recidief of onbehandelbare toxiciteit, afhankelijk van wat zich het eerst voordoet.</p>	<p>remboursement pour maximum 6 cycles dans le cadre néo-adjuvant s'il est administré en association à trastuzumab et à une chimiothérapie, dans le traitement de patients adultes atteints d'un cancer du sein précoce HER2 positif avec une atteinte ganglionnaire confirmée par une FNAC (fine needle aspiration cytology) ou histologie.</p> <p>Pertuzumab peut être remboursé dans le cadre néo-adjuvant en association à trastuzumab et à la chimiothérapie pendant maximum 6 cycles ou jusqu'à rechute de la maladie ou survenue d'une toxicité inacceptable, en fonction de l'évènement se produisant en premier.</p>



Drug	Trade name	Date start reimbursement	Indication NI	Indication Fr
			<p>verderzetting na maximaal 6 cycli in neo-adjuvant kader (volgens § 150318) in geval geen pathologische complete respons bekomen is, indien het wordt toegediend in combinatie met trastuzumab en chemotherapie voor de behandeling van volwassen patiënten met HER2-positieve vroege borstkanker met lymfeklierpositieve ziekte welke bevestigd is met een FNAC (fine needle aspiration cytology) of histologie. Als de behandeling met pertuzumab werd gestart voor de operatie (neo-adjuvant kader) met maximaal 6 cycli waarna geen pathologische complete respons (pCR) werd bekomen op het moment van de chirurgie, dan kan de behandeling met pertuzumab in combinatie met trastuzumab en chemotherapie worden verdergezet. De neo-adjuvante behandeling en de voortzetting (adjuvante behandeling) zal samen maximaal 18 cycli bevatten.</p>	<p>remboursement pour la prolongation d'un traitement néo-adjuvant de maximum 6 cycles (selon le § 150318) en cas de non obtention d'une réponse pathologique complète s'il est administré en association à trastuzumab et à une chimiothérapie, dans le traitement de patients adultes atteints d'un cancer du sein précoce HER2 positif avec une atteinte ganglionnaire confirmée par une FNAC (fine needle aspiration cytology) ou histologie.</p> <p>Si le traitement avec pertuzumab a commencé avant la chirurgie (dans le cadre néo-adjuvant) avec 6 cycles maximum, et une réponse pathologique complète (pCR) n'a pas été obtenue au moment de la chirurgie, le traitement avec pertuzumab en association à trastuzumab et chimiothérapie peut être continué. Le traitement néo-adjuvant et la continuation du traitement (traitement adjuvant) comportera maximum 18 cycles au total.</p>
		1/7/2019	<p>verderzetting na maximaal 6 cycli in neo-adjuvant kader (volgens § 150318) in geval een pathologische complete respons bekomen is, indien het wordt toegediend in combinatie met trastuzumab en chemotherapie voor de behandeling van volwassen patiënten met HER2-positieve vroege borstkanker met lymfeklierpositieve ziekte welke bevestigd is met een FNAC (fine needle aspiration cytology) of histologie.</p> <p>Als de behandeling met pertuzumab werd gestart voor de operatie (neo-adjuvant kader) met maximaal 6 cycli waarna een pathologische complete respons (pCR) werd bekomen op het moment van chirurgie, dan kan de behandeling met pertuzumab in combinatie met trastuzumab en chemotherapie worden verdergezet. De neo-adjuvante behandeling en de voortzetting (adjuvante behandeling) zal samen maximaal 18 cycli bevatten.</p>	<p>remboursement en continuation d'un traitement de maximum 6 cycles dans le cadre néo-adjuvant (selon le § 150318) en cas de réponse pathologique complète s'il est administré en association à trastuzumab et à une chimiothérapie, dans le traitement de patients adultes atteints d'un cancer du sein précoce HER2 positif avec une atteinte ganglionnaire confirmée par une FNAC (fine needle aspiration cytology) ou histologie.</p> <p>Si le traitement avec pertuzumab a commencé avant la chirurgie (dans le cadre néo-adjuvant) avec 6 cycles maximum, et une réponse pathologique complète (pCR) a été obtenue au moment de la chirurgie, le traitement avec pertuzumab en association à trastuzumab et à la chimiothérapie peut être poursuivi. Le traitement néo-adjuvant et la continuation du traitement (traitement adjuvant) comportera maximum 18 cycles au total.</p>
		1/7/2019	<p>Pertuzumab komt voor vergoeding in aanmerking in zuiver adjuvant kader, zonder voorafgaande neo-adjuvante behandeling, indien het wordt toegediend in combinatie met trastuzumab en chemotherapie voor de behandeling van</p>	<p>remboursement dans le cadre adjuvant, sans traitement néo-adjuvant préalable s'il est administré en association à trastuzumab et à une chimiothérapie, dans le traitement de patients adultes atteints d'un cancer du sein précoce HER2</p>



Drug	Trade name	Date start reimbursement	Indication NI	Indication Fr
			<p>volwassen patiënten met HER2-positieve vroege borstkanker met lymfeklierpositieve ziekte welke bevestigd is met een FNAC (fine needle aspiration cytology) of histologie.</p> <p>De patiënt mag nog geen vergoeding genoten hebben volgens § 150318. Pertuzumab in combinatie met trastuzumab en chemotherapie kan in zuiver adjuvant kader (wanneer de behandeling start na de operatie) vergoed worden gedurende maximaal 18 cycli of tot recidief of onbehandelbare toxiciteit, afhankelijk van wat zich het eerst voordoet.</p>	<p>positif avec une atteinte ganglionnaire confirmée par une FNAC (fine needle aspiration cytology) ou histologie.</p> <p>Le patient ne peut pas avoir bénéficié d'un remboursement selon le § 150318.</p> <p>Pertuzumab peut être remboursé dans le cadre adjuvant (lorsque le traitement débute après l'opération) en association à trastuzumab et chimiothérapie pendant une période maximale de 18 cycles ou jusqu'à rechute de la maladie ou survenue d'une toxicité inacceptable, en fonction de l'évènement se produisant en premier.</p>
trastuzumab emtansine	Kadcyla	1/12/2014	<p>toegediend in het kader van de behandeling van volwassen patiënten met niet-reseceerbare, lokaal gevorderde of gemetastaseerde borstkanker met een amplificatie van het gen van de Humane Epidermale groeifactor Receptor-2 (HER2).</p> <p>De terugbetaling wordt toegestaan in monotherapie bij patiënten die eerder trastuzumab en een taxaan, afzonderlijk of in combinatie, hebben ontvangen. Patiënten dienen eerdere therapie te hebben ontvangen voor lokaal gevorderde of gemetastaseerde ziekte, of een recidief te hebben ontwikkeld tijdens een adjuvante therapie of binnen zes maanden na het voltooien ervan.</p>	<p>administrée dans le cadre du traitement de patients adultes atteints d'un cancer du sein métastatique ou localement avancé non résécable avec une amplification du gène du Récepteur 2 du facteur de croissance Epidermique Humain (HER2).</p> <p>Le remboursement est accordé en monothérapie chez les patients ayant reçu au préalable du trastuzumab et un taxane, séparément ou en association. Les patients doivent : avoir reçu un traitement antérieur pour la maladie localement avancée ou métastatique ou avoir présenté une progression de la maladie pendant un traitement adjuvant ou dans les six mois suivant sa fin.</p>
palbociclib	Ibrance	1/12/2017	<p>vergoed, in combinatie met een niet-steroïdale aromatase inhibitor, voor de behandeling van vrouwen met hormoonreceptor-positieve, HER2-negatieve, lokaal gevorderde of gemetastaseerde borstkanker die reeds een eerdere adjuvante hormonale behandeling met tamoxifen hebben gekregen en die tijdens of binnen de 12 maanden na het beëindigen van de adjuvante behandeling zijn hervallen.</p>	<p>remboursée, en combinaison avec un inhibiteur de l'aromatase non stéroïdien, pour le traitement des patientes présentant un cancer du sein localement avancé ou métastatique à récepteur hormonal positif et HER2-négatif, ayant reçu antérieurement un traitement hormonal en adjuvant avec tamoxifen et présentant une rechute de leur maladie pendant le traitement en adjuvant ou endéans une période de 12 mois après la fin du traitement en adjuvant.</p>
		1/12/2017	<p>vergoed in combinatie met fulvestrant voor de behandeling van vrouwen met hormoonreceptor-positieve, HER2-negatieve, lokaal gevorderde of gemetastaseerde borstkanker die reeds een eerdere adjuvante behandeling met een aromatase inhibitor hebben gekregen en die tijdens</p>	<p>remboursée, en combinaison avec le fulvestrant, pour le traitement des patientes présentant un cancer du sein localement avancé ou métastatique à récepteur hormonal positif et HER2-négatif, ayant reçu antérieurement un traitement en adjuvant contenant un inhibiteur de</p>



Drug	Trade name	Date start reimbursement	Indication NI	Indication Fr
			of binnen de 12 maanden na het beëindigen van de adjuvante behandeling zijn hervallen.	l'aromatase et présentant une rechute de leur maladie pendant le traitement en adjuvant ou endéans une période de 12 mois après la fin du traitement en adjuvant.
		1/12/2017	vergoed in combinatie met een niet-steroidale aromatase inhibitor voor de behandeling van vrouwen met hormoonreceptor-positieve, HER2-negatieve, symptomatische lokaal gevorderde of gemetastaseerde borstkanker, die reeds een eerdere adjuvante hormonale behandeling hebben gekregen en die meer dan 12 maanden na het beëindigen van de adjuvante behandeling hervallen zijn.	remboursée, en combinaison avec un inhibiteur de l'aromatase non stéroïdien, pour le traitement des patientes présentant un cancer du sein symptomatique, localement avancé ou métastatique à récepteur hormonal positif et HER2-négatif, ayant reçu antérieurement un traitement hormonal en adjuvant et présentant une rechute au-delà de 12 mois après la fin de leur traitement en adjuvant.
		1/12/2017	vergoed, in combinatie met een niet-steroidale aromatase inhibitor, voor de behandeling van vrouwen met hormoonreceptor-positieve, HER2-negatieve, symptomatische lokaal gevorderde of gemetastaseerde borstkanker bij initiële diagnose (de novo).	remboursée, en combinaison avec un inhibiteur de l'aromatase non stéroïdien, pour le traitement des patientes présentant lors d'un diagnostic initial (de novo) un cancer du sein symptomatique, localement avancé ou métastatique à récepteur hormonal positif et HER2-négatif.
		1/12/2017	vergoed, in combinatie met fulvestrant voor de behandeling van vrouwen met hormoonreceptor-positieve, HER2-negatieve, lokaal gevorderde of gemetastaseerde borstkanker die reeds een eerdere hormoonbehandeling hebben gekregen voor gevorderde of gemetastaseerde borstkanker.	remboursée, en combinaison avec le fulvestrant, pour le traitement des patientes présentant un cancer du sein localement avancé ou métastatique à récepteur hormonal positif et HER2-négatif, ayant reçu antérieurement un traitement hormonal pour leur cancer du sein avancé ou métastatique.
abemaciclib	Verzenios	1/6/2019	<p>in combinatie met een niet-steroidale aromatase inhibitor, voor de behandeling van vrouwen met hormoonreceptor-positieve, HER2-negatieve, lokaal gevorderde of gemetastaseerde borstkanker die reeds een eerdere adjuvante hormonale behandeling met tamoxifen hebben gekregen en die tijdens of binnen de 12 maanden na het beëindigen van de adjuvante behandeling zijn hervallen.</p> <p>De vergoeding wordt niet toegestaan indien de patiënte voor gevorderde of gemetastaseerde borstkanker reeds eerder werd behandeld met een CDK4/6 inhibitor (vergoedingsgroep A-128) en hieronder progressie vertoonde.</p>	<p>remboursement, en combinaison avec un inhibiteur de l'aromatase non stéroïdien, pour le traitement des patientes présentant un cancer du sein localement avancé ou métastatique à récepteur hormonal positif et HER2-négatif, ayant reçu antérieurement un traitement hormonal en adjuvant avec le tamoxifène et présentant une rechute de leur maladie pendant le traitement en adjuvant ou endéans une période de 12 mois après la fin du traitement en adjuvant.</p> <p>Le remboursement n'est pas autorisé si la patiente a déjà été traitée auparavant et a progressé sous un inhibiteur CDK4/6 (groupe de remboursement A-128), pour un cancer du sein avancé ou métastatique.</p>



Drug	Trade name	Date start reimbursement	Indication NI	Indication Fr
		1/6/2019	<p>in combinatie met fulvestrant voor de behandeling van vrouwen met hormoonreceptor-positieve, HER2-negatieve, lokaal gevorderde of gemetastaseerde borstkanker die reeds een eerdere adjuvante behandeling met een aromatase inhibitor hebben gekregen en die tijdens of binnen de 12 maanden na het beëindigen van de adjuvante behandeling zijn hervallen.</p> <p>De vergoeding wordt niet toegestaan indien de patiënte voor gevorderde of gemetastaseerde borstkanker reeds eerder werd behandeld met een CDK4/6 inhibitor (vergoedingsgroep A-128) en hieronder progressie vertoonde.</p>	<p>Le remboursement n'est pas autorisé si la patiente a déjà été traitée auparavant et a progressé sous un inhibiteur CDK4/6 (groupe de remboursement A-128), pour un cancer du sein avancé ou métastatique.</p> <p>Le remboursement n'est pas autorisé si la patiente a déjà été traitée auparavant et a progressé sous un inhibiteur CDK4/6 (groupe de remboursement A-128), pour un cancer du sein avancé ou métastatique.</p>
		1/6/2019	<p>in combinatie met een niet-steroïdale aromatase inhibitor voor de behandeling van vrouwen met hormoonreceptor-positieve, HER2-negatieve, symptomatische lokaal gevorderde of gemetastaseerde borstkanker, die reeds een eerdere adjuvante hormonale behandeling hebben gekregen en die meer dan 12 maanden na het beëindigen van de adjuvante behandeling hervallen zijn.</p> <p>De vergoeding wordt niet toegestaan indien de patiënte voor gevorderde of gemetastaseerde borstkanker reeds eerder werd behandeld met een CDK4/6 inhibitor (vergoedingsgroep A-128) en hieronder progressie vertoonde.</p>	<p>remboursement, en combinaison avec un inhibiteur de l'aromatase non stéroïdien, pour le traitement des patientes présentant un cancer du sein symptomatique, localement avancé ou métastatique à récepteur hormonal positif et HER2-négatif, ayant reçu antérieurement un traitement hormonal en adjuvant et présentant une rechute au-delà de 12 mois après la fin de leur traitement en adjuvant.</p> <p>Le remboursement n'est pas autorisé si la patiente a déjà été traitée auparavant et a progressé sous un inhibiteur CDK4/6 (groupe de remboursement A-128), pour un cancer du sein avancé ou métastatique.</p>
		1/6/2019	<p>in combinatie met een niet-steroïdale aromatase inhibitor, voor de behandeling van vrouwen met hormoonreceptor-positieve, HER2-negatieve, symptomatische lokaal gevorderde of gemetastaseerde borstkanker bij initiële diagnose (de novo).</p>	<p>remboursement, en combinaison avec un inhibiteur de l'aromatase non stéroïdien, pour le traitement des patientes présentant lors d'un diagnostic initial (de novo) un cancer du sein symptomatique, localement avancé ou métastatique à récepteur hormonal positif et HER2-négatif.</p>
		1/6/2019	<p>in combinatie met fulvestrant voor de behandeling van vrouwen met hormoonreceptor-positieve, HER2-negatieve, lokaal gevorderde of gemetastaseerde borstkanker die reeds een eerdere hormoonbehandeling hebben gekregen voor gevorderde of gemetastaseerde borstkanker.</p>	<p>en combinaison avec le fulvestrant, pour le traitement des patientes présentant un cancer du sein localement avancé ou métastatique à récepteur hormonal positif et HER2-négatif, ayant reçu antérieurement un traitement hormonal pour leur cancer du sein avancé ou métastatique.</p>



Drug	Trade name	Date start reimbursement	Indication NI	Indication Fr
ribociclib	Kisqali		De vergoeding wordt niet toegestaan indien de patiënte voor gevorderde of gemetastaseerde borstkanker reeds eerder werd behandeld met een CDK4/6 inhibitor (vergoedingsgroep A-128) of fulvestrant en hieronder progressie vertoonde	en combinaison avec le fulvestrant, pour le traitement des patientes présentant un cancer du sein localement avancé ou métastatique à récepteur hormonal positif et HER2-négatif, ayant reçu antérieurement un traitement hormonal pour leur cancer du sein avancé ou métastatique.
		1/8/2018	vergoed, in combinatie met een niet-steroïdale aromatase inhibitor, voor de behandeling van vrouwen met hormoonreceptor-positieve, HER2-negatieve, lokaal gevorderde of gemetastaseerde borstkanker die reeds een eerdere adjuvante hormonale behandeling met tamoxifen hebben gekregen en die tijdens of binnen de 12 maanden na het beëindigen van de adjuvante behandeling zijn hervallen.	remboursée, en combinaison avec un inhibiteur de l'aromatase non stéroïdien, pour le traitement des femmes présentant un cancer du sein localement avancé ou métastatique à récepteur hormonal positif et HER2-négatif, ayant reçu antérieurement un traitement hormonal en adjuvant avec tamoxifen et présentant une rechute de leur maladie pendant le traitement en adjuvant ou endéans une période de 12 mois après la fin du traitement en adjuvant.
			De vergoeding wordt niet toegestaan indien de patiënte voor gevorderde of gemetastaseerde borstkanker reeds eerder werd behandeld met een CDK4/6 inhibitor (vergoedingsgroep A-128) en hieronder progressie vertoonde	Le remboursement n'est pas autorisé si la patiente a déjà été traitée auparavant et a progressé sous un inhibiteur CDK4/6 (groupe de remboursement A-128), pour un cancer du sein avancé ou métastatique
		1/11/2019	vergoed in combinatie met fulvestrant voor de behandeling van vrouwen met hormoonreceptor-positieve, HER2-negatieve, lokaal gevorderde of gemetastaseerde borstkanker die reeds een eerdere adjuvante behandeling met een aromatase inhibitor hebben gekregen en die tijdens of binnen de 12 maanden na het beëindigen van de adjuvante behandeling zijn hervallen.	remboursée, en combinaison avec le fulvestrant, pour le traitement des patientes présentant un cancer du sein localement avancé ou métastatique à récepteur hormonal positif et HER2-négatif, ayant reçu antérieurement un traitement en adjuvant contenant un inhibiteur de l'aromatase et présentant une rechute de leur maladie pendant le traitement en adjuvant ou endéans une période de 12 mois après la fin du traitement en adjuvant.
			De vergoeding wordt niet toegestaan indien de patiënte voor gevorderde of gemetastaseerde borstkanker reeds eerder werd behandeld met een CDK4/6 inhibitor (vergoedingsgroep A-128) en hieronder progressie vertoonde	Le remboursement n'est pas autorisé si la patiente a déjà été traitée auparavant et a progressé sous un inhibiteur CDK4/6 (groupe de remboursement A-128), pour un cancer du sein avancé ou métastatique.
		1/8/2018	vergoed in combinatie met een niet-steroïdale aromatase inhibitor voor de behandeling van vrouwen met hormoonreceptor-positieve, HER2-negatieve, symptomatische lokaal gevorderde of gemetastaseerde borstkanker, die reeds een eerdere adjuvante hormonale	remboursée, en combinaison avec un inhibiteur de l'aromatase non stéroïdien, pour le traitement des femmes présentant un cancer du sein symptomatique, localement avancé ou métastatique à récepteur hormonal positif et HER2-négatif, ayant reçu antérieurement un traitement



Drug	Trade name	Date start reimbursement	Indication NI	Indication Fr
			<p>behandeling hebben gekregen en die meer dan 12 maanden na het beëindigen van de adjuvante behandeling hervallen zijn.</p> <p>De vergoeding wordt niet toegestaan indien de patiënte voor gevorderde of gemetastaseerde borstkanker reeds eerder werd behandeld met een CDK4/6 inhibitor (vergoedingsgroep A-128) en hieronder progressie vertoonde.</p>	<p>hormonal en adjuvant et présentant une rechute au-delà de 12 mois après la fin de leur traitement en adjuvant.</p> <p>Le remboursement n'est pas autorisé si la patiente a déjà été traitée auparavant et a progressé sous un inhibiteur CDK4/6 (groupe de remboursement A-128), pour un cancer du sein avancé ou métastatique</p>
		1/8/2018	<p>vergoed, in combinatie met een niet-steroidale aromatase inhibitor, voor de behandeling van vrouwen met hormoonreceptor-positieve, HER2-negatieve, symptomatische lokaal gevorderde of gemetastaseerde borstkanker bij initiële diagnose (de novo).</p>	<p>remboursée, en combinaison avec un inhibiteur de l'aromatase non stéroïdien, pour le traitement des femmes présentant lors d'un diagnostic initial (de novo) un cancer du sein symptomatique, localement avancé ou métastatique à récepteur hormonal positif et HER2-négatif.</p>
		1/11/2019	<p>vergoed, in combinatie met fulvestrant voor de behandeling van vrouwen met hormoonreceptor-positieve, HER2-negatieve, lokaal gevorderde of gemetastaseerde borstkanker die reeds een eerdere hormoonbehandeling hebben gekregen voor gevorderde of gemetastaseerde borstkanker.</p> <p>De vergoeding wordt niet toegestaan indien de patiënte voor gevorderde of gemetastaseerde borstkanker reeds eerder werd behandeld met een CDK4/6 inhibitor (vergoedingsgroep A-128) en hieronder progressie vertoonde</p>	<p>remboursée, en combinaison avec le fulvestrant, pour le traitement des patientes présentant un cancer du sein localement avancé ou métastatique à récepteur hormonal positif et HER2-négatif, ayant reçu antérieurement un traitement hormonal pour leur cancer du sein avancé ou métastatique.</p> <p>Le remboursement n'est pas autorisé si la patiente a déjà été traitée auparavant et a progressé sous un inhibiteur CDK4/6 (groupe de remboursement A-128), pour un cancer du sein avancé ou métastatique.</p>

Appendix 1.3. Medical literature: Search for evidence

Appendix 1.3.1. Search medical literature (systematic reviews)

The search for systematic reviews in MEDLINE, PreMedline and the Cochrane library of systematic reviews (inception to search date) specifically developed for this research question, yielded 512 records (Figure 38). After de-duplication, 110 (2020-2019) of the 512 remaining reviews were screened based on title and abstract, of which 89 were excluded. In total 21 full text articles were assessed for eligibility. Based on full text evaluation, 15 reviews were excluded (Figure 39).

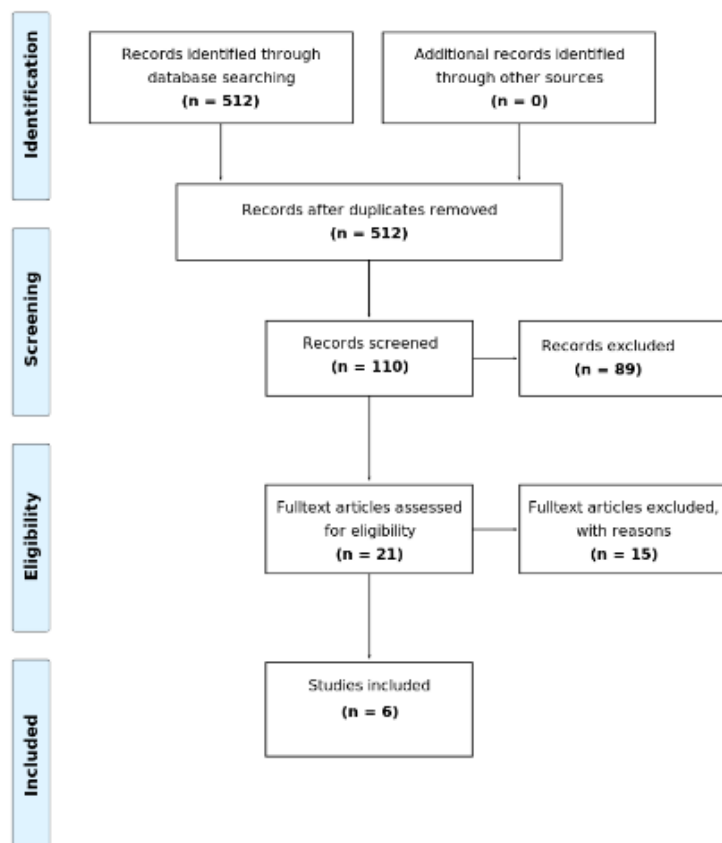
**Figure 26 – Female breast cancer – Selection of SRs - Study flow**

**Table 13 – Female breast cancer: excluded reviews and reason for exclusion**

	Year	Publication	Reason for exclusion
1	2020	Li, J. Fu, F. Yu, L. et al. Cyclin-dependent kinase 4 and 6 inhibitors in hormone receptor-positive, human epidermal growth factor receptor-2 negative advanced breast cancer: a meta-analysis of randomized clinical trials Breast Cancer Res Treat 2020;18(1):21-32	Included
2	2020	Paracha, N. Reyes, A. Dieras, V. et al. Evaluating the clinical effectiveness and safety of various HER2-targeted regimens after prior taxane/trastuzumab in patients with previously treated, unresectable, or metastatic HER2-positive breast cancer: a systematic review and network meta-analysis Breast Cancer Res Treat 2020;180(3):597-609	Included
3	2020	Shimoi, T. Sagara, Y. Hara, F. et al. First-line endocrine therapy for postmenopausal patients with hormone receptor-positive, HER2-negative metastatic breast cancer: a systematic review and meta-analysis Breast Cancer 2020;published online Feb 11	Wrong outcomes
4	2020	Xie, B. J. Zhu, L. N. Ma, C. et al. A network meta-analysis on the efficacy of HER2-targeted agents in combination with taxane-containing regimens for treatment of HER2-positive metastatic breast cancer 2020;27(2):186-196	No critical appraisal, 13 studies included
5	2020	Yu, L. Fu, F. Li, J. et al. Dual HER2 Blockade versus a Single Agent in Trastuzumab-Containing Regimens for HER2-Positive Early Breast Cancer: A Systematic Review and Meta-Analysis of Randomized Controlled Trials J Oncol 2020 Mar 16	Included
6	2019	Bottcher, T. M. Cold, S. Jensen, A. B. Treatment of advanced HR+/HER2- breast cancer with new targeted agents in combination with endocrine therapy: a review of efficacy and tolerability based on available randomized trials on everolimus, ribociclib, palbociclib and abemaciclib. Acta Oncol 2019; 58(2a):147-153	searched only 1 database, wrong outcome
7	2019	Buyukkaramikli, N. C. de Groot, S. Riemsma, R. et al. Ribociclib with an Aromatase Inhibitor for Previously Untreated, HR-Positive, HER2-Negative, Locally Advanced or Metastatic Breast Cancer: An Evidence Review Group Perspective of a NICE Single Technology Appraisal. Pharmacoeconomics 2019; 37(2):141-153	Not a systematic review. Full HTA report linked to this article is already included in the economic part.
8	2019	Chen, S. Liang, Y. Feng, Z. et al. Efficacy and safety of HER2 inhibitors in combination with or without pertuzumab for HER2-positive breast cancer: a systematic review and meta-analysis BMC Cancer 2019 19(1):973	No critical appraisal, also, single arm studies included
9	2019	D'Avanzo, F. Saggia, C. Rossi, V. et al. CDK 4/6 inhibitors plus endocrine therapy in ER positive metastatic breast cancer (MBC): Systematic review and meta-analysis of randomized clinical trials Ann Oncol 2019;	abstract
10	2019	Feng, F. Zhang, T. Yin, F. et al. Efficacy and safety of targeted therapy for metastatic HER2-positive breast cancer in the first-line treatment: a Bayesian network meta-analysis. Onco Targets Ther 2019;12:959-974	included
11	2019	Gogate, A. Rotter, J. S. Trogon, J. G. An updated systematic review of the cost-effectiveness of therapies for metastatic breast cancer Breast Cancer Res Treat 2019;174(2):343-355	No full HTA report with primary economic evaluation.
12	2019	Guo, L. Hu, Y. Chen, X. et al. Safety and efficacy profile of cyclin-dependent kinases 4/6 inhibitor palbociclib in cancer therapy: A meta-analysis of clinical trials. Cancer Med 2019;8(4):1389-1400	no meta-analysis of OS results, single arm trials included



Year	Publication	Reason for exclusion
13	2019 Guo, Q. Lin, X. Ye, L. et al. Comparative Efficacy of CDK4/6 Inhibitors Plus Aromatase Inhibitors Versus Fulvestrant for the First-Line Treatment of Hormone Receptor-Positive Advanced Breast Cancer: A Network Meta-Analysis. <i>Target Oncol</i> 2019;14(2):139-148	Full text could not be obtained
14	2019 Han, Y. Wang, J. Liu, W. Trastuzumab treatment after progression in HER2-positive metastatic breast cancer following relapse of trastuzumab-based regimens: a meta-analysis. <i>Cancer Manag Res</i> 2019;11:4699-4706	wrong research question
15	2019 Huang, H. W. Huang, L. S. Xu, Q. N. et al. CDK4/6 inhibition versus mTOR blockade as second-line strategy in postmenopausal patients with hormone receptor-positive advanced breast cancer: A network meta-analysis <i>Medicine (Baltimore)</i> 2019;98(1):e13909	wrong outcomes
16	2019 Ma, W. Zhao, F. Zhou, C. et al. Targeted neoadjuvant therapy in the HER-2-positive breast cancer patients: a systematic review and meta-analysis <i>Onco Targets Ther</i> 2019;12:379-390	wrong interventions
17	2019 Park, S. K. Chun, H. K. Park, C. Economic evaluations of oral medications for breast cancer treatment in the U.S.: a systematic review with a focus on cost-effectiveness threshold. <i>Expert Rev Pharmacoecon Outcomes Res</i> 2019;19(6):633-643	Full text could not be obtained
18	2019 Patterson-Lomba, O. Dalal, A. A. Ayyagari, R. et al. Systematic literature review of clinical trials of endocrine therapies for premenopausal women with metastatic HR+ HER2- breast cancer <i>Breast J</i> 2019;25(5):880-888	No additional information
19	2019 Petrelli, F. Ghidini, A. Pedersini, R. et al. Comparative efficacy of palbociclib, ribociclib and abemaciclib for ER+ metastatic breast cancer: an adjusted indirect analysis of randomized controlled trials <i>Breast Cancer Res Treat</i> 2019;174(3):597-604	No additional info
20	2019 Wang, L. Gao, S. Li, D. et al. CDK4/6 inhibitors plus endocrine therapy improve overall survival in advanced HR+/HER2- breast cancer: A meta-analysis of randomized controlled trials <i>Breast J</i> 2019; Dec 11 DOI 10.1111/tbj.13703	no critical appraisal, details of included studies not reported
21	2019 Wu, D. Chen, T. Jiang, H. et al. Comparative Efficacy and Tolerability of Neoadjuvant Immunotherapy Regimens for Patients with HER2-Positive Breast Cancer: A Network Meta-Analysis <i>J Oncol</i> 2019; Mar 19 DOI 10.1155/2019/3406972	Included



Appendix 1.3.2. Critical appraisal systematic reviews

	Paracha 2020 ¹		Yu 2020 ²	
	Score	Rationale/comment	score	Rationale/comment
1. PICO	Y		Y	
2. A priori study design	N		N	
3. Inclusion study designs	Y		Y	
4. Comprehensive literature search	partial Y		partial Y	Did not search reference lists, trial registers, no consultation of experts
5. Duplicate study selection	Y		N	unclear
6. Duplicate data extraction	N	unclear	Y	
7. List of excluded studies and rationale	N		N	
8. Characteristics of included studies provided	Y		Y	
9. Assessment of risk of bias	Y		Y	
10. Sources of funding reported	N	Funding for MA received from F. Hoffmann-La Roche AG. Funding source of the individual studies not reported.	N	
11. Appropriate methods to combine findings	Y		Y	
12. Assessment of impact RoB in included studies on results MA	N		N	
13. RoB assessment used in interpretation of results and in conclusions	N		N	
14. Explanation for and discussion of any observed heterogeneity	N	consequences of differences in population size and treatment line among studies insufficiently discussed	Y	
15. Adequate investigation of publication bias and its impact on the results	N		Y	
16. Potential sources of conflict of interest reported	Y		Y	no potential conflicts reported



	Feng 2019 ³		Wu 2019 ⁴	
	Score	Rationale/comment	score	Rationale/comment
1. PICO	Y		Y	
2. A priori study design	N		N	
3. Inclusion study designs	Y		Y	
4. Comprehensive literature search	N	No explicit justification for language restriction, no search of trial registers, no search of grey literature	Partial Y	no search of trial registries, no search of grey literature
5. Duplicate study selection	Y		Y	
6. Duplicate data extraction	Y		Y	
7. List of excluded studies and rationale	N	aggregated data only	N	
8. Characteristics of included studies provided	Y		Y	
9. Assessment of risk of bias	Y		Y	
10. Sources of funding reported	Y	Supported by grants from the National Science Foundation of China. Individual studies supported by related companies.	N	Funded by the National natural Science Foundation of China and Guangdong Province Medical Scientific Research Foundation. Funding of individual studies not reported
11. Appropriate methods to combine findings	Y		Y	
12. Assessment of impact RoB in included studies on results MA	N		N	
13. RoB assessment used in interpretation of results and in conclusions	N		Y	
14. Explanation for and discussion of any observed heterogeneity	Y		Y	
15. Adequate investigation of publication bias and its impact on the results	Y		Y	
16. Potential sources of conflict of interest reported	Y		Y	



Li 2020 ⁵		
	Score	Rationale/comment
1. PICO	Y	
2. A priori study design	N	
3. Inclusion study designs	Y	
4. Comprehensive literature search	N	No justification for language restriction, no search of reference lists, no inclusion of content experts, no search of trial registries
5. Duplicate study selection	Y	
6. Duplicate data extraction	Y	
7. List of excluded studies and rationale	N	
8. Characteristics of included studies provided	Y	
9. Assessment of risk of bias	Y	
10. Sources of funding reported	N	No funding received, funding of individual studies not reported (although collected)
11. Appropriate methods to combine findings	Y	
12. Assessment of impact RoB in included studies on results MA	N	
13. RoB assessment used in interpretation of results and in conclusions	N	
14. Explanation for and discussion of any observed heterogeneity	N	(insufficient)
15. Adequate investigation of publication bias and its impact on the results	Y	
16. Potential sources of conflict of interest reported	Y	



Appendix 1.3.3. Search strategy

Appendix 1.3.3.1. Cochrane library of systematic reviews

Date	24/06/2020 14:45:17	
Database	Cochrane@Wiley.com	
Search strategy		
#1	[mh "Breast neoplasms"]	12761
#2	(breast* NEAR/3 (neoplasm* or cancer* or carcinoma* or adenocarcinoma* or tumour* or tumor* or malignan* or sarcoma*)):ab,ti	33098
#3	(mammary NEAR/3 (neoplasm* or cancer* or carcinoma* or adenocarcinoma* or tumour* or tumor* or malignan* or sarcoma*)):ab,ti	208
#4	(breast* NEAR/3 (neoplasm* or cancer* or carcinoma* or adenocarcinoma* or tumour* or tumor* or malignan* or sarcoma*)):jw.	14387
#5	(lobular NEAR/3 (neoplasm* or cancer* or carcinoma* or adenocarcinoma* or tumour* or tumor* or malignan* or sarcoma*)):ab,ti	162
#6	((duct or ductal) NEAR/3 (neoplasm* or cancer* or carcinoma* or adenocarcinoma* or tumour* or tumor* or malignan* or sarcoma*)):ab,ti	1495
#7	(hboc NEAR/3 syndrome?):ab,ti	6
#8	#2 or #3 or #4 or #5 or #6 or #7	48230
#9	#1 or #8	49277
#10	abemaciclib:ab,ti	116
#11	verzenio:ab,ti	0
#12	verzenios:ab,ti	1
#13	60UAB198HK:ab,ti	0
#14	LY2835219:ab,ti	29
#15	"LY 2835219":ab,ti	0
#16	"1231929-97-7":ab,ti	6
#17	#10 or #11 or #12 or #13 or #14 or #15 or #16	118
#18	[mh ^"Maytansine"]	63
#19	Maytansine:ab,ti	7
#20	emtansine:ab,ti	196
#21	Maitansine:ab,ti	0
#22	"Maytansinoid DM1":ab,ti	1
#23	"Maytansinoid DM4":ab,ti	6
#24	Mertansine:ab,ti	2
#25	Soravtansine:ab,ti	16
#26	Ravtansine:ab,ti	12



Date	24/06/2020 14:45:17	
#27	"dm1-smcc":ab,ti	0
#28	"dm1-spp":ab,ti	0
#29	"smcc-dm1":ab,ti	0
#30	"spp-dm1":ab,ti	0
#31	"1228105-51-8":ab,ti	0
#32	14083FR882:ab,ti	0
#33	"35846-53-8":ab,ti	0
#34	"252-754-7":ab,ti	0
#35	"NSC-153858":ab,ti	0
#36	#19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35	232
#37	#18 or #36	238
#38	pertuzumab:ab,ti	497
#39	"RHUMAB 2C4":ab,ti	23
#40	PERJETA:ab,ti	30
#41	omnitarg:ab,ti	2
#42	K16AIQ8CTM:ab,ti	0
#43	"RG 1273":ab,ti	0
#44	RG1273:ab,ti	0
#45	2C4:ab,ti	23
#46	"r 1273":ab,ti	1
#47	r1273:ab,ti	0
#48	#38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47	498
#49	palbociclib:ab,ti	317
#50	IBRANCE:ab,ti	15
#51	G9ZF61LE7G:ab,ti	0
#52	"PD 0332991":ab,ti	41
#53	PD0332991:ab,ti	6
#54	"pd 332991":ab,ti	0
#55	pd332991:ab,ti	0
#56	"pf 00080665 73":ab,ti	0
#57	"pf00080665 73":ab,ti	0
#58	"571190-30-2":ab,ti	10
#59	"827022-33-3":ab,ti	3
#60	#49 or #50 or #51 or #52 or #53 or #54 or #55 or #56 or #57 or #58 or #59	324
#61	ribociclib:ab,ti	172
#62	kisqali:ab,ti	9



Date	24/06/2020 14:45:17	
#63	TK8ERE8P56:ab,ti	0
#64	lee011:ab,ti	49
#65	"lee-011":ab,ti	1
#66	"lee-011A":ab,ti	0
#67	lee011A:ab,ti	0
#68	"lee 011bba":ab,ti	0
#69	lee011bba:ab,ti	0
#70	"lee 11bba":ab,ti	0
#71	lee11bba:ab,ti	0
#72	"1211441-98-3":ab,ti	1
#73	"1374639-75-4":ab,ti	5
#74	#61 or #62 or #63 or #64 or #65 or #66 or #67 or #68 or #69 or #70 or #71 or #72 or #73	192
#75	[mh ^"trastuzumab"]	678
#76	TRASTUZUMAB:ab,ti	2412
#77	Herceptin:ab,ti	472
#78	Trazimera:ab,ti	1
#79	HERZUMA:ab,ti	1
#80	"RHUMAB HER2":ab,ti	12
#81	KANJINTI:ab,ti	0
#82	ONTRUZANT:ab,ti	0
#83	OGIVRI:ab,ti	2
#84	herticad:ab,ti	0
#85	hertraz:ab,ti	0
#86	hervelous:ab,ti	0
#87	trasturel:ab,ti	1
#88	vivitra:ab,ti	0
#89	zedora:ab,ti	0
#90	aryotrust:ab,ti	3
#91	P188ANX8CK:ab,ti	0
#92	4D5V8:ab,ti	0
#93	"ABP 980":ab,ti	20
#94	ABP980:ab,ti	1
#95	"bcd 022":ab,ti	6
#96	bcd022:ab,ti	0
#97	"bx 2318":ab,ti	0
#98	bx2318:ab,ti	0



Date	24/06/2020 14:45:17	
#99	"ct p06":ab,ti	0
#100	ctp06:ab,ti	0
#101	"DMB-3111":ab,ti	2
#102	"da 3111":ab,ti	1
#103	da3111:ab,ti	0
#104	"gb 221":ab,ti	0
#105	gb221:ab,ti	3
#106	"hd 201":ab,ti	0
#107	hd201:ab,ti	8
#108	"hermyl 1401o":ab,ti	0
#109	hermyl1401o:ab,ti	0
#110	"hlx 02":ab,ti	0
#111	hlx02:ab,ti	8
#112	"myl 1401o":ab,ti	8
#113	myl1401o:ab,ti	4
#114	"ons 1050":ab,ti	0
#115	ons1050:ab,ti	0
#116	EG12014:ab,ti	2
#117	"EG 12014":ab,ti	0
#118	"PF 05280014":ab,ti	22
#119	PF05280014:ab,ti	1
#120	"PF 5280014":ab,ti	0
#121	PF5280014:ab,ti	0
#122	"R-597":ab,ti	0
#123	R597:ab,ti	2
#124	"RG-597":ab,ti	0
#125	RG597:ab,ti	0
#126	"SB-3":ab,ti	23
#127	SB3:ab,ti	27
#128	"SYD 977":ab,ti	0
#129	SYD977:ab,ti	0
#130	"tx 05":ab,ti	0
#131	tx05:ab,ti	7
#132	"ub 921":ab,ti	0
#133	ub921:ab,ti	0
#134	"zrc 3256":ab,ti	1



Date	24/06/2020 14:45:17	
#135	zrc3256:ab,ti	0
#136	"1446410-98-5":ab,ti	1
#137	"180288-69-1":ab,ti	91
#138	#76 or #77 or #78 or #79 or #80 or #81 or #82 or #83 or #84 or #85 or #86 or #87 or #88 or #89 or #90 or #91 or #92 or #93 or #94 or #95 or #96 or #97 or #98 or #99 or #100 or #101 or #102 or #103 or #104 or #105 or #106 or #107 or #108 or #109 or #110 or #111 or #112 or #113 or #114 or #115 or #116 or #117 or #118 or #119 or #120 or #121 or #122 or #123 or #124 or #125 or #126 or #127 or #128 or #129 or #130 or #131 or #132 or #133 or #134 or #135 or #136 or #137	2549
#139	#75 or #138	2587
#140	"1018448-65-1":ab,ti	16
#141	"RG-3502":ab,ti	0
#142	RG3502:ab,ti	0
#143	KADCYLA:ab,ti	14
#144	"t-DM1":ab,ti	190
#145	"PRO-132365":ab,ti	0
#146	PRO132365:ab,ti	0
#147	"ADO-TRASTUZUMAB":ab,ti	35
#148	ADOTRASTUZUMAB:ab,ti	36
#149	"trastuzumab-mcc-dm1":ab,ti	15
#150	#140 or #141 or #142 or #143 or #144 or #145 or #146 or #147 or #148 or #149	210
#151	#17 or #37 or #48 or #60 or #74 or #139 or #150	3256
#152	#9 and #151	2696
#153	((HER2 or HER-2) NEAR/5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)):ab,ti	892
#154	((CDK or CDK4 or CDK6) NEAR/5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)):ab,ti	332
#155	(D1 NEAR/5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)):ab,ti	128
#156	(cyclin NEAR/5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)):ab,ti	152
#157	#153 or #154 or #155 or #156	1395
#158	[mh "Cyclin-Dependent Kinases"/AI]	15
#159	[mh ^"Receptor, ErbB-2"/AI]	82
#160	[mh ^"Cyclin D1"/AI]	0
#161	#158 or #159 or #160	97
#162	#157 or #161	1437
#163	#9 and #162	1085
#164	[mh "Protein-Tyrosine Kinases"/AI]	640
#165	[mh ^"Protein Kinase Inhibitors"]	762
#166	[mh "Antibodies, Monoclonal"]	12727



Date	24/06/2020 14:45:17	
#167	#164 or #165 or #166	13669
#168	tki:ab,ti	1225
#169	(kinase? NEAR/3 (inhibit* or antagonist? or target* or block* or against or anti or multi-targets or multi-target or multi-targeting or reduc*)):ab,ti	3959
#170	(monoclonal NEAR/3 antibod*):ab,ti	8824
#171	#168 or #169 or #170	13179
#172	#167 or #171	23942
#173	#9 and #172	1770
#174	((("new class" or "new classes" or innovative or target*) NEAR/3 (drug? or therapy or therapies or therapeutic* or treatment? or chemotherap*)):ab,ti	11940
#175	#9 and #174	886
#176	#152 or #163 or #173 or #175	4333
#177	#176 in Cochrane Reviews	15
Comments		

Appendix 1.3.3.2. Medline + PreMedline

Date	June 22, 2020	
Database	Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946 to June 22, 2020>	
Search strategy		
1	exp Breast neoplasms/	291158
2	(breast* adj3 (neoplasm* or cancer* or carcinoma* or adenocarcinoma* or tumour* or tumor* or malignan* or sarcoma*)):ab,ti,kf.	332005
3	(mammary adj3 (neoplasm* or cancer* or carcinoma* or adenocarcinoma* or tumour* or tumor* or malignan* or sarcoma*)):ab,ti,kf.	30586
4	(breast* adj3 (neoplasm* or cancer* or carcinoma* or adenocarcinoma* or tumour* or tumor* or malignan* or sarcoma*)):jw.	17668
5	(lobular adj3 (neoplasm* or cancer* or carcinoma* or adenocarcinoma* or tumour* or tumor* or malignan* or sarcoma*)):ab,ti,kf.	4973
6	((duct or ductal) adj3 (neoplasm* or cancer* or carcinoma* or adenocarcinoma* or tumour* or tumor* or malignan* or sarcoma*)):ab,ti,kf.	34819
7	(hboc adj3 syndrome?):ab,ti,kf.	162
8	2 or 3 or 4 or 5 or 6 or 7	373174
9	1 or 8	428335
10	abemaciclib.ab,ti,kf,m.	273



Date	June 22, 2020	
11	verzenio.ab,ti,kf,rn.	6
12	verzenios.ab,ti,kf,rn.	0
13	60UAB198HK.ab,ti,kf,rn.	108
14	LY2835219.ab,ti,kf,rn.	29
15	LY 2835219.ab,ti,kf,rn.	1
16	1231929-97-7.ab,ti,kf,rn.	1
17	10 or 11 or 12 or 13 or 14 or 15 or 16	280
18	Maytansine/	695
19	Maytansine.ab,ti,kf,rn.	789
20	emtansine.ab,ti,kf,rn.	545
21	Maitansine.ab,ti,kf,rn.	0
22	Maytansinoid DM1.ab,ti,kf,rn.	30
23	Maytansinoid DM4.ab,ti,kf,rn.	7
24	Mertansine.ab,ti,kf,rn.	61
25	Soravtansine.ab,ti,kf,rn.	25
26	Ravtansine.ab,ti,kf,rn.	27
27	dm1-smcc.ab,ti,kf,rn.	1
28	dm1-spp.ab,ti,kf,rn.	0
29	smcc-dm1.ab,ti,kf,rn.	13
30	spp-dm1.ab,ti,kf,rn.	6
31	1228105-51-8.ab,ti,kf,rn.	0
32	14083FR882.ab,ti,kf,rn.	695
33	35846-53-8.ab,ti,kf,rn.	0
34	252-754-7.ab,ti,kf,rn.	0
35	NSC-153858.ab,ti,kf,rn.	2
36	19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35	1134
37	18 or 36	1134
38	pertuzumab.ab,ti,kf,rn.	1069
39	RHUMAB 2C4.ab,ti,kf,rn.	11
40	PERJETA.ab,ti,kf,rn.	23
41	omnitarg.ab,ti,kf,rn.	19
42	K16AIQ8CTM.ab,ti,kf,rn.	534
43	RG 1273.ab,ti,kf,rn.	1
44	RG1273.ab,ti,kf,rn.	0
45	2C4.ab,ti,kf,rn.	129
46	r 1273.ab,ti,kf,rn.	2



Date	June 22, 2020	
47	r1273.ab,ti,kf,rn.	0
48	38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47	1178
49	palbociclib.ab,ti,kf,rn.	928
50	IBRANCE.ab,ti,kf,rn.	21
51	G9ZF61LE7G.ab,ti,kf,rn.	491
52	"PD 0332991".ab,ti,kf,rn.	86
53	PD0332991.ab,ti,kf,rn.	79
54	pd 332991.ab,ti,kf,rn.	3
55	pd332991.ab,ti,kf,rn.	3
56	"pf 00080665 73".ab,ti,kf,rn.	0
57	pf00080665 73.ab,ti,kf,rn.	0
58	571190-30-2.ab,ti,kf,rn.	1
59	827022-33-3.ab,ti,kf,rn.	0
60	49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59	976
61	ribociclib.ab,ti,kf,rn.	348
62	kisqali.ab,ti,kf,rn.	10
63	TK8ERE8P56.ab,ti,kf,rn.	152
64	lee011.ab,ti,kf,rn.	52
65	lee-011.ab,ti,kf,rn.	1
66	lee-011A.ab,ti,kf,rn.	0
67	lee011A.ab,ti,kf,rn.	1
68	lee 011bba.ab,ti,kf,rn.	0
69	lee011bba.ab,ti,kf,rn.	0
70	lee 11bba.ab,ti,kf,rn.	0
71	lee11bba.ab,ti,kf,rn.	0
72	1211441-98-3.ab,ti,kf,rn.	1
73	1374639-75-4.ab,ti,kf,rn.	0
74	61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73	359
75	trastuzumab/	6829
76	TRASTUZUMAB.ab,ti,kf,rn.	11369
77	Herceptin.ab,ti,kf,rn.	1926
78	Trazimera.ab,ti,kf,rn.	3
79	HERZUMA.ab,ti,kf,rn.	5
80	RHUMAB HER2.ab,ti,kf,rn.	16
81	KANJINTI.ab,ti,kf,rn.	4
82	ONTRUZANT.ab,ti,kf,rn.	6



Date	June 22, 2020	
83	OGIVRI.ab,ti,kf,rn.	5
84	herticad.ab,ti,kf,rn.	0
85	hertraz.ab,ti,kf,rn.	1
86	hervelous.ab,ti,kf,rn.	0
87	trasturel.ab,ti,kf,rn.	2
88	vivitra.ab,ti,kf,rn.	1
89	zedora.ab,ti,kf,rn.	0
90	aryotrust.ab,ti,kf,rn.	0
91	P188ANX8CK.ab,ti,kf,rn.	6830
92	4D5V8.ab,ti,kf,rn.	2
93	ABP 980.ab,ti,kf,rn.	10
94	ABP980.ab,ti,kf,rn.	2
95	"bcd 022".ab,ti,kf,rn.	0
96	bcd022.ab,ti,kf,rn.	0
97	bx 2318.ab,ti,kf,rn.	0
98	bx2318.ab,ti,kf,rn.	0
99	ct p06.ab,ti,kf,rn.	0
100	ctp06.ab,ti,kf,rn.	0
101	DMB-3111.ab,ti,kf,rn.	1
102	da 3111.ab,ti,kf,rn.	0
103	da3111.ab,ti,kf,rn.	0
104	gb 221.ab,ti,kf,rn.	0
105	gb221.ab,ti,kf,rn.	0
106	hd 201.ab,ti,kf,rn.	2
107	hd201.ab,ti,kf,rn.	2
108	hermyl 1401o.ab,ti,kf,rn.	0
109	hermyl1401o.ab,ti,kf,rn.	0
110	"hlx 02".ab,ti,kf,rn.	0
111	hlx02.ab,ti,kf,rn.	1
112	myl 1401o.ab,ti,kf,rn.	5
113	myl1401o.ab,ti,kf,rn.	0
114	ons 1050.ab,ti,kf,rn.	0
115	ons1050.ab,ti,kf,rn.	0
116	EG12014.ab,ti,kf,rn.	0
117	EG 12014.ab,ti,kf,rn.	0
118	"PF 05280014".ab,ti,kf,rn.	11



Date	June 22, 2020	
119	PF05280014.ab,ti,kf,rn.	0
120	PF 5280014.ab,ti,kf,rn.	0
121	PF5280014.ab,ti,kf,rn.	0
122	R-597.ab,ti,kf,rn.	13
123	R597.ab,ti,kf,rn.	5
124	RG-597.ab,ti,kf,rn.	0
125	RG597.ab,ti,kf,rn.	0
126	SB-3.ab,ti,kf,rn.	222
127	SB3.ab,ti,kf,rn.	241
128	SYD 977.ab,ti,kf,rn.	0
129	SYD977.ab,ti,kf,rn.	0
130	"tx 05".ab,ti,kf,rn.	5
131	tx05.ab,ti,kf,rn.	1
132	ub 921.ab,ti,kf,rn.	0
133	ub921.ab,ti,kf,rn.	0
134	zrc 3256.ab,ti,kf,rn.	0
135	zrc3256.ab,ti,kf,rn.	0
136	1446410-98-5.ab,ti,kf,rn.	0
137	180288-69-1.ab,ti,kf,rn.	1
138	76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102 or 103 or 104 or 105 or 106 or 107 or 108 or 109 or 110 or 111 or 112 or 113 or 114 or 115 or 116 or 117 or 118 or 119 or 120 or 121 or 122 or 123 or 124 or 125 or 126 or 127 or 128 or 129 or 130 or 131 or 132 or 133 or 134 or 135 or 136 or 137	12337
139	75 or 138	12337
140	1018448-65-1.ab,ti,kf,rn.	1
141	RG-3502.ab,ti,kf,rn.	0
142	RG3502.ab,ti,kf,rn.	0
143	KADCYLA.ab,ti,kf,rn.	98
144	t-DM1.ab,ti,kf,rn.	468
145	PRO-132365.ab,ti,kf,rn.	1
146	PRO132365.ab,ti,kf,rn.	1
147	ADO-TRASTUZUMAB.ab,ti,kf,rn.	450
148	ADOTRASTUZUMAB.ab,ti,kf,rn.	5
149	trastuzumab-mcc-dm1.ab,ti,kf,rn.	11
150	140 or 141 or 142 or 143 or 144 or 145 or 146 or 147 or 148 or 149	691
151	17 or 37 or 48 or 60 or 74 or 139 or 150	14339
152	9 and 151	9678



Date	June 22, 2020	
153	((HER2 or HER-2) adj5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)).ab,ti,kf.	8217
154	((CDK or CDK4 or CDK6) adj5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)).ab,ti,kf.	7412
155	(D1 adj5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)).ab,ti,kf.	9030
156	(cyclin adj5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)).ab,ti,kf.	17689
157	153 or 154 or 155 or 156	35327
158	exp Cyclin-Dependent Kinases/ai [Antagonists & Inhibitors]	4671
159	Receptor, ErbB-2/ai [Antagonists & Inhibitors]	2348
160	Cyclin D1/ai	290
161	158 or 159 or 160	7240
162	157 or 161	37946
163	9 and 162	8795
164	exp Protein-Tyrosine Kinases/ai	38027
165	Protein Kinase Inhibitors/	45220
166	exp Antibodies, Monoclonal/	235214
167	164 or 165 or 166	299683
168	tki.ab,ti,kf.	7575
169	(kinase? adj3 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)).ab,ti,kf.	118086
170	(monoclonal adj3 antibod*).ab,ti,kf.	196407
171	168 or 169 or 170	312261
172	167 or 171	468138
173	9 and 172	22277
174	((new class* or innovative or target*) adj3 (drug? or therapy or therapies or therapeutic* or treatment? or chemotherap*)).ab,ti,kf.	330072
175	9 and 174	22241
176	152 or 163 or 173 or 175	44944
177	((systematic review or systematic literature review or systematic scoping review or systematic narrative review or systematic qualitative review or systematic evidence review or systematic quantitative review or systematic meta-review or systematic critical review or systematic mixed studies review or systematic mapping review or systematic cochrane review or "systematic search and review" or systematic integrative review).ti. not comment.pt. not (protocol or protocols).ti. not medline.st.) or (Cochrane Database Syst Rev.ja. and review.pt.) or systematic review.pt.	159328
178	meta-analys*.ti.	108916
179	meta-analysis.pt.	116279
180	exp Technology Assessment, Biomedical/	11062
181	health technology assessment.ti,kf.	1917
182	HtA.ti,kf.	593
183	177 or 178 or 179 or 180 or 181 or 182	252947



Date	June 22, 2020	
184	176 and 183	506
185	remove duplicates from 184	497
Comments		

Appendix 1.4. Economic literature

Appendix 1.4.1. Search economic literature (HTA reports)

The search strategy in CRD's HTA database identified 476 references (Table 14). In a first round, 17 references were selected based on a review of title, keywords and abstract. The 459 remaining references were excluded for the following reasons: intervention (456) or design (3). In a second round, the full text of the 17 selected references was reviewed. 16 references were excluded (design (12), language (2), update available (1) or full text that could not be retrieved (1)). Only one reference was retained. This reference is indicated in Table 15 with an asterisk (*).

Furthermore, in May 2020, the website of the National Institute for Health Research (NIHR) was searched for relevant reports. The following search terms were used: pertuzumab (4 hits, 3 with a focus on breast cancer, 3 not previously identified); trastuzumab emtansine (23 hits, 1 with a focus on breast cancer, 1 not previously identified); palbociclib (5 hits, 2 with a focus on breast cancer, 2 not previously identified); abemaciclib (3 hits, 2 with a focus on breast cancer, 2 not previously identified); ribociclib (5 hits, 2 with a focus on breast cancer, 2 not previously identified).

Finally, also in May 2020, the website of the National Institute for Health and Care Excellence (NICE) was searched. The search term 'breast cancer' was used. This provided 251 results. In the 'guidance category', 69 reports in the category 'Technology appraisal guidance' were identified. Of these 69 reports, 10 were related to the selected drugs (pertuzumab, trastuzumab emtansine, palbociclib, abemaciclib, and ribociclib). Nine of these reports were not previously identified.

An overview of the identified references is provided in Table 15.

Table 14 – Search strategy and results for CRD: HTA

Date	
Date covered	All
Search Strategy	1 MeSH DESCRIPTOR Breast Neoplasms EXPLODE ALL TREES 1798
	2 * IN HTA 17351
	3 #1 AND #2 476 references
Note	/

**Table 15 – Female breast cancers – Identified HTA reports for the selected drugs****Selected reports****Pertuzumab**

- NICE, TA569. March 2019. Pertuzumab for adjuvant treatment of HER2-positive early stage breast cancer.^{6 β}
 - Grove, A., Andronis, L., Gallacher, D., Nduka, C., Court, R., Vepa, A., Sutcliffe, P. Single technology appraisal pertuzumab for adjuvant treatment of HER2-positive early breast cancer (ID1192): A Single Technology Appraisal. Warwick Evidence, 2018.^{7 α}
- NICE, TA509. March 2018. Pertuzumab with trastuzumab and docetaxel for treating HER2-positive breast cancer.^{8 α β}
 - Fleeman N, Bagust A, Beale S, Dwan K, Dickson R, Proudlove C, Dundar Y, O'Reilly S. Pertuzumab in combination with trastuzumab and docetaxel for the treatment of HER2 positive metastatic or locally recurrent unresectable breast cancer: A Single Technology Appraisal. LRIg, The University of Liverpool, 2013.^{9 *}
- NICE, TA424. December 2016. Pertuzumab for the neoadjuvant treatment of HER2-positive breast cancer.^{10 β}
 - Pertuzumab for treating early, HER 2 positive breast cancer [ID767] ^α → no link to a full report.

Trastuzumab emtansine

- NICE, TA458. July 2017. Trastuzumab emtansine for treating HER2-positive advanced breast cancer after trastuzumab and a taxane.^{11 β}
 - Trastuzumab emtansine for locally advanced or metastatic HER2 positive breast cancer after trastuzumab & a taxane (review of TA371)(ID1013) ^α → no link to a full report.

Palbociclib

- NICE, TA619. January 2020. Palbociclib with fulvestrant for treating hormone receptor-positive, HER2-negative, advanced breast cancer.^{12 β}
 - Fleeman N, Houten R, Nevitt S, Stainthorpe A, Beale S, Boland A, Dundar Y, McEntee J, Marsden A, Palmieri C. Palbociclib in combination with fulvestrant for treating advanced oestrogen-receptor positive, HER2-negative breast cancer [ID916]: A Single Technology Appraisal. LRIg, University of Liverpool, 2019.^{13 α}
- NICE, TA495. December 2017. Palbociclib with an aromatase inhibitor for previously untreated, hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer.^{14 β}
 - Fleeman N, Stainthorpe A, Bagust A, Richardson M, Nolan S, Houten R, Boland A, Beale S, Kotas E, McEntee J, Malik Z. Palbociclib in combination with an aromatase inhibitor for previously untreated metastatic, hormone receptor-positive, HER2- breast cancer [ID915]: A Single Technology Appraisal. LRIg, University of Liverpool, 2016.^{15 α}



Abemaciclib

- NICE, TA579. May 2019. Abemaciclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy.^{16 β}
 - Edwards SJ, Karner C, Bacelar M, Kew K, Marceniuk G. Abemaciclib with fulvestrant for treating advanced hormone-receptor positive, HER2-negative breast cancer after endocrine therapy: A Single Technology Appraisal. BMJ-TAG, 2018.^{17 α}
- NICE, TA563. February 2019. Abemaciclib with an aromatase inhibitor for previously untreated, hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer.^{18 β}
 - Shepherd, J., Onyimadu, O., Colquitt, J., Harris, P., Loveman, E., Lord, J. Abemaciclib with an aromatase inhibitor for untreated advanced hormone receptor-positive, HER2-negative breast cancer: A Single Technology Appraisal. Southampton Health Technology Assessments Centre (SHTAC), 2018.^{19 α}

Ribociclib

- NICE, TA593. August 2019. Ribociclib with fulvestrant for treating hormone receptor-positive, HER2-negative, advanced breast cancer.^{20 β}
 - Edwards SJ, Barton S, Cain P, Karner CK, Marceniuk G. Ribociclib in combination with fulvestrant for treating advanced hormone-receptor positive, HER2-negative breast cancer: A Highly Specialised Technology Appraisal. BMJ-TAG, 2018.^{21 α}
- NICE, TA496. December 2017. Ribociclib with an aromatase inhibitor for previously untreated, hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer.^{22 β}
 - Riemsma R, Büyükkaramikli N, De Groot S, Fayter D, Armstrong N, Wei C-Y, Portegijs P, Duffy S, Worthy G, Al M, Kleijnen J. Ribociclib in combination with an aromatase inhibitor for previously untreated advanced or metastatic hormone receptor-positive, HER2-negative breast cancer: a Single Technology Assessment. York: Kleijnen Systematic Reviews Ltd, 2017.^{23 α}

* These references were identified in CRD's HTA database. α References identified on NIHR's website. β References identified on NICE's website.



Appendix 1.4.2. Results economic literature (HTA reports)

Appendix 1.4.2.1. NICE, TA569 (2019): pertuzumab

- QoL:
 - “Health-related quality of life was measured using a number of validated outcome measures (the EuroQoL 5-Dimension, the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core30, and the EORTCQLQ-BR23).”⁶
 - “The company states that no major differences were observed between treatment arms in the five EQ-5D domains.”⁷
 - “The company state in the cost-effectiveness section ... that “the schedule of EQ-5D administration was designed to capture differences in [Quality of Life] QoL across the various stages of disease, not between treatment arms”. This same schedule was used for all HRQoL measures in the APHINITY trial.²⁴ The rationale for this approach is unclear to the ERG.”⁷
 - “The ERG is concerned about the infrequency of the collection of the patient reported outcome measures (PROMs) during the APHINITY trial.”⁷ “The ERG considers that due to the increased frequency of adverse events, there is evidence that pertuzumab may be associated with a slightly worse HRQoL, although this is not represented in the summaries of the PROMs.”⁷
 - “the EQ-5D questionnaire was not administered to patients who presented with disease progression (either non metastatic or metastatic) in the APHINITY study.”⁷
 - “The committee concluded that the long-term QALY gain is highly uncertain.”⁶
- Results:
 - “The company reported a deterministic ICER of £34,084 per QALY gained for PHC compared to HC.”⁷
 - “Implementing the ERG’s suggested base case analysis, resulted in a considerable increase in the ICER, by approximately £26,600. The ERG’s base case ICER for the node-positive population was calculated to be £60,679 per QALY gained.”⁷
 - “When the weighted-average biosimilar discount and market share estimates were taken into account in the updated model the company’s base-case ICER was comfortably lower than £20,000 per QALY gained.”⁶
- Uncertainty/sensitivity:
 - “The committee was aware that this ICER incorporated considerable uncertainty in: the size of the effect of pertuzumab on overall survival based on the APHINITY trial ..., the specific benefit of pertuzumab in the lymph node-positive group ..., a modelled QALY gain of 0.4 ..., and the estimate weighted-average discount applicable to biosimilar intravenous trastuzumab.”⁶
 - “Pertuzumab’s acquisition cost has a notable impact on the generated ICER values.”⁶
 - “The overall survival data are immature and, at the time of the primary analysis, there was no apparent difference in overall survival between the treatment groups.”⁶ ... “the extent to which invasive disease-free survival translates into long-term overall survival benefit is not known.”⁶



- Conclusions:
 - “Because of the uncertainty in the clinical-effectiveness evidence, the cost-effectiveness estimates are very uncertain. Given this uncertainty, an estimate above £20,000 per quality-adjusted life year (QALY) gained is not considered a cost-effective use of NHS resources. The company's final model includes only people with lymph node-positive disease, and incorporates the committee's preferred conservative estimates of how long treatment benefit with pertuzumab lasts after treatment is stopped. If the commercial discount to the price of pertuzumab, together with a weighted discount for biosimilar intravenous trastuzumab are taken into consideration, the cost-effectiveness estimate is comfortably below £20,000 per QALY gained. Therefore, adjuvant pertuzumab is recommended for HER2-positive early stage breast cancer in people with lymph node-positive disease.”⁶
- (Confidential) prices:
 - “The company has a commercial arrangement. This makes pertuzumab available to the NHS with a discount. The size of the discount is commercial in confidence.”⁶ “The updated model included ... a new commercial discount to the price of pertuzumab.”⁶



Reference Costs (list prices & remarks)	Population, Intervention & comparator IC, IE and ICERs	Remarks on use of generic utility instrument (e.g. EQ- 5D) to measure impact on QoL in economic evaluations	Most uncertain variables or important variables in sensitivity analysis																																				
Pertuzumab																																							
NICE, TA569 (2019) ⁶	Patients with HER2-positive early stage breast cancer.																																						
Grove (2018) ⁷	Pertuzumab + trastuzumab +chemotherapy (PHC) against trastuzumab + chemotherapy (HC).																																						
List prices, negotiated discounts are hidden. Drug costs: Pertuzumab costs £2,395 per 420-mg vial; trastuzumab costs £407.40 per 150-mg vial (excluding VAT; British national formulary).	Results of the incremental analysis (with discount): A) The company's updated cost-effectiveness model focused on the lymph node-positive population. <table><thead><tr><th></th><th>Costs (£)</th><th>IC</th><th>QALYs</th><th>IE</th><th>ICER</th></tr></thead><tbody><tr><td>HC</td><td>conf.</td><td></td><td>conf.</td><td></td><td></td></tr><tr><td>PHC</td><td>conf.</td><td>conf.</td><td>conf.</td><td>conf.</td><td>£34 087</td></tr></tbody></table> B) ERG suggested base case analysis <table><thead><tr><th></th><th>Costs (£)</th><th>IC</th><th>QALYs</th><th>IE</th><th>ICER</th></tr></thead><tbody><tr><td>HC</td><td>conf.</td><td></td><td>conf.</td><td></td><td></td></tr><tr><td>PHC</td><td>conf.</td><td>conf.</td><td>conf.</td><td>conf.</td><td>£60 679</td></tr></tbody></table> Remark: the committee concluded that the incremental treatment benefit of pertuzumab for the whole population is likely to be small. The committee accepted that the subgroup with lymph node-positive disease represents a population at increased risk of recurrence, and that the company's decision to focus on people with lymph node-positive disease is reasonable. If the commercial discount to the price of pertuzumab, together with a weighted discount for biosimilar intravenous trastuzumab are taken into consideration, the cost-effectiveness estimate is comfortably below £20,000 per QALY gained.		Costs (£)	IC	QALYs	IE	ICER	HC	conf.		conf.			PHC	conf.	conf.	conf.	conf.	£34 087		Costs (£)	IC	QALYs	IE	ICER	HC	conf.		conf.			PHC	conf.	conf.	conf.	conf.	£60 679	EQ-5D is used in the APHINITY trial. ERG is concerned about the infrequency of the collection of the patient reported outcome measures.	Overall survival Specific benefit of pertuzumab in the lymph node-positive group Modelled QALY gain Discounts biosimilars.
	Costs (£)	IC	QALYs	IE	ICER																																		
HC	conf.		conf.																																				
PHC	conf.	conf.	conf.	conf.	£34 087																																		
	Costs (£)	IC	QALYs	IE	ICER																																		
HC	conf.		conf.																																				
PHC	conf.	conf.	conf.	conf.	£60 679																																		

Conf.: confidential; HC: trastuzumab + chemotherapy; PHC: Pertuzumab + trastuzumab + chemotherapy.



Appendix 1.4.2.2. NICE, TA509 (2018): pertuzumab

- QoL:
 - No generic utility instrument is used in the underlying trial.
 - “Using the Lloyd et al.²⁵ model a common health state utility value of 0.5 was obtained for the progressed health state for patients in both treatment arms.²⁶ To estimate utility values for patients in the PFS state the manufacturer calculated a treatment-specific weighted average of the Lloyd et al.²⁷ model values for stable disease and treatment response based on the reported objective response rate (79.6% for pertuzumab, 69.4% for control) observed in the CLEOPATRA²⁷ trial.”⁹
- Results:
 - “The base-case incremental results generated by the manufacturer’s model Compared with trastuzumab and docetaxel therapy, treatment with trastuzumab and paclitaxel ***** and the ICER for pertuzumab, trastuzumab and docetaxel is ***** per QALY gained and ***** per life-year gained.”⁹
 - “the ERG considers that a revised ICER of £***** per QALY gained best reflects the cost effectiveness of pertuzumab use in this population.”⁹
 - “The committee considered the way in which progression-free survival and overall survival data had been extrapolated in the company’s model. It noted that the company’s base-case cost-effectiveness estimate for pertuzumab in combination with trastuzumab and docetaxel is associated with a 0% probability of being cost effective at £30,000 per quality-adjusted life year (QALY) gained.”⁸
 - “The committee accepted that the commercial access arrangement reduced the ICER from the original submission, but that it still remained in excess of what is considered to be a cost-effective use of NHS resources for technologies that are not given special consideration as life-extending treatments for people with a short life expectancy.”⁸
- Uncertainty/sensitivity:
 - “the model was sensitive to the long-term projection of overall survival.”⁸
- Conclusions:
 - “The committee concluded that pertuzumab plus trastuzumab and docetaxel would not be a cost-effective use of NHS resources for treating HER2-positive metastatic or locally recurrent unresectable breast cancer compared with trastuzumab and docetaxel alone.”⁸
 - “The committee noted that the life expectancy of patients on chemotherapy alone based on the unadjusted median overall survival in the control arm of CLEOPATRA was 40.8months, which exceeds the 24months stated in the end-of-life criteria. However, people in the CLEOPATRA trial may have a better prognosis than people in UK clinical practice ... The committee agreed that although life expectancy in the trial was greater than 24 months, the exceptional proportional gain in survival with pertuzumab in people with a relatively modest life expectancy should be taken into account. The committee concluded that it was fair and reasonable to accept that pertuzumab fulfilled the criteria for special consideration on this basis.”
 - “The committee acknowledged the flexibilities in the application of the end-of-life criteria. The committee considered that the unprecedented survival benefit with the addition of pertuzumab should be considered in the light of modest life expectancy of these patients and concluded that it was fair and



reasonable to accept that pertuzumab fulfils the end-of-life criteria. The committee further accepted that in the context of the exceptional circumstance this case presents, it would be reasonable not to be asked to have to apply the maximum weight to the QALYs gained by pertuzumab. The committee accepted that the ICER, taking into account the commercial access arrangement, provides for an acceptable use of NHS resources.”⁸

- (Confidential) prices:
 - “The company has agreed a commercial access arrangement for pertuzumab with NHS England. The commercial access arrangement replaces the patient access scheme agreed with the Department of Health for pertuzumab. The details of this commercial access arrangement are commercial in confidence.”⁸



Reference	Costs (list prices & remarks)	Population, Intervention & comparator IC, IE and ICERs	Remarks on use of generic utility instrument (e.g. EQ-5D) to measure impact on QoL in economic evaluations	Most uncertain variables or important variables in sensitivity analysis
Pertuzumab				
NICE, TA509 (2018) ⁸		Patients with HER2-positive metastatic breast cancer.		
Fleeman (2013) ⁹		Pertuzumab plus trastuzumab and docetaxel compared with trastuzumab and docetaxel.		
List prices, negotiated discounts are hidden.		Results of the incremental analysis: manufacturer's base case:	HRQoL data were not collected with a generic utility instrument.	Overall survival
Drug costs per cycle		Costs (£) IC QALYs IE ICER		
1 st cycle		H & doc. Conf. Conf. Conf. -		
next cycle		H & pac. Conf. Conf. Conf. 0		
Pertuzumab: £4790	£2395	Pert. & H & doc. Conf. Conf. Conf. 0.833		
Trastuzumab: £1630	£1222			
Docetaxel: £35	All cycles	The manufacturer's PSA results suggest that pertuzumab, trastuzumab and docetaxel has a 0% probability of being cost-effective at a willingness-to-pay threshold of £30,000 per QALY gained.		
Paclitaxel: £19.50		Remark: revised submission for the Cancer Drugs Fund reconsideration: The ICER is commercial in confidence to protect the confidentiality of the commercial access agreement. The committee accepted that the commercial access arrangement reduced the ICER from the original submission, but that it still remained in excess of what is considered to be a cost-effective use of NHS resources for technologies that are not given special consideration as life-extending treatments for people with a short life expectancy.		

Conf.: confidential; doc.: docetaxel; H: trastuzumab; pac.: paclitaxel; pert: pertuzumab.



Appendix 1.4.2.3. NICE, TA424 (2016): pertuzumab

- QoL:
 - No generic utility instrument is used in the underlying trial.
- Results:
 - “The committee agreed that because of the high levels of uncertainty in the cost-effectiveness assumptions, it would be prudent to use the more conservative ICERs from the ERG, and to focus on scenarios that excluded any cost offsets from metastatic treatments funded by the CDF. The committee noted that in these more conservative scenarios, and incorporating the simple discount patient access scheme for pertuzumab, the ICERs fell within the range normally considered to be a cost-effective use of NHS resources.”¹⁰
- Uncertainty/sensitivity:
 - “The committee noted that the comparatively early regulatory approval for pertuzumab had limited the clinical trial evidence available such that it was suboptimal for the purposes of long-term modelling and health technology assessment. In these uncertain circumstances, the committee welcomed the company's approach to discount the cost of pertuzumab as it increased the likelihood that pertuzumab would be cost effective with more conservative assumptions than had been used in the model.”¹⁰
 - “... in the original company submission and ERG report, there were a number of different base-case scenarios, but that all were subject to uncertainty. Particular issues of relevance included assumptions about the future costs and availability of CDF-funded treatments, and also effectiveness assumptions. In exploratory analyses, both the company and ERG models were most sensitive to assumptions about clinical effectiveness (that is, assumptions about the rates of pathological complete response, which influenced survival estimates in the model).”¹⁰
 - “The committee was also aware that the ERG had reviewed the wider evidence in this area, and had stated that the evidence of a positive treatment effect translating into a positive effect on survival was not convincing.”¹⁰
 - “the committee raised concerns about the company's precise drug costs. The company used list prices for the CDF-funded treatments, but the NHS may be paying lower prices for these drugs which would increase the ICER.”¹⁰
 - “The company submitted evidence from 2 phase II randomised controlled trials relevant to the population in the scope, NeoSphere and TRYPHAENA. However, the committee considered both of these to have substantial limitations for the purposes of providing comparative effectiveness data for pertuzumab. Both trials were at an early stage of research (phase II) and lacked longer-term efficacy data, had small patient numbers, were open label, and were not powered for key outcomes of interest including progression-free survival and overall survival.”¹⁰
- Conclusions:
 - “The committee noted that in these more conservative scenarios, and incorporating the simple discount patient access scheme for pertuzumab, the ICERs fell within the range normally considered to be a cost-effective use of NHS resources.”¹⁰
 - “It [pertuzumab] is recommended only if the company provides pertuzumab with the discount agreed in the patient access scheme.”¹⁰
- (Confidential) prices:



- “The company has agreed a patient access scheme with the Department of Health. This scheme provides a simple discount to the list price of pertuzumab, with the discount applied at the point of purchase or invoice. The level of the discount is commercial in confidence.”¹⁰

Reference Costs (list prices & remarks)	Population, Intervention & comparator IC, IE and ICERs	Remarks on use of generic utility instrument (e.g. EQ- 5D) to measure impact on QoL in economic evaluations	Most uncertain variables or important variables in sensitivity analysis
Pertuzumab			
NICE, TA424 (2016) ¹⁰	Patients with HER2-positive, locally advanced, inflammatory or early-stage breast cancer at high risk of recurrence. Pertuzumab plus trastuzumab and docetaxel compared with trastuzumab and docetaxel.		
List prices, negotiated discounts are hidden. Pertuzumab costs £2,395 per 420-mg vial (excluding VAT).	Results are not transparently reported. Only the following ICERs were mentioned: The committee noted that the ERG had done a sensitivity analysis (without the patient access scheme discount) varying the number of cycles of pertuzumab, which caused the ICER to increase from £23,467 per QALY gained (ERG's base case, based on 4cycles of pertuzumab) to £42,955 per QALY gained (using 6 cycles of pertuzumab and amending the costs but not the effectiveness of treatment), suggesting that the results were sensitive to this assumption.	HRQoL data were not collected with a generic utility instrument.	Clinical effectiveness assumptions. Treatment cost (related to number of treatment cycles).



Appendix 1.4.2.4. NICE, TA458 (2017): *trastuzumab emtansine*

- QoL:
 - No generic utility instrument is used in the underlying trial.
 - “The committee considered the utility values used in the company's model. It noted that in the progression-free state, the company applied a higher utility value for trastuzumab emtansine than for its comparators. The company considered that the favourable side effect profile of trastuzumab emtansine supports using a distinct utility value for trastuzumab emtansine. The committee questioned whether utility values should differ for each treatment because the clinical experts indicated that most adverse events resolve within a few weeks, whereas in the model the utility values were applied throughout the entire progression-free state.”¹¹
- Results:
 - See details in the following table: in the first three presented situations, the intervention was not considered a cost-effective use of resources. In the fourth situation, a comparator was chosen that was considered to be dominated in the first situations. In this situation, based on updated evidence, the intervention was considered to be cost effective when applying the end-of-life criteria.
 - No information is provided on the ICERs with price discounts for the intervention.
- Uncertainty/sensitivity:
 - No head-to-head comparison: “... only indirect evidence of its effectiveness compared with trastuzumab plus capecitabine.”¹¹
 - No information provided versus the other comparators.
- Conclusions:
 - “Despite only indirect evidence of its effectiveness compared with trastuzumab plus capecitabine, there was no reason to consider that the benefits would not be comparable. Based on the clinical and cost-effectiveness analyses, including an updated complex patient access scheme (that was subsequently replaced by a commercial access agreement), the most plausible ICER for trastuzumab emtansine compared with trastuzumab plus capecitabine was within the range that would normally be considered cost effective if the end-of-life criteria apply.”¹¹
 - “Trastuzumab emtansine is recommended only if the company provides it with the discount agreed in the patient access scheme..”¹¹
- (Confidential) prices:
 - “The pricing arrangement considered during guidance development was one in which Roche had agreed a complex patient access scheme with the Department of Health. In October 2017 Roche agreed a simple discount patient access scheme with the Department of Health. The discount to the list price is applied at the point of purchase or invoice. The level of the discount is commercial in confidence.”¹¹



Reference Costs (list prices & remarks)	Population, Intervention & comparator IC, IE and ICERs	Remarks on use of generic utility instrument (e.g. EQ- 5D) to measure impact on QoL in economic evaluations	Most uncertain variables or important variables in sensitivity analysis
Trastuzumab emtansine			
NICE, TA458 (2017) ¹¹	Patients with HER2-positive, unresectable, locally advanced or metastatic breast cancer, who previously received trastuzumab and a taxane, separately or in combination. Trastuzumab emtansine versus trastuzumab plus capecitabine or trastuzumab plus vinorelbine or lapatinib plus capecitabine.		
List prices, negotiated discounts are hidden. The list price for trastuzumab emtansine is £1,641.01 for a 100-mg vial and £2,625.62 for a 160-mg vial (excluding VAT, British national formulary online, accessed February 2017). The company estimates that the average cost of a course of treatment is £91,614, using the list price, and based on a 3-weekly dose of 3.6mg/kg, a patient weight of 70.1kg and an average length of treatment of 14.5months.	1 st situation: the committee discussed the most plausible ICERs for trastuzumab emtansine <u>without the patient access scheme</u> : ...in both the company's and ERG's base case, trastuzumab plus capecitabine and trastuzumab plus vinorelbine were more costly and less effective than lapatinib plus capecitabine (that is, they were dominated). The company's base-case ICER for trastuzumab emtansine compared with lapatinib plus capecitabine was £167,200 per QALY gained. The committee noted that the ERG's base-case ICER was very similar at £166,400 per QALY gained. At its first meeting, the committee agreed that the most plausible ICER was above the ICER range that would normally be considered a cost-effective use of NHS resources. 2 nd situation: revised cost-effectiveness results <u>incorporating the patient access scheme</u> : ... disappointment that the patient access scheme did not reduce the ICER to a level close to one that could be accepted as a cost-effective use of NHS resources. The committee concluded that the size of the discount in the patient access scheme meant that it was still unable to recommend trastuzumab emtansine for treating HER2-positive, unresectable, locally advanced or metastatic breast cancer after trastuzumab and a taxane. 3 rd situation: after accepting the criteria for end-of-life consideration: ... even taking into account additional weights applied to QALY benefits for a life-extending treatment at the end of life, the ICER incorporating the patient access scheme remained well above the	HRQoL data were not collected with a generic utility instrument.	Only indirect evidence of its effectiveness compared with trastuzumab plus capecitabine.



range that could be considered a cost-effective use of NHS resources. The committee concluded that trastuzumab emtansine could not be recommended for treating HER2-positive, unresectable, locally advanced or metastatic breast cancer previously treated with trastuzumab and a taxane.

4th situation: Cancer Drugs Fund reconsideration

The committee noted that the updated evidence available since the original appraisal confirms that trastuzumab emtansine is clinically effective, with a statistically significant survival benefit compared with lapatinib plus capecitabine. Despite only indirect evidence of its effectiveness compared with trastuzumab plus capecitabine, there was no reason to consider that the relative benefits would not be comparable. Based on what the committee heard from experts at the committee meeting and in light of the consultation comments, it concluded that trastuzumab plus capecitabine is the most relevant comparator. Based on the clinical and cost-effectiveness analyses, including the updated complex patient access scheme, the most plausible ICER for trastuzumab emtansine compared with trastuzumab plus capecitabine was within the range that would normally be considered cost effective if the end-of-life criteria apply. The committee therefore concluded that trastuzumab emtansine could be recommended for use in the NHS for treating HER2-positive advanced breast cancer.



Appendix 1.4.2.5. NICE, TA619 (2020): palbociclib

- QoL:
 - “HRQoL data were collected in the PALOMA-3 trial [palbociclib with fulvestrant compared with fulvestrant alone] using three instruments [QLQ-C30, QLQ-BR23 & EQ-5D-3L].”¹²
 - “Pre-progression utility values for treatment with fulvestrant in the PALOMA-3 trial were used as a proxy for pre-progression utility values for treatment with everolimus plus exemestane.”¹³
- Results:
 - “... results have been generated using the PAS price for palbociclib and the list prices for fulvestrant, everolimus plus exemestane.”¹²
 - “Without the discount for everolimus, the company’s base-case incremental cost-effectiveness ratio (ICER) compared with everolimus plus exemestane was £8,176 per quality-adjusted life year (QALY) gained.”¹² “The most plausible ICERs for palbociclib plus fulvestrant are uncertain.”¹²
 - “The company’s base case results, and results from the ERG’s scenarios, generated using PAS prices for palbociclib and everolimus are provided in Confidential Appendix”¹³
 - “Most of the plausible estimates are likely to be higher than what NICE normally considers an acceptable use of NHS resources.”¹²
- Uncertainty/sensitivity:
 - “Because there are no direct trials comparing palbociclib plus fulvestrant with everolimus plus exemestane, the company did network meta-analyses (NMAs).”¹² “it is uncertain whether people having palbociclib with fulvestrant live longer because the final overall survival data are not yet available. The results of indirect comparisons of palbociclib with fulvestrant and everolimus with exemestane are very uncertain.”¹²
 - “Incremental QALYs are most affected by the utility value for the progressed disease state and the utility value for the pre-progression state.”¹³
 - “The committee did not accept all the assumptions in either the company’s or ERG’s preferred base case. It concluded that the plausible ICERs from both approaches were uncertain.”¹²
 - “The committee concluded that palbociclib with fulvestrant increased progression-free survival compared with fulvestrant alone, but its effect on overall survival is currently uncertain.”
 - “Both the company’s and ERG’s methods to model time to treatment discontinuation are uncertain”¹²
 - “... The committee therefore concluded that both the company’s and ERG’s assumptions about subsequent therapies were uncertain and collecting further data could potentially reduce this uncertainty.”¹²



- Conclusions:
 - “The cost-effectiveness estimates are also very uncertain. Most of the plausible estimates are likely to be higher than what NICE normally considers an acceptable use of NHS resources. Therefore, palbociclib with fulvestrant cannot be recommended for routine use in the NHS.”¹²
 - “there was plausible potential for palbociclib plus fulvestrant to be cost effective compared with exemestane plus everolimus. It therefore concluded that palbociclib plus fulvestrant met the criteria to be considered for inclusion in the Cancer Drugs Fund. It recommended palbociclib plus fulvestrant for use within the Cancer Drugs Fund”¹²
- (Confidential) prices:
 - “The company has a commercial arrangement. This makes palbociclib available to the NHS with a discount. The size of the discount is commercial in confidence.”¹²

Reference Costs (list prices & remarks)	Population, Intervention & comparator IC, IE and ICERs	Remarks on use of generic utility instrument (e.g. EQ- 5D) to measure impact on QoL in economic evaluations	Most uncertain variables or important variables in sensitivity analysis
Palbociclib			
NICE, TA619 (2020) ¹² Fleeman (2019) ¹³	Patients with hormone receptor-positive, HER2-negative advanced breast cancer. Palbociclib with fulvestrant compared with everolimus plus exemestane.		
List prices, negotiated discounts are hidden. The cost is £2950 for a 21-capsule pack of 125mg capsules (excluding VAT; British national formulary).	The company base case cost effectiveness results have been generated using the <u>PAS price for palbociclib and the list prices for fulvestrant, everolimus plus exemestane</u> . All ERG scenario results presented in this report have been generated using these prices. Without the discount for everolimus, the company's base-case incremental cost-effectiveness ratio (ICER) compared with everolimus plus exemestane was £8,176 per quality-adjusted life year (QALY) gained. ... The ERG's revised ICERs per QALY gained range between dominant and £8,731. The exact ICERs are commercial in confidence and cannot be reported here. Most of the plausible estimates are likely to be higher than what NICE normally considers an acceptable use of NHS resources.	EQ-5D is used in the PALOMA-3 trial (which compares palbociclib with fulvestrant versus fulvestrant alone).	Effect on overall survival. The results of the company's OWSA indicate that incremental costs are most affected by varying administration costs, health-care professional resource use and health-care professional unit costs. Incremental QALYs are most affected by the utility value for the progressed disease state and the utility value for the pre-progression state.

OWSA: one-way sensitivity analysis.



Appendix 1.4.2.6. NICE, TA495 (2017): palbociclib

- QoL:
 - “In its original base case, the company used different utility values for people in the progression-free state having palbociclib plus letrozole (0.74) or letrozole alone (0.71). These values were derived from the corresponding treatment arms of PALOMA-2. Taking into account that the difference in the EQ-5D values between the 2 arms of PALOMA-2 was not statistically significant, the ERG estimated an average utility value (0.72) by pooling EQ-5D values for European patients from the first 21 cycles in PALOMA-2.”¹⁴
 - Common to trials that report HRQoL outcomes, patients in the PALOMA-1 and PALOMA-2 trials were only asked to complete questionnaires up until the time of disease progression. ... Thus, in later cycles, the numbers of patients responding are very small and the data are only reflective of the experience of relatively healthy patients. Nonetheless, the data from the earlier cycles in both trials do appear to show there is no difference in HRQoL between treatment arms for patients in either the PALOMA-1 trial or the PALOMA-2 trial.”¹⁵
 - The EQ-5D utility values and completion rates over time for the PALOMA-2 trial are presented as confidential.
- Results:
 - Using list prices, “the company base case ICER for the comparison of treatment with PAL+LET versus LET is £150,869 per QALY gained.”¹⁵ “The company’s base case cost effectiveness results and the results generated following the application of either of the ERG’s combined revision scenarios, are all considerably higher than the range normally considered acceptable by NICE.”¹⁵
 - “The committee agreed that using a more realistic cost for progressive disease, and applying the discount agreed in the patient access scheme on the list price of the palbociclib, produced ICERs within the range considered a cost-effective use of NHS resources. (These ICERs incorporated a confidential patient access scheme, and were presented as commercial in confidence.)”¹⁴
- Uncertainty/sensitivity:
 - “Data from the trials showed that palbociclib improved progression-free survival, but no significant improvement in overall survival had been shown. An improved progression-free survival with metastatic breast cancer would be expected to have some benefit on overall survival. However, the size of benefit is uncertain.”¹⁴
 - “... an assumption of overall survival gain equal to the progression-free survival gain is not supported by any evidence.”¹⁴
 - “The approaches to modelling overall survival, the utility values for progression-free state and cost for post-progression disease states were the key drivers of the cost-effectiveness results.”¹⁴
 - “More evidence for the impact of palbociclib in combination with an aromatase inhibitor on OS is required. While OS data from the PALOMA-2 trial will add to the evidence base when the data become available, more mature data from the PALOMA-1 trial would also be informative.”¹⁴



- Conclusions:
 - “The committee concluded that palbociclib improves progression-free survival, but no significant improvement in overall survival has been shown. The committee agreed that with the discount agreed in the patient access scheme, palbociclib is a cost-effective use of NHS resources and it can be recommended.”¹⁴
- (Confidential) prices:
 - “The company has agreed a patient access scheme with the Department of Health. This scheme provides a simple discount to the list price of palbociclib, with the discount applied at the point of purchase or invoice. The level of the discount is commercial in confidence.”¹⁴



Reference Costs (list prices & remarks)	Population, Intervention & comparator IC, IE and ICERs	Remarks on use of generic utility instrument (e.g. EQ- 5D) to measure impact on QoL in economic evaluations	Most uncertain variables or important variables in sensitivity analysis
Palbociclib			
NICE, TA495 (2017) ¹⁴	Patients with previously untreated, hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer.		
Fleeman, 2016 ¹⁵	Palbociclib plus letrozole versus letrozole alone.		
List prices, negotiated discounts are hidden. £2,950 for a 21-capsule pack of 125-mg capsules (excluding VAT; MIMS Online)	Results of the incremental analysis (<u>with list prices</u>): all considerably higher than the range normally considered acceptable by NICE. A) The company's base case ICER: Costs (£) IC QALYs IE ICER LET £21,843 1.77 PAL+LET £116,696 £94,853 2.40 0.63 £150,869 B) ERG's revisions, using PALOMA-1 trial data: Costs (£) IC QALYs IE ICER LET £27,544 1.83 PAL+LET £87,478 £59,934 2.28 0.45 £132,872 C) ERG's revisions, using PALOMA-2 trial data: Costs (£) IC QALYs IE ICER LET £22,518 1.97 PAL+LET £110,970 £88,452 2.39 0.42 £213,206 Remark: <u>applying the discount</u> agreed in the patient access scheme on the list price of the palbociclib, produced ICERs within the range considered a cost-effective use of NHS resources.	EQ-5D is used in the underlying PALOMA-2 trial.	Modelling of overall survival. Utility value progression-free disease. Cost subsequent treatments.

LET: letrozole; Pal: palbociclib



Appendix 1.4.2.7. NICE, TA579 (2019): abemaciclib

- QoL:
 - “The company used EQ-5D data from MONARCH 2 to derive a utility value for the pre-progression health state in its base case. For post-progression survival in its base case, the company used a utility value of 0.505, taken from a study by Lloyd et al. (2006).”¹⁶
 - Results of EQ-5D-5L in de MONARCH 2 trial are presented confidential: “Mean change from baseline within each treatment group and the mean differences between treatment groups were similar for the EQRTC QLQ-C30 global health status and the functional scales and for EQ-5D-5L, indicating that neither ABE-FUL [abemaciclib & fulvestrant] or PBO-FUL [placebo & fulvestrant] treatment adversely affect functioning, HRQoL or the overall health status of patients.”¹⁷
 - “The VAS and EQ-5D-5L index values were similar between the treatment groups for both baseline and change from baseline assessments, indicating that the overall health status of patients was maintained throughout the study in both treatment arms.”¹⁷
- Results:
 - “The company's base case included the confidential commercial arrangement for abemaciclib but not the discount for everolimus (which reduces the costs of exemestane plus everolimus). Without this reduction included, abemaciclib plus fulvestrant dominated exemestane plus everolimus (that is, was both cheaper and more effective).”¹⁶
 - “In the ERG's base-case results, abemaciclib plus fulvestrant still dominated exemestane plus everolimus based on the confidential discount of abemaciclib but not everolimus. When the confidential discount for everolimus was included, the company's base-case ICER compared with exemestane plus everolimus was below £30,000 per quality-adjusted life year (QALY) gained, and the ERG's base-case ICER was above £30,000 per QALY gained. The exact ICERs are commercial in confidence and cannot be reported here.”¹⁶
 - “abemaciclib plus fulvestrant was not cost effective in people who would otherwise have treatments other than exemestane plus everolimus. The company's base-case ICERs (including the ERG corrections for the cost of subsequent treatment) and the ERG's base-case ICERs were £50,687 and £70,634 per QALY gained compared with fulvestrant, £57,247 and £63,436 per QALY gained compared with exemestane and the company's base-case ICER was £82,621 compared with tamoxifen. Exemestane plus everolimus was included in the model as a subsequent treatment. The committee noted that when the confidential discount for everolimus was included with the ERG's model corrections, the ICERs for abemaciclib plus fulvestrant compared with each of the above comparators were substantially above what could be considered a cost-effective use of NHS resources.”¹⁶
- Uncertainty/sensitivity:
 - “The cost-effectiveness estimates are based on an indirect comparison. Also, survival data are incomplete. Therefore the cost-effectiveness estimates are highly uncertain.”¹⁶
 - “The committee was concerned that both the company's and the ERG's base-case models were based on the network meta-analyses that the committee had agreed contained heterogeneity and were uncertain because of the immaturity of the overall survival data in MONARCH 2 The committee concluded that the model structure was appropriate for decision making but that overall survival data used in the model were too immature to reliably predict the relative survival benefit of abemaciclib plus fulvestrant.”¹⁶



- “time to treatment discontinuation was uncertain”¹⁶
- “the exact treatments that people would have after abemaciclib plus fulvestrant were uncertain.”¹⁶
- “The key drivers of the economic analysis are: the method used to estimate relative treatment effectiveness in the model ...; the assumptions made around the estimation of TTD [time to treatment discontinuation] curves ...; the assumptions around subsequent treatments received and duration of the latter; the follow-up and CAP cost assumptions; and finally, the PPS-related utility value used in the analysis.”¹⁷
- Conclusions:
 - “The committee agreed that the ICERs for abemaciclib plus fulvestrant were uncertain. Further trial data would be available within 2 years, which would give further information on overall survival and time on treatment which could reduce this uncertainty, but at present the committee concluded that it could not be confident enough that abemaciclib plus fulvestrant was a cost-effective use of NHS resources to recommend it for routine commissioning in the NHS in England.”¹⁶
 - “The committee considered that on the basis of the cost-effectiveness analyses including all commercial discounts, there was plausible potential that abemaciclib plus fulvestrant would be cost effective compared with exemestane plus everolimus if subsequent data confirm the company's preferred assumptions. It therefore concluded that abemaciclib plus fulvestrant met the criteria to be considered for inclusion in the Cancer Drugs Fund. It recommended abemaciclib plus fulvestrant for use within the Cancer Drugs Fund as an option for people with advanced hormone receptor-positive, HER2-negative breast cancer after endocrine therapy, if the conditions in the managed access agreement are followed.”¹⁶
- (Confidential) prices:
 - “The company has a commercial arrangement. This makes abemaciclib available to the NHS with a discount. The size of the discount is commercial in confidence.”¹⁶



Reference Costs (list prices & remarks)	Population, Intervention & comparator IC, IE and ICERs	Remarks on use of generic utility instrument (e.g. EQ- 5D) to measure impact on QoL in economic evaluations	Most uncertain variables or important variables in sensitivity analysis
Abemaciclib			
NICE, TA579 (2019) ¹⁶	Patients with advanced hormone receptor-positive, HER2-negative breast cancer after endocrine therapy.		
Edwards (2018) ¹⁷	Abemaciclib plus fulvestrant compared with exemestane plus everolimus (and other comparators, e.g. fulvestrant, and exemestane).		
List prices, negotiated discounts are hidden.	Results of the incremental analysis, <u>including the confidential commercial arrangement for abemaciclib</u> but <u>not the discount for everolimus</u> :	No head-to-head comparison. EQ-5D data measured in MONARCH 2 trial.	Overall survival data
Abemaciclib: £2,950 for 56 × 150mg tablets (excluding VAT, British national formulary).	A) Company's corrected base case: ABE-FUL versus comparator		Time to treatment discontinuation
Drug costs per cycle:	Costs (£) IC QALYs IE ICER		Subsequent treatments
ABE: Confidential	ABE-FUL conf. conf. conf. conf.		Utilities
FUL: £522.41	FUL conf. conf. conf. conf. £50,687		
EXE: £3.69	EXE conf. conf. conf. conf. £57,247		
EVE: £2,673	EXE-EVE conf. conf. conf. conf. dominant		
CAP: £15.88	CAP conf. conf. conf. conf. £82,621		
	B) ERG's base case: ABE-FUL versus comparator		
	Costs (£) IC QALYs IE ICER		
	ABE-FUL conf. conf. conf. conf.		
	versus		
	FUL conf. conf. conf. conf. £70,634		
	EXE conf. conf. conf. conf. £63,436		
	EXE-EVE conf. conf. conf. conf. dominant		
	CAP conf. conf. conf. conf. dominated		

ABE: abemaciclib; BEV: bevacizumab; Conf.: confidential; EVE: everolimus; EXE: exemestane; CAP: capecitabine; FUL: fulvestrant.

[illegible]



- Conclusions:
 - “Taking into account the commercial arrangements for all the CDK 4/6 inhibitors, abemaciclib is a cost-effective use of NHS resources and it can be recommended.”¹⁸
- (Confidential) prices:
 - “The company has a commercial arrangement. This makes abemaciclib available to the NHS with a discount. The size of the discount is commercial in confidence.”¹⁸

Reference	Costs (list prices & remarks)	Population, Intervention & comparator IC, IE and ICERs	Remarks on use of generic utility instrument (e.g. EQ-5D) to measure impact on QoL in economic evaluations	Most uncertain variables or important variables in sensitivity analysis
Abemaciclib				
NICE, TA563 (2019) ¹⁸		Patients with previously untreated, hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer.		
Shepherd (2018) ¹⁹		Abemaciclib in combination with a non-steroidal aromatase inhibitor (NSAI) in comparison with palbociclib with an NSAI or ribociclib with an NSAI.		
List prices, negotiated discounts are hidden.		Results of the incremental analysis (with list prices):		EQ-5D-5L was administered in the MONARCH 3 trial.
Drug costs per cycle:		A) Company base case results		Impact on overall survival
		Costs (£)	IC	QALYs
ABE: confidential	NSAI	£56,449		2.997
PAL: £2,950	PAL+NSAI	£145,266	/	3.225
RIBO: £2,950	RIBO+NSAI	£148,170	/	3.222
	ABE+NSAI	£129,803	/	3.291
				ICER
				Referent
				Dominated
				Dominated
				£250,065
		B) ERG's corrected company base case results: £195,730 instead of £250,065.		



Appendix 1.4.2.9. NICE, TA593 (2019): ribociclib

- QoL:
 - “Utilities were sourced from EQ-5D-5L data collected in the MONALEESA-3 trial, which were mapped onto the EQ-5D-3L measure using the algorithm published by van Hout et al. 2012. A number of regressions were performed on the data to estimate the utilities for the different health-states, and while on or off either ribociclib plus fulvestrant or fulvestrant monotherapy. Time to death was also included to capture the deterioration of quality-of-life later as patients age.”²¹
 - Summary results of the patient reported outcomes for the MONALEESA-3 trial were published confidentially in the underlying HTA report.²¹
- Results:
 - All results are presented as confidential.
 - “The most plausible ICERs for ribociclib with fulvestrant are uncertain with very small QALY gains”²⁰
 - “the company’s revised base case resulted in an ICER of less than £30,000 per QALY gained. This ICER was presented as commercial in confidence to maintain the confidentiality of the proposed commercial access agreement for ribociclib and the patient access scheme for everolimus. Therefore, it cannot be reported here. However, the committee noted that the proposed commercial access agreement for ribociclib is only for this indication, so it could not take this price into account when considering ribociclib with fulvestrant for routine commissioning. The committee also noted that, when the current patient access scheme for ribociclib (which is the offered price for routine commissioning) was used in the cost-effectiveness analyses, the ICERs were all substantially above the range considered to be a cost-effective use of NHS resources.”²⁰
- Uncertainty/sensitivity:
 - “Ribociclib with fulvestrant increases progression-free survival compared with fulvestrant alone but overall survival data are immature”²⁰
 - “The committee concluded that, unless further long-term data were available, the most appropriate extrapolation of progression-free survival was uncertain.”²⁰
 - “It’s not known whether ribociclib increases the length of time people live because the final trial results are not available yet. The results of an indirect comparison of ribociclib and fulvestrant with exemestane and everolimus are very uncertain.”²⁰
 - “The committee also noted the ERG’s comment that the company’s analysis was based on a very small increase in quality-adjusted life years (QALYs) for ribociclib, so the resulting ICER was very unstable, and sensitive to even small changes in both costs and QALYs.”²⁰
 - “A greater concern for the ERG was the inaccurate estimation of treatment discontinuation times, and therefore drug acquisition costs, due to the ill-fitting TTD curves”²¹
 - “Further to this, for the first-line model, the ERG considers the assumption of a full surrogacy between PFS and OS to be highly uncertain and considers the company’s ICERs to be potentially seriously underestimated.”²¹
 - “...issue that the ERG was concerned with was the estimation of health-state utility values.”²¹



- Conclusions:
 - “The cost-effectiveness estimates are also very uncertain, and are above the range NICE normally considers an acceptable use of NHS resources. Therefore, ribociclib with fulvestrant cannot be recommended for routine use in the NHS.”²⁰
 - “Ribociclib with fulvestrant has the potential to be cost effective for the population considered in this appraisal, but more data are needed to resolve the uncertainties in the clinical evidence. Therefore, ribociclib with fulvestrant is recommended for this population in the Cancer Drugs Fund while these data are collected.”²⁰
- (Confidential) prices:
 - “The company has a commercial arrangement. This makes ribociclib available to the NHS with a discount. The size of the discount is commercial in confidence.”²⁰
 - “For everolimus, the current list price is £2,673.00 per pack. However, a simple PAS discount of xxx has been agreed with the Department of Health, and this was applied to the list price in the company’s analysis as the marketing authorisation for the drug is also held by Novartis.”²¹



Reference Costs (list prices & remarks)	Population, Intervention & comparator IC, IE and ICERs	Remarks on use of generic utility instrument (e.g. EQ- 5D) to measure impact on QoL in economic evaluations	Most uncertain variables or important variables in sensitivity analysis
Ribociclib			
NICE, TA593 (2019) ²⁰ Edwards, 2018 ²¹	Patients with hormone receptor-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer who have had previous endocrine therapy. ribociclib with fulvestrant compared with exemestane with everolimus.		
List prices, negotiated discounts are hidden. Drug costs per cycle (28 days): Ribociclib confidential fulvestrant: 1 st cycle £1,045 next cycles £522 letrozole: £2.71 everolimus: confidential exemestane: £3.44 palbociclib: £2,950 capecitabine: £225	Remark: Results are confidential. The ICERs were all substantially above the range considered to be a cost-effective use of NHS resources.	EQ-5D-5L data collected in the MONALEESA-3 trial.	Overall survival Utilities Treatment duration.



Appendix 1.4.2.10. NICE, TA496 (2017): ribociclib

- QoL:
 - “The company's original base case used EQ-5D 5-level data from MONALEESA-2 to inform PFS1; the BOLERO-2 adjusted value of 0.774 to inform PFS2; and the Lloyd et al. 2006 value of 0.505 for the progression state.”²²
 - “Quality of life scores showed no clinically meaningful changes from baseline and no meaningful differences between treatment arms.”²³ Results are not published transparently (i.e. per treatment arm for all points in time).
- Results:
 - “Without the patient access scheme, incremental QALYs are 0.96 and incremental costs are xxxxxxx. The corresponding ICER is xxxxxxx for ribociclib plus letrozole compared to letrozole monotherapy. With the patient access scheme, incremental costs reduce to xxxxxxx, and the corresponding ICER is xxxxxxx.”²³
 - “The company's revised base case resulted in an ICER of less than £30,000 per quality-adjusted life year (QALY) gained. These ICERs were presented as commercial in confidence to maintain the confidentiality around the patient access scheme and therefore cannot be reported here.”²²
- Uncertainty/sensitivity:
 - “It [the committee] emphasised that the survival data for MONALEESA-2 are immature ... , and that the relationship between progression-free survival and overall survival is unknown The committee agreed that the cost-effectiveness estimates are subject to high uncertainty given the assumptions about overall survival surrogacy ... , progression-free survival and time to treatment discontinuation extrapolation ... , and cost of subsequent treatments”²²
 - “The overall survival data from MONALEESA-2 are immature. ... The committee concluded that there are insufficient data to allow them to decide whether ribociclib, compared with letrozole alone, improves overall survival.”²²
 - “Relationship between progression-free and overall survival. The size of the overall survival benefit is uncertain.”²²
 - “The committee agreed that ribociclib improves progression-free survival, and it is likely that this would result in some improvement in overall survival, but the size of this benefit is uncertain. ... The assumption of full surrogacy was made by the company in the face of immaturity of the survival data from MONALEESA-2. The committee concluded that a degree of partial surrogacy is probably more likely than full surrogacy, however the magnitude of the relationship is highly uncertain.”²²
 - “One of the main concerns of the ERG with the company submission was the assumption in the model that any gain in PFS is 100% translated into OS gain in the base-case. The ERG considers this assumption speculative, as there are studies indicating that duration of PFS gain would translate into an OS gain that is shorter, especially in HER2-negative patients. This trend can be also observed in the PALOMA-1 trial (comparing palbociclib plus letrozole vs letrozole) where a “gain in median OS/gain in median PFS” ratio close to 38.5% was observed. The ERG considered the observed ratio of 38.5% more evidence-based than the completely arbitrary 100% that the company assumed.”²³
- Conclusions:



- “The committee concluded that there are uncertainties in the modelling, but the most plausible ICERs for ribociclib compared with letrozole are broadly within the range normally considered a cost-effective use of NHS resources. It noted the innovative nature of ribociclib and the importance of progression-free survival to patients with this disease. The committee recommended ribociclib as a cost-effective use of NHS resources for treating hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer.”²²
- (Confidential) prices:
 - “The company has agreed a patient access scheme with the Department of Health. This scheme provides a simple discount to the list price of ribociclib, with the discount applied at the point of purchase or invoice. The level of the discount is commercial in confidence.”²²

Reference Costs (list prices & remarks)	Population, Intervention & comparator IC, IE and ICERs	Remarks on use of generic utility instrument (e.g. EQ- 5D) to measure impact on QoL in economic evaluations	Most uncertain variables or important variables in sensitivity analysis
Ribociclib			
NICE, TA496 (2017) ²² Riemsma (2017) ²³	Patients with previously untreated, hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer. Ribociclib versus aromatase inhibitor therapy (ribociclib combined with letrozole against placebo plus letrozole).		
List prices, negotiated discounts are hidden. Ribociclib: £2,950 for a 63-tablet pack of 200-mg tablets (excluding VAT). Drug acquisition costs for letrozole (2.5 mg) were estimated to be £0.05 per day and £1.52 per 28-day cycle.	Remark: results are confidential: Without the patient access scheme, incremental QALYs are 0.96 and incremental costs are xxxxxxx. The corresponding ICER is xxxxxxx for ribociclib plus letrozole compared to letrozole monotherapy. With the patient access scheme, incremental costs reduce to xxxxxxx, and the corresponding ICER is xxxxxxx.	EQ-5D-5L is used in the MONALEESA-2 trial.	Overall survival Treatment duration Subsequent treatment costs.



APPENDIX 2. CHRONIC MYELOID LEUKAEMIA

Appendix 2.1. BCR data

Appendix 2.1.1. Descriptive statistics

Appendix 2.1.1.1. Chronic myeloid leukaemia, exploration

Table 16 – Chronic myeloid leukaemia (2004-2017): Frequency table of patient and tumour characteristics

Characteristic	Incidence period			
	Total	2004-2008	2009-2013	2014-2017
Overall	2,064	650	754	660
Gender				
Male	1,112 (53.9)	354 (54.5)	394 (52.3)	364 (55.2)
Female	952 (46.1)	296 (45.5)	360 (47.7)	296 (44.8)
Age at diagnosis (year)				
<50 years	581 (28.1)	183 (28.2)	210 (27.9)	188 (28.5)
50-59 years	376 (18.2)	111 (17.1)	137 (18.2)	128 (19.4)
60-69 years	432 (20.9)	127 (19.5)	161 (21.4)	144 (21.8)
70-79 years	438 (21.2)	152 (23.4)	159 (21.1)	127 (19.2)
80+ years	237 (11.5)	77 (11.8)	87 (11.5)	73 (11.1)
WHO - Performance Status				
0 – Asymptomatic	658 (31.9)	156 (24.0)	252 (33.4)	250 (37.9)
1 – Symptomatic but completely ambulatory	851 (41.2)	208 (32.0)	334 (44.3)	309 (46.8)
2 – Symptomatic, <50% in bed during the day	74 (3.6)	28 (4.3)	25 (3.3)	21 (3.2)
3 – Symptomatic, >50% in bed, but not bedbound	13 (0.6)	2 (0.3)	7 (0.9)	4 (0.6)
4 – Bedbound	8 (0.4)	4 (0.6)	1 (0.1)	3 (0.5)
Not reported	460 (22.3)	252 (38.8)	135 (17.9)	73 (11.1)

Note: the values between parentheses are column percentages.



Table 17 – Chronic myeloid leukaemia (2004-2017): Frequency table of patient and tumour characteristics (cut-off point: 2010)

Characteristic	Incidence period		
	Total	2004-2009	2011-2017
Overall	1 901	773	1 128
Gender			
Male	1 027 (54.0)	428 (55.4)	599 (53.1)
Female	874 (46.0)	345 (44.6)	529 (46.9)
Age at diagnosis (year)			
<50 years	538 (28.3)	219 (28.3)	319 (28.3)
50-59 years	343 (18.0)	129 (16.7)	214 (19.0)
60-69 years	401 (21.1)	153 (19.8)	248 (22.0)
70-79 years	404 (21.3)	182 (23.5)	222 (19.7)
80+ years	215 (11.3)	90 (11.6)	125 (11.1)
WHO - Performance Status			
0 – Asymptomatic	592 (31.1)	192 (24.8)	400 (35.5)
1 – Symptomatic but completely ambulatory	791 (41.6)	264 (34.2)	527 (46.7)
2 – Symptomatic, <50% in bed during the day	68 (3.6)	30 (3.9)	38 (3.4)
3 – Symptomatic, >50% in bed, but not bedbound	12 (0.6)	3 (0.4)	9 (0.8)
4 – Bedbound	8 (0.4)	5 (0.6)	3 (0.3)
Not reported	430 (22.6)	279 (36.1)	151 (13.4)

Note: the values between parentheses are column percentages.



Appendix 2.1.1.2. *Chronic myeloid leukaemia, Observed and Relative Survival graphs*

Chronic myeloid leukaemia (2004-2017)

Figure 27 – Chronic myeloid leukaemia (2004-2017), Kaplan-Meier graphs observed survival by incidence period

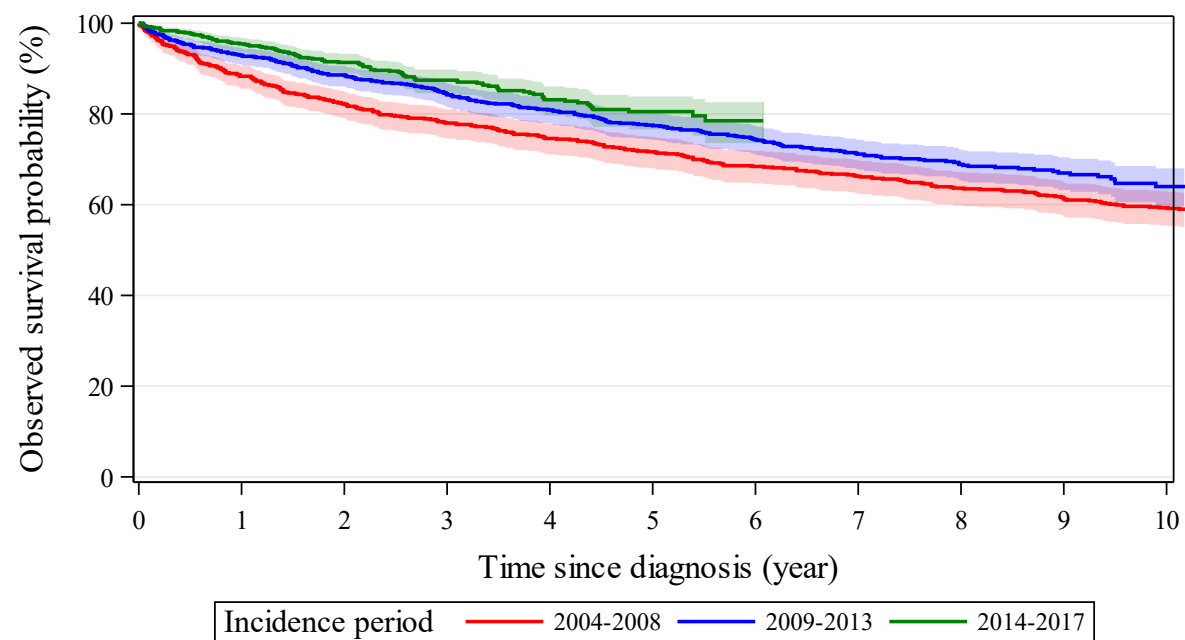




Figure 28 – Chronic myeloid leukaemia (2004-2017), Kaplan-Meier graphs observed survival by incidence period (cut-off point: 2010)

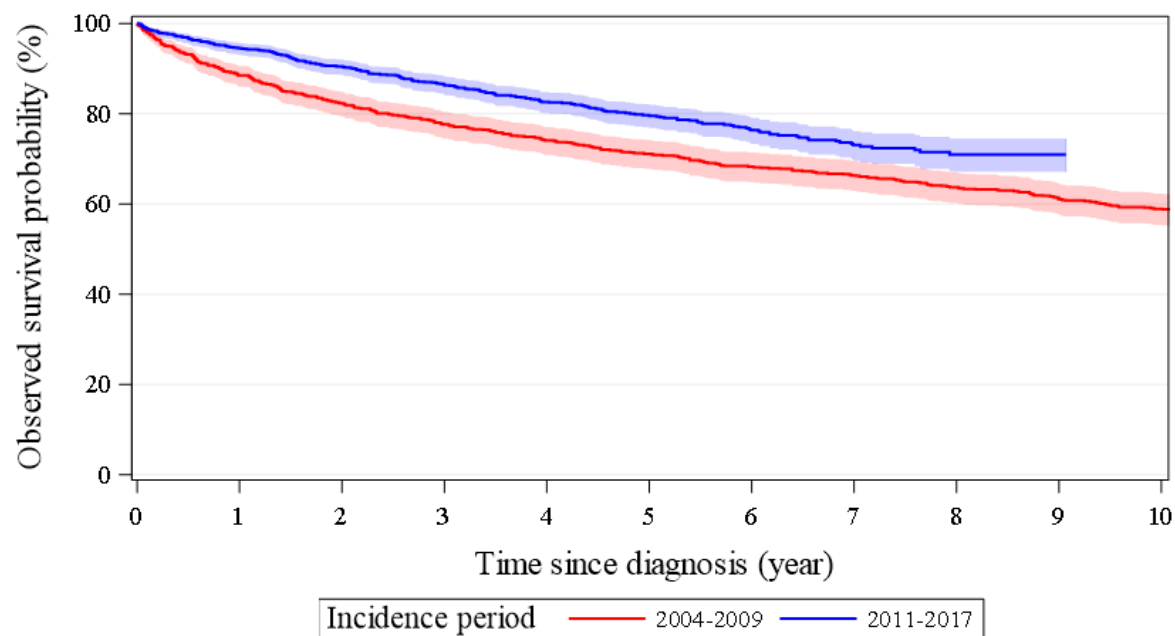




Figure 29 – Chronic myeloid leukaemia (2004-2017), relative survival graphs by incidence period

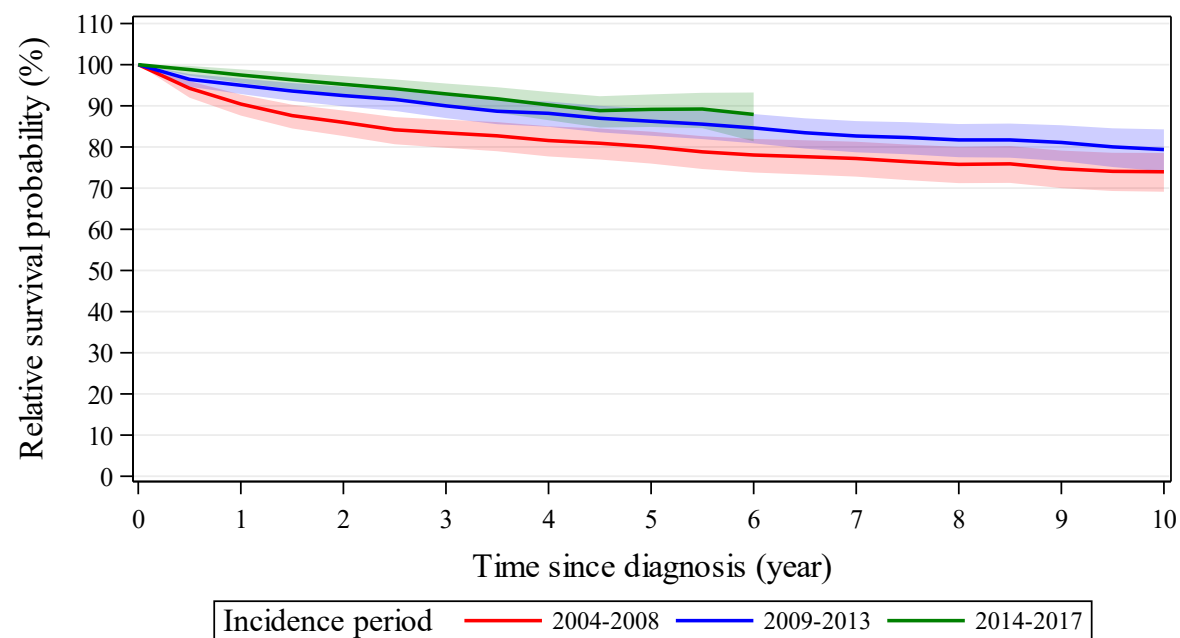
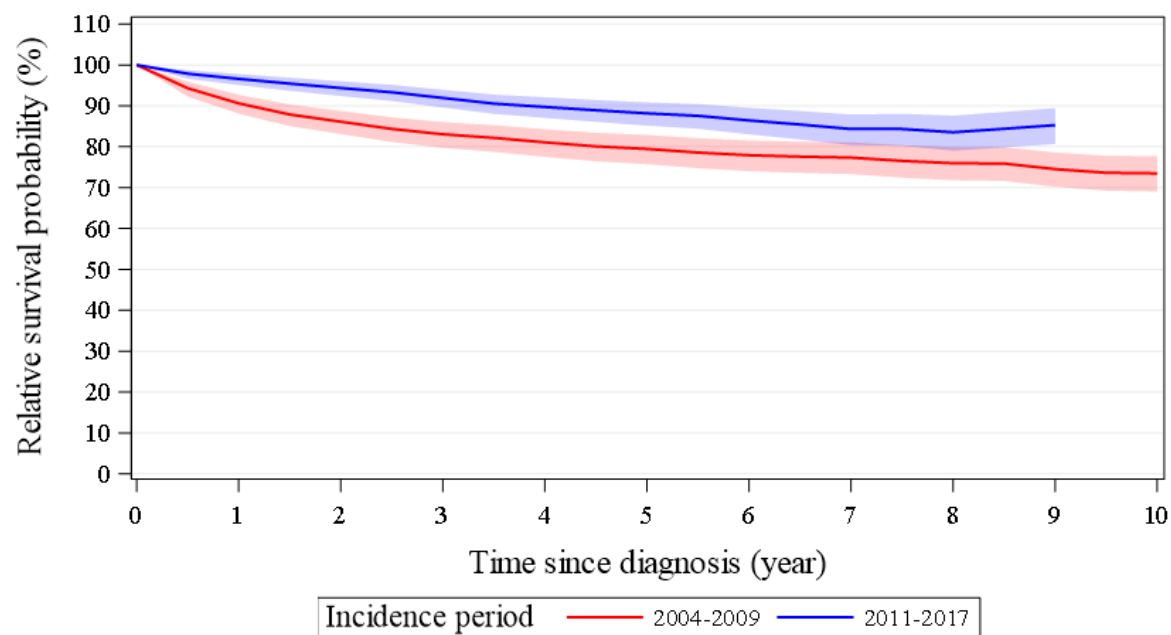




Figure 30 – Chronic myeloid leukaemia (2004-2017), relative survival graphs by incidence period (cut-off point: 2010)

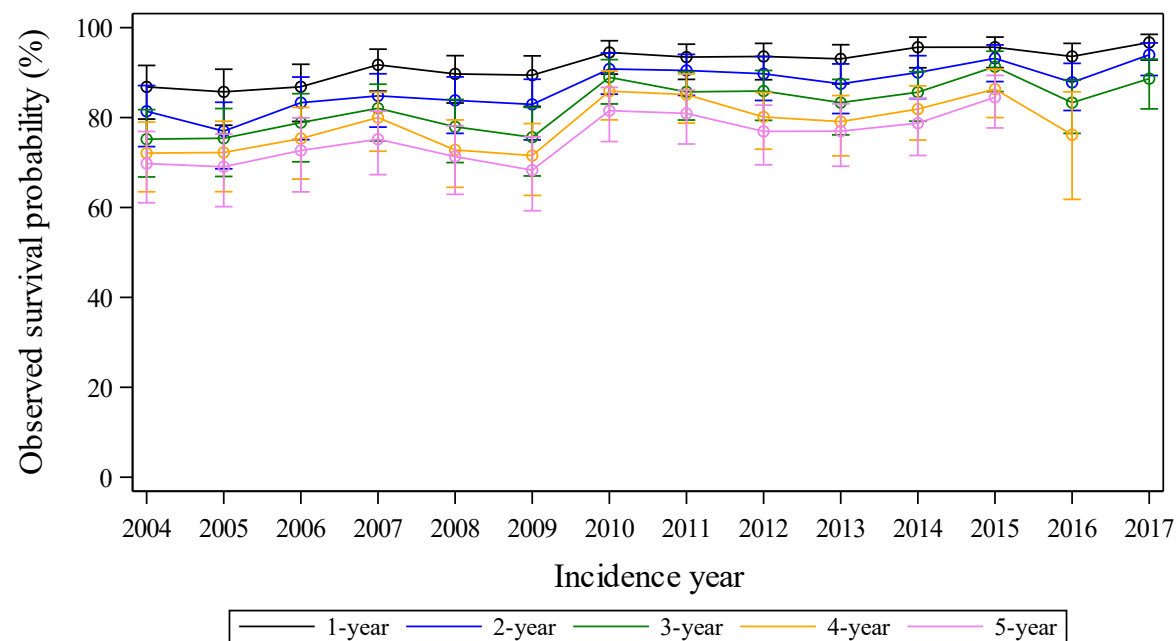




Appendix 2.1.1.3. Chronic myeloid leukaemia, time trend Observed and Relative Survival

Chronic myeloid leukaemia (2004-2017)

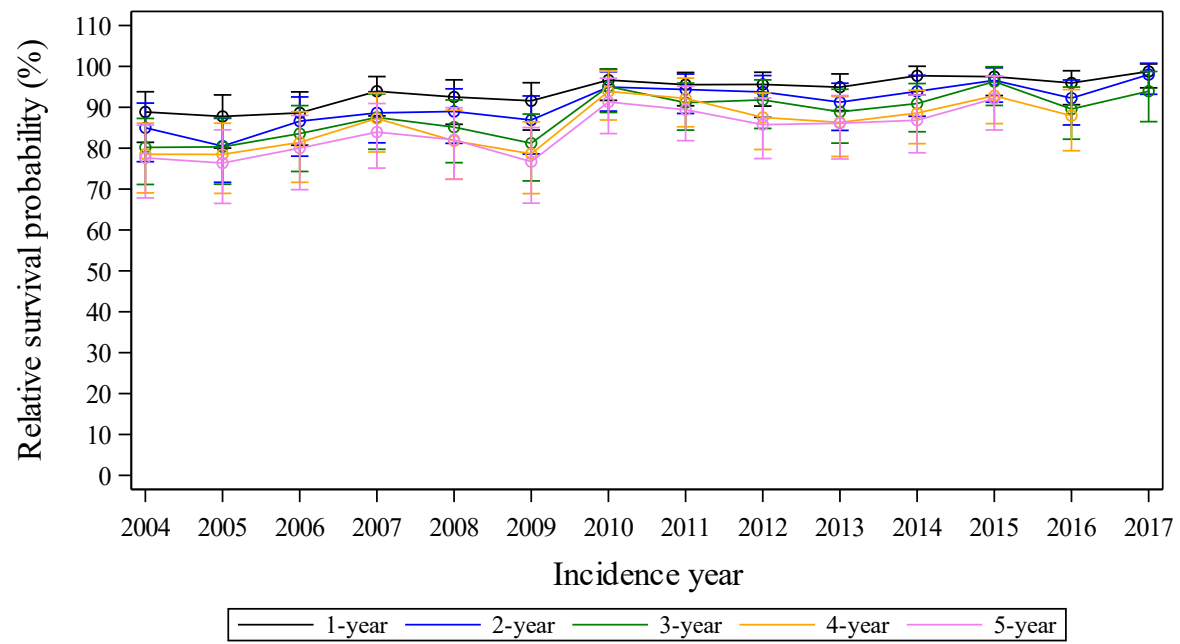
Figure 31 – Chronic myeloid leukaemia (2004-2017), time trend observed survival with incidence year



Note: the error bars represent the 95% CI.



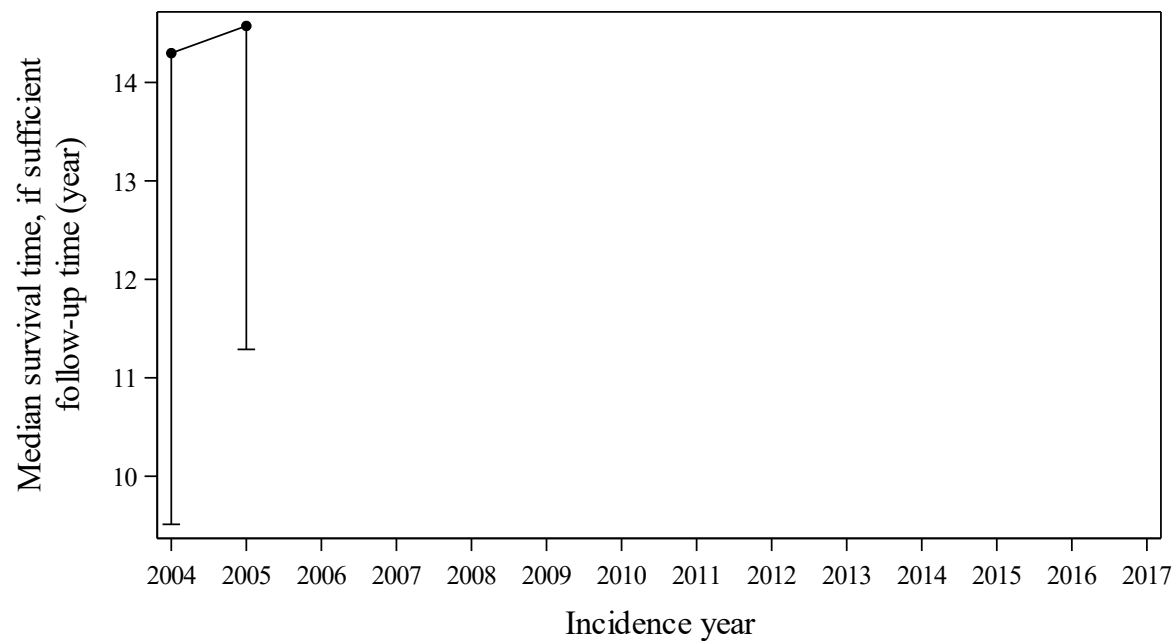
Figure 32 – Chronic myeloid leukaemia (2004-2017), time trend relative survival with incidence year



Note: the error bars represent the 95% CI.



Figure 33 – Chronic myeloid leukaemia (2004-2017), Median time observed survival



Note: the error bars represent the 95% CI. When the upper error is not plotted, the upper limit could not be determined with the follow-up available.



Appendix 2.1.1.4. Chronic myeloid leukaemia, time trend tables Observed and Relative Survival

Table 18 – Chronic myeloid leukaemia (2004-2017), time trend observed survival with incidence year

Unadjusted observed survival, %													
Characteristic	N at risk	1 year		2 year		3 year		4 year		5 year		Median survival time (year)	
		%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI	T	95% CI
All													
2004	129	86.8	[79.7, 91.6]	81.4	[73.5, 87.1]	75.2	[66.8, 81.8]	72.1	[63.5, 79.0]	69.8	[61.0, 76.9]	14.3	[9.5, .]
2005	126	85.7	[78.3, 90.7]	77.0	[68.6, 83.4]	75.4	[66.9, 82.0]	72.2	[63.5, 79.2]	69.0	[60.2, 76.3]	14.6	[11.3, .]
2006	114	86.8	[79.1, 91.8]	83.3	[75.1, 89.0]	78.9	[70.2, 85.3]	75.3	[66.3, 82.3]	72.7	[63.5, 79.9]	>14	
2007	145	91.7	[85.9, 95.2]	84.8	[77.9, 89.7]	82.1	[74.8, 87.4]	80.0	[72.5, 85.6]	75.2	[67.3, 81.4]	>13	
2008	136	89.7	[83.2, 93.8]	83.8	[76.5, 89.0]	77.9	[70.0, 84.0]	72.8	[64.5, 79.5]	71.3	[62.9, 78.1]	>12	
2009	123	89.4	[82.5, 93.7]	82.9	[75.0, 88.5]	75.6	[67.0, 82.3]	71.5	[62.7, 78.7]	68.3	[59.3, 75.7]	>11	
2010	163	94.5	[89.7, 97.1]	90.8	[85.2, 94.3]	88.9	[83.0, 92.9]	85.9	[79.5, 90.4]	81.5	[74.7, 86.7]	>10	
2011	168	93.5	[88.5, 96.3]	90.5	[84.9, 94.1]	85.7	[79.4, 90.2]	85.1	[78.8, 89.7]	80.9	[74.1, 86.1]	>9	
2012	156	93.6	[88.4, 96.5]	89.7	[83.8, 93.6]	85.9	[79.4, 90.5]	80.1	[73.0, 85.6]	76.9	[69.5, 82.8]	>8	
2013	144	93.1	[87.5, 96.2]	87.5	[80.9, 91.9]	83.3	[76.1, 88.5]	79.1	[71.5, 84.9]	77.0	[69.2, 83.0]	>7	
2014	161	95.6	[91.1, 97.9]	90.0	[84.2, 93.8]	85.6	[79.2, 90.2]	81.9	[75.0, 87.0]	78.7	[71.6, 84.3]	>6	
2015	161	95.7	[91.1, 97.9]	93.2	[88.0, 96.2]	91.3	[85.8, 94.8]	86.3	[80.0, 90.8]	84.5	[77.7, 89.4]	>5	
2016	156	93.6	[88.4, 96.5]	87.8	[81.6, 92.1]	83.3	[76.5, 88.3]	76.2	[61.8, 85.7]	no FU	—	>4	
2017	182	96.7	[92.8, 98.5]	94.0	[89.4, 96.6]	88.7	[81.9, 93.0]	no FU	—	no FU	—	>3	



Table 19 – Chronic myeloid leukaemia (2004-2017), time trend relative survival with incidence year

Unadjusted relative survival, %											
	N at risk	%	1 year 95% CI	%	2 year 95% CI	%	3 year 95% CI	%	4 year 95% CI	%	5 year 95% CI
All											
2004	129	88.8	[81.4, 93.8]	85.0	[76.7, 91.0]	80.2	[71.1, 87.3]	78.5	[69.1, 86.1]	77.6	[67.8, 85.6]
2005	126	87.8	[80.0, 93.0]	80.5	[71.7, 87.3]	80.3	[71.2, 87.4]	78.5	[68.9, 86.1]	76.4	[66.5, 84.5]
2006	114	88.6	[80.7, 93.8]	86.6	[78.0, 92.5]	83.6	[74.3, 90.4]	81.4	[71.7, 88.9]	80.0	[69.9, 88.0]
2007	145	93.9	[87.9, 97.5]	88.6	[81.3, 93.8]	87.5	[79.7, 93.3]	87.3	[79.1, 93.5]	83.9	[75.1, 90.9]
2008	136	92.5	[85.8, 96.7]	89.0	[81.2, 94.5]	85.1	[76.5, 91.8]	81.8	[72.4, 89.3]	82.0	[72.4, 89.9]
2009	123	91.6	[84.4, 96.0]	86.9	[78.6, 92.8]	81.2	[72.0, 88.3]	78.6	[68.9, 86.4]	76.7	[66.6, 85.1]
2010	163	96.7	[91.7, 99.3]	95.0	[89.1, 98.7]	95.1	[88.7, 99.3]	93.9	[86.9, 98.8]	91.3	[83.6, 97.1]
2011	168	95.5	[90.4, 98.5]	94.3	[88.5, 98.1]	91.1	[84.4, 95.9]	92.2	[85.2, 97.1]	89.4	[81.8, 95.2]
2012	156	95.6	[90.3, 98.6]	93.7	[87.5, 97.8]	91.8	[84.8, 96.7]	87.5	[79.7, 93.5]	85.8	[77.5, 92.3]
2013	144	94.9	[89.2, 98.2]	91.2	[84.3, 95.9]	88.9	[81.2, 94.4]	86.3	[78.0, 92.6]	86.1	[77.4, 92.9]
2014	161	97.7	[93.0, 100.0]	93.9	[87.8, 97.8]	90.9	[84.0, 95.8]	88.6	[81.1, 94.2]	86.8	[78.9, 93.0]
2015	161	97.5	[92.9, 99.8]	96.6	[91.2, 99.7]	96.3	[90.5, 99.9]	92.8	[86.0, 97.6]	92.1	[84.5, 97.6]
2016	156	95.9	[90.6, 98.9]	92.2	[85.7, 96.7]	89.6	[82.2, 94.9]	87.9	[79.4, 94.3]	no FU	–
2017	182	98.8	[94.8, 100.6]	98.0	[93.2, 100.8]	93.9	[86.5, 98.8]	no FU	–	no FU	–



Appendix 2.1.1.5. Chronic myeloid leukaemia - Flanders, exploration

Table 20 – Chronic myeloid leukaemia Flanders (2000-2017): Frequency table of patient and tumour characteristics

Characteristic	Total	Incidence period			
		2000-2003	2004-2008	2009-2013	2014-2017
Overall	1,449	309	377	408	355
Gender					
Male	775 (53.5)	171 (55.3)	203 (53.8)	213 (52.2)	188 (53.0)
Female	674 (46.5)	138 (44.7)	174 (46.2)	195 (47.8)	167 (47.0)
Age at diagnosis (year)					
<50 years	387 (26.7)	78 (25.2)	102 (27.1)	113 (27.7)	94 (26.5)
50-59 years	245 (16.9)	43 (13.9)	61 (16.2)	77 (18.9)	64 (18.0)
60-69 years	305 (21.0)	80 (25.9)	69 (18.3)	82 (20.1)	74 (20.8)
70-79 years	332 (22.9)	70 (22.7)	100 (26.5)	87 (21.3)	75 (21.1)
80+ years	180 (12.4)	38 (12.3)	45 (11.9)	49 (12.0)	48 (13.5)
WHO - Performance Status					
0 – Asymptomatic	358 (24.7)	25 (8.1)	88 (23.3)	122 (29.9)	123 (34.6)
1 – Symptomatic but completely ambulatory	561 (38.7)	55 (17.8)	132 (35.0)	195 (47.8)	179 (50.4)
2 – Symptomatic, <50% in bed during the day	47 (3.2)	7 (2.3)	22 (5.8)	11 (2.7)	7 (2.0)
3 – Symptomatic, >50% in bed, but not bedbound	12 (0.8)	2 (0.6)	2 (0.5)	5 (1.2)	3 (0.8)
4 – Bedbound	9 (0.6)	3 (1.0)	3 (0.8)	1 (0.2)	2 (0.6)
Not reported	462 (31.9)	217 (70.2)	130 (34.5)	74 (18.1)	41 (11.5)

Note: the values between parentheses are column percentages.



Appendix 2.1.1.6. Chronic myeloid leukaemia - Flanders, Observed and Relative Survival graphs

Chronic myeloid leukaemia - Flanders (2000-2017)

Figure 34 – Chronic myeloid leukaemia Flanders (2000-2017), Kaplan-Meier graphs observed survival by incidence period

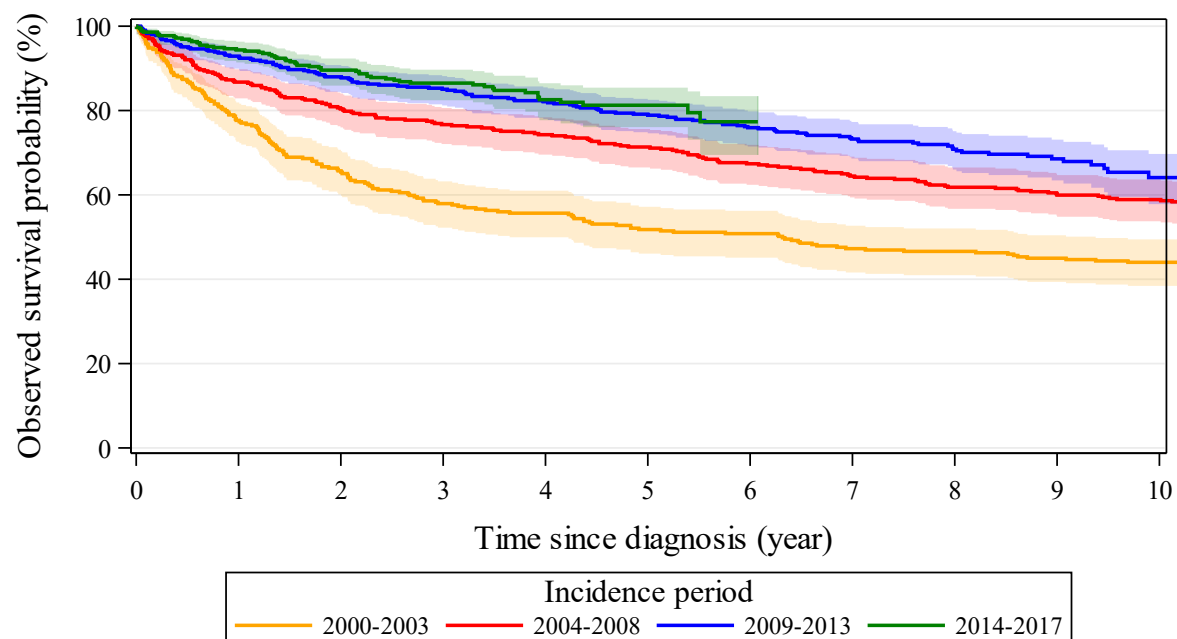
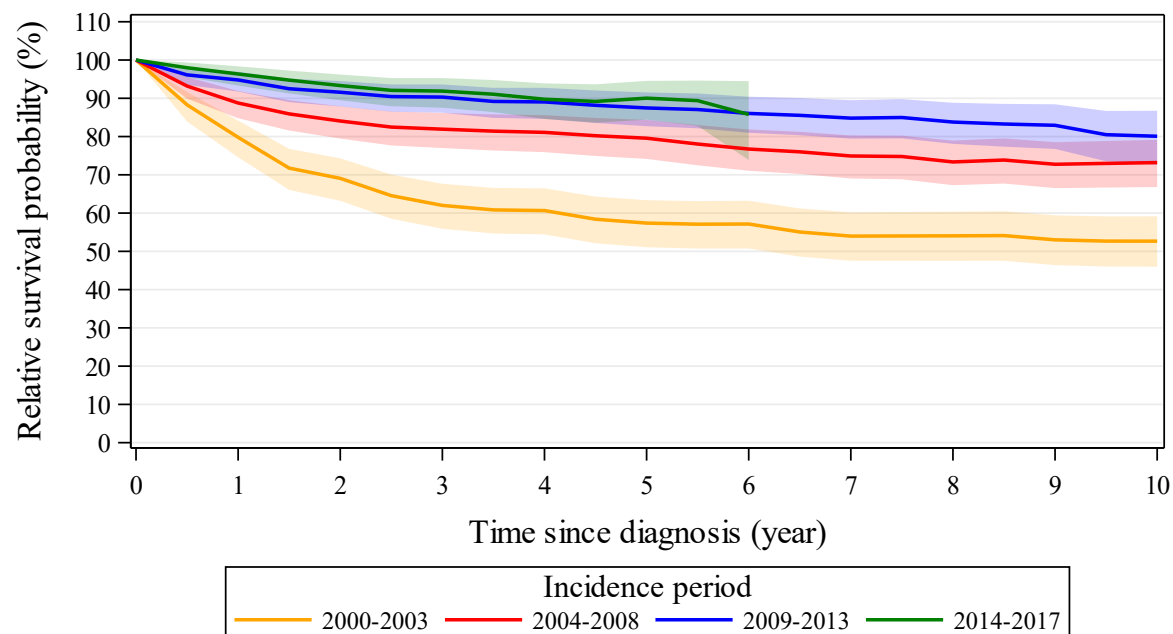




Figure 35 – Chronic myeloid leukaemia Flanders (2000-2017), relative survival graphs by incidence period

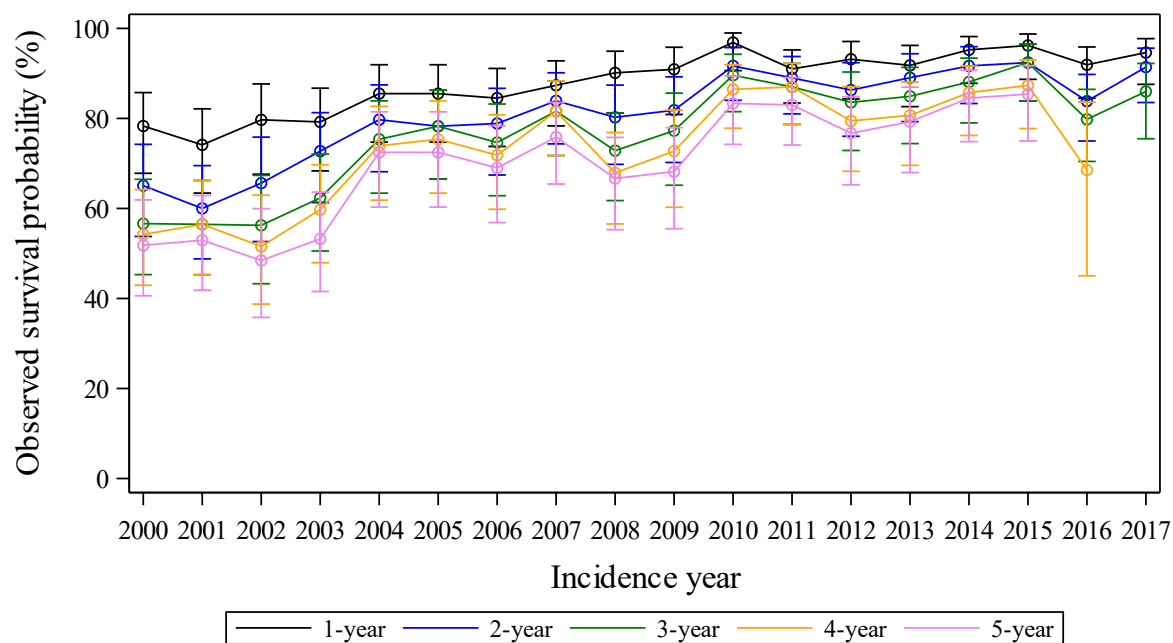




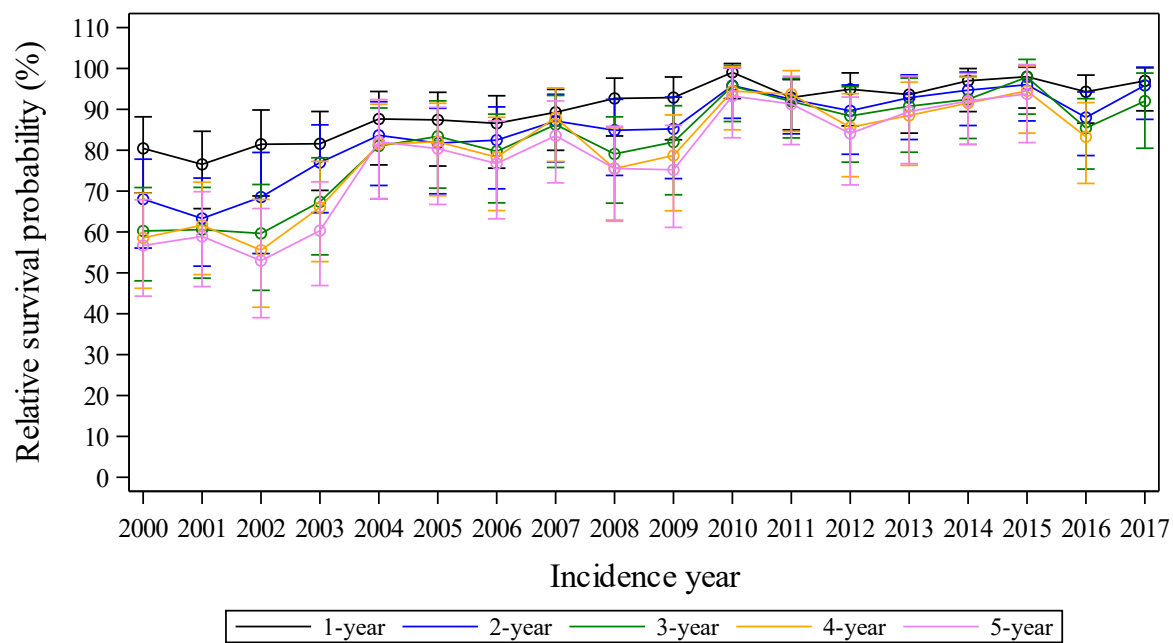
Appendix 2.1.1.7. Chronic myeloid leukaemia - Flanders, time trend Observed and Relative Survival

Chronic myeloid leukaemia - Flanders (2000-2017)

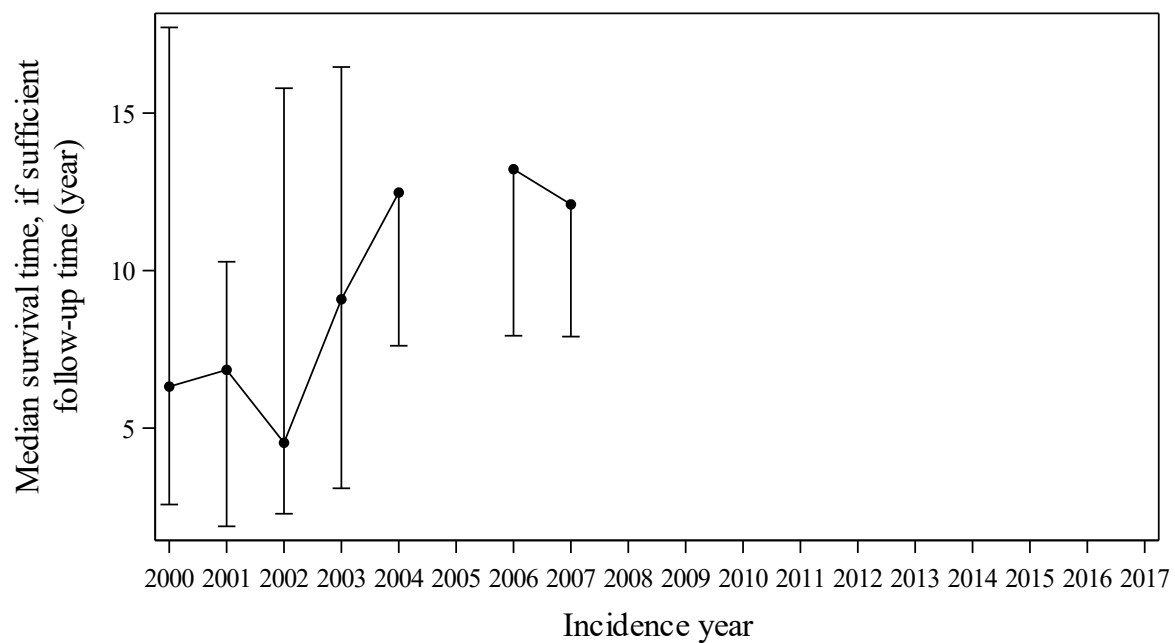
Figure 36 – Chronic myeloid leukaemia Flanders (2000-2017), time trend observed survival with incidence year



Note: the error bars represent the 95% CI.

**Figure 37 – Chronic myeloid leukaemia Flanders (2000-2017), time trend relative survival with incidence year**

Note: the error bars represent the 95% CI.

**Figure 38 – Chronic myeloid leukaemia Flanders (2000-2017), Median time observed survival**

Note: the error bars represent the 95% CI. When the upper error is not plotted, the upper limit could not be determined with the follow-up available.



Appendix 2.1.1.8. Chronic myeloid leukaemia - Flanders, time trend tables Observed and Relative Survival

Table 21 – Chronic myeloid leukaemia Flanders (2000-2017), time trend observed survival with incidence year

Unadjusted observed survival, %													
	1 year			2 year		3 year		4 year		5 year		Median survival time (year)	
	N at risk	%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI	T	95% CI
All													
2000	83	78.3	[67.8, 85.7]	65.1	[53.8, 74.2]	56.6	[45.3, 66.5]	54.2	[42.9, 64.2]	51.8	[40.6, 61.9]	6.3	[2.6, 17.7]
2001	85	74.1	[63.4, 82.1]	60.0	[48.8, 69.5]	56.5	[45.3, 66.2]	56.5	[45.3, 66.2]	52.9	[41.8, 62.9]	6.8	[1.9, 10.3]
2002	64	79.7	[67.6, 87.7]	65.6	[52.6, 75.8]	56.3	[43.3, 67.4]	51.6	[38.8, 63.0]	48.4	[35.8, 60.0]	4.5	[2.3, 15.8]
2003	77	79.2	[68.3, 86.7]	72.7	[61.3, 81.3]	62.3	[50.5, 72.1]	59.7	[47.9, 69.7]	53.2	[41.5, 63.6]	9.1	[3.1, 16.5]
2004	69	85.5	[74.7, 91.9]	79.7	[68.2, 87.4]	75.4	[63.4, 83.9]	73.9	[61.8, 82.7]	72.5	[60.3, 81.5]	12.5	[7.6, .]
2005	69	85.5	[74.7, 91.9]	78.3	[66.6, 86.3]	78.3	[66.6, 86.3]	75.4	[63.4, 83.9]	72.5	[60.3, 81.5]	>15	
2006	71	84.5	[73.8, 91.1]	78.9	[67.4, 86.7]	74.6	[62.8, 83.2]	71.8	[59.8, 80.8]	69.0	[56.9, 78.4]	13.2	[7.9, .]
2007	87	87.4	[78.3, 92.8]	83.9	[74.3, 90.1]	81.6	[71.7, 88.3]	81.6	[71.7, 88.3]	75.9	[65.4, 83.5]	12.1	[7.9, .]
2008	81	90.1	[81.2, 94.9]	80.2	[69.8, 87.4]	72.8	[61.7, 81.2]	67.9	[56.6, 76.9]	66.7	[55.3, 75.8]	>12	
2009	66	90.9	[80.9, 95.8]	81.8	[70.2, 89.2]	77.3	[65.2, 85.6]	72.7	[60.3, 81.9]	68.2	[55.5, 78.0]	>11	
2010	96	96.9	[90.6, 99.0]	91.7	[84.0, 95.7]	89.6	[81.5, 94.3]	86.5	[77.8, 91.9]	83.3	[74.2, 89.4]	>10	
2011	100	91.0	[83.4, 95.2]	89.0	[81.0, 93.8]	87.0	[78.7, 92.2]	87.0	[78.7, 92.2]	83.0	[74.1, 89.1]	>9	
2012	73	93.2	[84.3, 97.1]	86.3	[76.0, 92.4]	83.6	[72.9, 90.3]	79.5	[68.3, 87.1]	76.7	[65.2, 84.8]	>8	
2013	73	91.8	[82.6, 96.2]	89.0	[79.3, 94.4]	84.9	[74.4, 91.3]	80.7	[69.6, 88.1]	79.3	[68.0, 87.0]	>7	
2014	84	95.2	[87.8, 98.2]	91.7	[83.3, 95.9]	88.1	[79.0, 93.4]	85.7	[76.2, 91.6]	84.5	[74.8, 90.7]	>6	
2015	79	96.2	[88.7, 98.8]	92.4	[83.9, 96.5]	92.4	[83.9, 96.5]	87.3	[77.8, 93.0]	85.4	[75.0, 91.7]	>5	
2016	99	91.9	[84.5, 95.9]	83.8	[75.0, 89.8]	79.8	[70.4, 86.5]	68.5	[45.0, 83.6]	no FU	—	>4	
2017	93	94.6	[87.6, 97.7]	91.4	[83.5, 95.6]	86.0	[75.5, 92.2]	no FU	—	no FU	—	>3	


Table 22 – Chronic myeloid leukaemia Flanders (2000-2017), time trend relative survival with incidence year

Unadjusted relative survival, %											
	N at risk	1 year		2 year		3 year		4 year		5 year	
		%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI
All											
2000	83	80.4	[69.5, 88.2]	68.0	[56.1, 77.8]	60.2	[48.0, 70.9]	58.5	[46.2, 69.5]	56.7	[44.3, 67.9]
2001	85	76.5	[65.7, 84.6]	63.3	[51.6, 73.2]	60.6	[48.7, 70.9]	61.7	[49.6, 72.2]	58.9	[46.6, 69.8]
2002	64	81.4	[68.8, 89.8]	68.5	[54.7, 79.4]	59.6	[45.7, 71.6]	55.5	[41.6, 68.0]	53.0	[39.0, 65.7]
2003	77	81.6	[70.2, 89.5]	77.0	[64.7, 86.2]	67.4	[54.4, 78.1]	66.0	[52.8, 77.3]	60.3	[46.9, 72.3]
2004	69	87.6	[76.4, 94.3]	83.6	[71.4, 91.9]	81.0	[68.0, 90.3]	81.5	[68.0, 91.2]	82.1	[68.2, 92.4]
2005	69	87.4	[76.1, 94.1]	81.7	[69.3, 90.2]	83.4	[70.7, 92.1]	82.1	[68.9, 91.5]	80.4	[66.7, 90.5]
2006	71	86.6	[75.6, 93.3]	82.5	[70.5, 90.6]	79.7	[67.1, 88.8]	78.3	[65.2, 88.1]	76.7	[63.2, 87.1]
2007	87	89.3	[80.0, 94.9]	87.1	[77.1, 93.7]	86.3	[75.8, 93.4]	88.0	[77.3, 95.2]	83.6	[72.0, 92.0]
2008	81	92.7	[83.5, 97.6]	84.9	[73.8, 92.4]	79.1	[67.0, 88.2]	75.5	[62.9, 85.5]	75.5	[62.6, 85.8]
2009	66	92.9	[82.5, 97.9]	85.2	[73.0, 93.0]	82.0	[69.1, 90.9]	78.7	[65.2, 88.6]	75.2	[61.1, 86.1]
2010	96	99.0	[92.6, 101.2]	95.8	[87.8, 100.1]	95.7	[87.0, 100.7]	94.5	[85.0, 100.4]	93.3	[83.0, 100.1]
2011	100	92.9	[85.0, 97.3]	92.4	[84.0, 97.5]	91.9	[83.0, 97.6]	93.7	[84.6, 99.5]	91.3	[81.4, 98.1]
2012	73	94.9	[85.9, 98.9]	89.6	[79.0, 95.9]	88.4	[77.1, 95.5]	85.6	[73.5, 93.8]	84.1	[71.5, 93.0]
2013	73	93.6	[84.2, 98.2]	92.8	[82.6, 98.4]	90.7	[79.5, 97.6]	88.5	[76.3, 96.6]	89.5	[76.7, 98.1]
2014	84	97.0	[89.4, 100.0]	94.7	[86.0, 99.1]	92.4	[82.9, 98.0]	91.5	[81.4, 97.8]	92.0	[81.5, 98.8]
2015	79	98.0	[90.3, 100.6]	96.0	[87.2, 100.3]	97.9	[88.8, 102.2]	94.5	[84.2, 100.6]	93.8	[81.9, 100.9]
2016	99	94.3	[86.6, 98.4]	88.0	[78.7, 94.2]	85.4	[75.4, 92.6]	83.3	[71.9, 91.6]	no FU	—
2017	93	96.9	[89.6, 100.2]	95.8	[87.5, 100.3]	92.0	[80.5, 98.9]	no FU	—	no FU	—



Appendix 2.1.2. Uptake of selected drugs

Table 23 – CML: proportion of patients who received at least one dose during 5-year period after diagnosis

Drug/incidence year (n)	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
	129	126	114	145	136	123	164	168	157	144	161	161	156	182
imatinib	79.1%	82.5%	81.6%	84.1%	75.7%	88.6%	82.3%	66.1%	63.1%	62.5%	58.4%	57.8%	67.3%	59.3%
nilotinib	0.8%	7.1%	8.8%	13.1%	14.7%	18.7%	27.4%	43.5%	45.2%	34.7%	26.7%	29.8%	17.9%	22.5%
dasatinib	5.4	5.6%	17.5%	21.4%	17.6%	27.6%	25.0%	26.2%	35.7%	36.1%	42.9%	46.6%	42.9%	45.1%
bosutinib							1.2%	1.8%	4.5%	3.5%	5.6%	3.7%	5.1%	3.8%
ponatinib								2.4%	3.2%	3.5%	4.3%	5.0%	3.8%	3.3%

* Numbers in yellow indicate the first calendar year of reimbursement. For example, nilotinib was first reimbursed in 2008. The columns in this table indicate the incidence year. For example, for incidence year 2006, 8.8% of patients received reimbursed nilotinib during the 5 years after diagnosis. Source: BCR-IMA



Appendix 2.2. reimbursement criteria for selected drugs

Table 24 – Targeted drugs in chronic myeloid leukemia: reimbursement criteria in Belgium

Drug	Trade name	Date start reimbursement	Indication NI	Indication Fr
imatinib	Glivec	1/3/2004 - 2016	vergoeding indien ze gebruikt wordt voor de behandeling van een Philadelphia chromosoom positieve chronische myeloïde leukemie (aanwezigheid van Bcr/Abl gen, of Breakpoint cluster region/Abelson gen) aangetoond met cytogenetische analyse en/of met PCR (Polymerase Chain Reaction) analyse, bij een rechthebbende, <u>vanaf de leeftijd van 3 jaar</u> , bij wie de chronische myeloïde leukemie zich in één van de volgende fasen bevindt: 1) fase van blastencrisis 2) acceleratiefase 3) chronische fase	remboursement que si elle est utilisée pour le traitement d'une leucémie myéloïde chronique avec chromosome de Philadelphie positif (présence d'un gène Bcr/Abl, ou Breakpoint cluster region/Abelson gene) mis en évidence par analyse cytogénétique et/ou par analyse PCR (Polymerase Chain Reaction), chez un bénéficiaire, <u>dès l'âge de 3 ans</u> , dont la leucémie myéloïde chronique se trouve dans une des phases suivantes : 1) Phase de crise blastique 2) Phase d'accélération 3) Phase chronique
		1/11/2016	behandeling van een kind tot en met de leeftijd van 18 jaar, met Philadelphia chromosoom (BCR/ABL1) positieve chronische myeloïde leukemie in één van de volgende situaties: - nieuw gediagnosticeerde Philadelphia chromosoom (BCR/ABL1) positieve chronische myeloïde leukemie, voor wie beenmergtransplantatie niet als eerste lijnsbehandeling wordt beschouwd; - in de chronische fase na falen van interferon-alfa therapie; - in de acceleratiefase of in de blastaire crisis;	du traitement d' un enfant jusqu'à l'âge de 18 ans compris, atteint de leucémie myéloïde chronique chromosome Philadelphie (BCR/ABL1) positive dans une des situations suivantes : - leucémie myéloïde chronique chromosome Philadelphie (BCR/ABL1) positive nouvellement diagnostiquée, lorsque la greffe de moelle osseuse ne peut être envisagée comme un traitement de première intention ; - en phase chronique après échec du traitement par l'interféron alpha; - en phase accélérée ou en crise blastique ;
		1/11/2016	behandeling van volwassen patiënten met nieuw gediagnosticeerde Philadelphia chromosoom (BCR/ABL1) positieve chronische myeloïde leukemie voor wie beenmergtransplantatie niet als eerste lijnsbehandeling wordt beschouwd.	traitement de patients adultes atteints de leucémie myéloïde chronique chromosome Philadelphie (BCR/ABL1) positive nouvellement diagnostiquée lorsque la greffe de moelle osseuse ne peut être envisagée comme un traitement de première intention.
		1/11/2016	behandeling van volwassen patiënten met Philadelphia chromosoom (BCR/ABL1) positieve chronische myeloïde leukemie in de chronische fase na falen van interferon-alfa therapie.	du traitement de patients adultes atteints de leucémie myéloïde chronique chromosome Philadelphie (BCR/ABL1) positive en phase chronique après échec du traitement par l'interféron alpha.



Drug	Trade name	Date start reimbursement	Indication NI	Indication Fr
nilotinib	Tasigna	1/11/2016	volwassen patiënten met Philadelphia chromosoom (BCR/ABL1) positieve chronische myeloïde leukemie in de blastaire crisis	traitement de patients adultes atteints de leucémie myéloïde chronique chromosome Philadelphia (BCR/ABL1) positive en crise blastique.
		1/11/2016	behandeling van volwassen patiënten met Philadelphia chromosoom (BCR/ABL1) positieve chronische myeloïde leukemie in de acceleratiefase	traitement de patients adultes atteints de leucémie myéloïde chronique chromosome Philadelphia (BCR/ABL1) positive en phase accélérée.
		1/9/2008	volwassen chronische myeloïde leukemie: behandeling van een nieuw gediagnosticeerde (< 6 maanden), Philadelphia chromosoom positieve, chronische myeloïde leukemie (aanwezigheid van het BCR/ABL1 of Breakpoint cluster region/Abelson gen), bij een rechthebbende vanaf de leeftijd van 18 jaar, bij wie de chronische myeloïde leukemie zich in chronische fase bevindt	dans la leucémie myéloïde chronique adulte : traitement d'une leucémie myéloïde chronique nouvellement diagnostiquée (< 6 mois), avec chromosome de Philadelphia positif (présence d'un gène BCR/ABL1, ou Breakpoint cluster region/Abelson gene), chez un bénéficiaire, âgé de 18 ans ou plus, dont la leucémie myéloïde chronique se trouve dans la phase chronique
		1/9/2008	volwassen chronische myeloïde leukemia: behandeling van chronische myeloïde leukemie met initiële aanwezigheid van het Philadelphia chromosoom (aanwezigheid van het BCR/ABL1 of Breakpoint cluster region/Abelson gen) in geval van resistentie aan een voorafgaandelijke behandeling met inbegrip van een andere tyrosinekinase inhibitor of in geval van intolerantie die, volgens het klinische oordeel van de arts-specialist vermeld onder punt c), het stopzetten van een behandeling met een andere tyrosinekinase inhibitor wettigt, bij een rechthebbende van 18 jaar of ouder en bij wie de chronische myeloïde leukemie zich in chronische of acceleratiefase bevindt.	dans la leucémie myéloïde chronique adulte : traitement d'une leucémie myéloïde chronique avec présence initiale d'un chromosome de Philadelphia positif (présence d'un gène BCR/ABL1 ou Breakpoint cluster region/Abelson gene) en cas de résistance à un traitement antérieur comprenant un autre inhibiteur de la tyrosine kinase , ou en cas d'intolérance qui, selon le jugement clinique du médecin spécialiste décrit au point c) , justifie l'arrêt du traitement par un autre inhibiteur de la tyrosine kinase chez un bénéficiaire, âgé de 18 ans ou plus, dont la leucémie myéloïde chronique se trouve dans la phase chronique ou accélérée
		1/12/2018	pediatrisch chronische myeloïde leukemia: behandeling van een nieuw gediagnosticeerde (< 6 maanden), Philadelphia chromosoom positieve, chronische myeloïde leukemie (aanwezigheid van het BCR/ABL1 of Breakpoint cluster region/Abelson gen), bij wie de chronische myeloïde leukemie zich in chronische fase bevindt;	chez un enfant de moins de 18 ans dans le cadre du traitement d'une leucémie myéloïde chronique nouvellement diagnostiquée (< 6 mois), avec chromosome de Philadelphia positif (présence d'un gène BCR/ABL1, ou Breakpoint cluster region/Abelson gene), dont la leucémie myéloïde chronique se trouve dans la phase chronique
		1/12/2018	pediatrisch chronische myeloïde leukemia: behandeling van chronische myeloïde leukemie met initiële aanwezigheid van het Philadelphia chromosoom (aanwezigheid van het BCR/ABL1 of Breakpoint cluster region/Abelson gen) in geval van resistentie aan een	chez un enfant de moins de 18 ans dans le cadre du : traitement d'une leucémie myéloïde chronique avec présence initiale d'un chromosome de Philadelphia positif (présence d'un gène BCR/ABL1 ou Breakpoint cluster region/Abelson gene) en cas de résistance à un traitement



Drug	Trade name	Date start reimbursement	Indication NI	Indication Fr
dasatinib	Sprycel		voorafgaandelijke behandeling met inbegrip van een andere tyrosinekinase inhibitor of in geval van intolerantie die, volgens het klinische oordeel van de arts-specialist vermeld onder punt c), het stopzetten van een behandeling met een andere tyrosinekinase inhibitor wettigt, bij een rechthebbende bij wie de chronische myeloïde leukemie zich in chronische fase bevindt.	antérieur comprenant un autre inhibiteur de la tyrosine kinase, ou en cas d'intolérance qui, selon le jugement clinique du médecin spécialiste décrit au point c), justifie l'arrêt du traitement par un autre inhibiteur de la tyrosine kinase, chez un bénéficiaire dont la leucémie myéloïde chronique se trouve dans la phase chronique.
		1/12/2011	bij volwassen chronische myeloïde leukemie: de behandeling van nieuw gediagnosticeerde (< 6 maanden) chronische myeloïde leukemie, in de chronische fase met aanwezigheid van het Philadelphia chromosoom (BCR/ABL1 of Breakpoint cluster region/Abelson fusiegen)	dans la leucémie myéloïde chronique adulte : traitement d'une leucémie myéloïde chronique, nouvellement diagnostiquée (< 6 mois), en phase chronique, avec présence d'un chromosome de Philadelphie gène de fusion BCR/ABL1, ou Breakpoint cluster region/Abelson)
		1/9/2007	bij volwassen chronische myeloïde leukemie: de behandeling van chronische myeloïde leukemie, in chronische of acceleratiefase of blastencrisis, met initiële aanwezigheid van het Philadelphia chromosoom (BCR/ABL1 of Breakpoint cluster region/Abelson fusiegen), in geval van resistentie aan een voorafgaandelijke behandeling met inbegrip van een andere tyrosinekinase inhibitor of in geval van intolerantie die, volgens het klinische oordeel van de arts-specialist vermeld onder punt c), het stopzetten van een behandeling met een andere tyrosinekinase inhibitor wettigt;	dans la leucémie myéloïde chronique adulte : traitement d'une leucémie myéloïde chronique, en phase chronique, en phase accélérée ou en crise blastique, avec présence initiale d'un chromosome de Philadelphie (gène de fusion BCR/ABL1, ou Breakpoint cluster region/Abelson) en cas de résistance à un traitement antérieur comprenant un autre inhibiteur de la tyrosine kinase, ou en cas d'intolérance qui, selon le jugement clinique du médecin spécialiste décrit au point c) , justifie l'arrêt du traitement par un autre inhibiteur de la tyrosine kinase
		1/11/2018	pediatrische chronische myeloïde leukemia: de behandeling van nieuw gediagnosticeerde (< 6 maanden) chronische myeloïde leukemie, in de chronische fase met aanwezigheid van het Philadelphia chromosoom (BCR/ABL1 of Breakpoint cluster region/Abelson fusiegen)	dans la leucémie myéloïde chronique pédiatrique : traitement d'une leucémie myéloïde chronique, nouvellement diagnostiquée (< 6 mois), en phase chronique, avec présence d'un chromosome de Philadelphie (gène de fusion BCR/ABL1, ou Breakpoint cluster region/Abelson)
		1/11/2018	pediatrische chronische myeloïde leukemia: of de behandeling van chronische myeloïde leukemie, in chronische fase, met initiële aanwezigheid van het Philadelphia chromosoom (BCR/ABL1 of Breakpoint cluster region/Abelson fusiegen), in geval van resistentie aan een voorafgaandelijke behandeling met inbegrip van een andere tyrosinekinase inhibitor of in geval van intolerantie die, volgens het klinische oordeel van de arts-specialist vermeld onder punt c), het stopzetten van een	dans la leucémie myéloïde chronique pédiatrique : traitement d'une leucémie myéloïde chronique, en phase chronique, avec présence initiale d'un chromosome de Philadelphie (gène de fusion BCR/ABL1, ou Breakpoint cluster region/Abelson), en cas de résistance à un traitement antérieur comprenant un autre inhibiteur de la tyrosine kinase, ou en cas d'intolérance qui, selon le jugement clinique du médecin spécialiste décrit au point



Drug	Trade name	Date start reimbursement	Indication NI	Indication Fr
Bosutinib	Bosulif	1/4/2014	<p>behandeling met een andere tyrosinekinase inhibitor wettigt</p> <p>bij een rechthebbende van 18 jaar of ouder, in het kader van de behandeling van chronische myeloïde leukemie in de chronische fase, de acceleratiefase of de blastencrisis, met initiële aanwezigheid van het Philadelphia chromosoom (BCR/ABL1 of Breakpoint cluster region/Abelson fusiegen) in geval van ongeschiktheid van een andere tyrosinekinaseinhibitor volgens het klinische oordeel van de arts-specialist (erkend is in de inwendige geneeskunde houder van de bijzondere beroepstitel in de klinische hematologie in de hematologie).</p> <p>De ongeschiktheid van een tyrosinekinaseinhibitor veronderstelt:</p> <ul style="list-style-type: none"> • Therapieresistentie aan de tyrosinekinaseinhibitor. Voor deze patiënten komt de specialiteit bovendien enkel in aanmerking bij wie geen mutatie van het type T315I of V299L aanwezig is zoals aangetoond in een daartoe geschikte analyse. • Of de aanwezigheid van medische aandoeningen of eerdere intoleranties die de patiënt kunnen voorbestemmen voor een onaanvaardbaar risico in het kader van een behandeling met de tyrosinekinaseinhibitor (TKI). <p>De ongeschiktheid van een behandeling met een andere TKI ten gevolge van therapieresistentie veronderstelt voor:</p> <ul style="list-style-type: none"> • Imatinib: <ul style="list-style-type: none"> - falen van een eerdere behandeling met imatinib (zie failure criteria van European Leukemia.Net (ELN) (Baccarani 2013)) • Nilotinib: <ul style="list-style-type: none"> - falen van een eerdere behandeling met nilotinib (zie failure criteria van European Leukemia.Net (ELN) (Baccarani 2013)) 	<p>c), justifie l'arrêt du traitement par un autre inhibiteur de la tyrosine kinase.</p> <p>administrée, chez un bénéficiaire, âgé de 18 ans ou plus, dans le cadre du traitement d'une leucémie myéloïde chronique en phase chronique, en phase accélérée ou en crise blastique avec présence initiale d'un chromosome de Philadelphie (gène de fusion BCR/ABL1, ou Breakpoint cluster region/Abelson) en cas d' inadéquation d'un autre inhibiteur de la tyrosine kinase, selon le jugement clinique du médecin spécialiste (agréé en médecine interne porteur du titre professionnel particulier en hématologie clinique).</p> <p>L'inadéquation d' inhibiteur de la tyrosine kinase implique :</p> <ul style="list-style-type: none"> • Une résistance de thérapie à l'inhibiteur de la tyrosine kinase. Pour ces patients, en plus, la spécialité fait seulement l'objet d'un remboursement chez qui une mutation du type T315I ou V299L n'est pas présente, comme démontrée dans une analyse adéquate. • Ou la présence des conditions médicales ou des intolérances antérieures qui peuvent prédestiner le patient à un risque inacceptable dans le cadre d'un traitement avec un inhibiteur de la tyrosine kinase (ITK). <p>L'inadéquation d'un traitement avec un autre ITK à cause d'une résistance de thérapie implique pour :</p> <ul style="list-style-type: none"> • Imatinib : <ul style="list-style-type: none"> - l'échec d'un traitement antérieur avec imatinib (voir failure criteria de European Leukemia.Net (ELN) (Baccarani 2013)) • Nilotinib : <ul style="list-style-type: none"> - l'échec d'un traitement antérieur avec nilotinib (voir failure criteria de European Leukemia.Net (ELN) (Baccarani 2013)) - ou la présence d'une des mutations suivantes, associée à la résistance de nilotinib : E255, Y253, F359 • Dasatinib :



Drug	Trade name	Date start reimbursement	Indication NI	Indication Fr
			<ul style="list-style-type: none"> - of de aanwezigheid van één van de volgende mutaties die gelinkt zijn aan resistentie aan nilotinib : E255, Y253, F359 • Dasatinib : - falen van een eerdere behandeling met dasitinib (zie failure criteria van European Leukemia.Net (ELN) (Baccarani 2013) - of de aanwezigheid van één van de volgende mutaties die gelinkt zijn aan resistentie aan dasatinib : F317, E255 <p>De ongeschiktheid van een behandeling met andere TKI ten gevolge van de aanwezigheid van medische aandoeningen of eerdere intoleranties die de patiënt kunnen voorbestemmen voor een onaanvaardbaar risico in het kader van een behandeling met de TKI veronderstelt de aanwezigheid van één of meerdere van de volgende aandoeningen:</p> <ul style="list-style-type: none"> • Voor nilotinib : Coronaire occlusie, coronaire stent of angioplastie of bypass, arteriële occlusieve ziekte, coronair lijden, arteriosclerose, gestoorde glucose tolerantie, hyperglycemie, hypertriglyceridemie, diabetes, pancreatitis. • Voor dasatinib: Pleura uitstorting, interstitieel longlijden, chronic obstructive pulmonary disease, chronische bronchitis, arteriële pulmonale hypertensie, pulmonale fibrose, longoedeem, emfyseem, hypertensie (Graad 3 of 4), cardiomyopathie, hartdecompensatie, ventrikel falen, ventriculaire dysfunctie, myocardi infarct, myocardiale ischemie, respiratoire aandoening. 	<ul style="list-style-type: none"> - l' échec d'un traitement antérieur avec dasitinib (voir failure criteria de European Leukemia.Net (ELN) (Baccarani 2013) - ou la présence d'une des mutations suivantes, associée à la résistance de dasatinib : F317, E255 <p>L' inadéquation d'un traitement avec un autre ITK à cause de la présence des conditions médicales ou des intolérances antérieures qui peuvent prédestiner le patient à un risque inacceptable dans le cadre d'un traitement avec l'ITK implique la présence d'une ou plus des conditions médicales suivantes :</p> <ul style="list-style-type: none"> • Pour nilotinib : occlusion coronaire, stent ou angioplastie ou pontage coronaire, maladie artérielle occlusive, coronaropathie, artériosclérose, une tolérance de glucose altérée, hyperglycémie, hypertriglycéridémie, diabète, pancréatite. • Pour dasatinib: épanchement pleural, maladie pulmonaire interstitielle, broncho-pneumopathie chronique obstructive, bronchite chronique, hypertension artérielle pulmonaire, fibrose pulmonaire, œdème pulmonaire, emphysème, hypertension (Grade 3 ou 4), cardiomyopathie, insuffisance cardiaque, insuffisance ventriculaire, dysfonction ventriculaire, infarctus du myocarde, ischémie myocardique, affection respiratoire.
		1/3/2019	de behandeling van nieuw gediagnosticeerde (< 6 maanden) chronische myeloïde leukemie in de chronische fase met initiële aanwezigheid van het Philadelphia chromosoom (BCR/ABL1 of Breakpoint cluster region/Abelson gen).	administrée, chez un bénéficiaire âgé de 18 ans ou plus, dans le cadre du traitement d'une leucémie myéloïde chronique nouvellement diagnostiquée (< 6 mois) en phase chronique avec présence initiale d'un chromosome de Philadelphie (gène de fusion BCR/ABL1 ou Breakpoint cluster region/Abelson).
ponatinib	Iclusig	1/3/2016	toegediend, bij een rechthebbende van 18 jaar of ouder, in het kader van :	administrée, chez un bénéficiaire âgé de 18 ans ou plus, dans le cadre :



Drug	Trade name	Date start reimbursement	Indication NI	Indication Fr
			<p>1. de behandeling van chronische myeloïde leukemie in de chronische fase, de accelaratiefase of de blastencrisis met initiële aanwezigheid van het Philadelphia chromosoom (aanwezigheid van het BCR/ABL1 of Breakpoint cluster region/Abelson gen)</p> <p>- die resistent voor dasatinib of nilotinib is of die intolerant voor dasatinib of nilotinib is en voor wie een vervolgbehandeling met imatinib klinisch niet aangewezen is, en die, volgens het klinische oordeel van de arts-specialist vermeld onder punt c) het stopzetten van een behandeling met deze andere tyrosinekinaseinhibitor wettigt</p> <p>- of die de T315I-mutatie heeft</p> <p>2. of de behandeling van een acute lymphoblasten leukemie met initiële aanwezigheid van het Philadelphia chromosoom (aanwezigheid van het BCR/ABL1 of Breakpoint cluster region/Abelson gen),</p> <p>- die resistent voor dasatinib is of die intolerant voor dasatinib is en voor wie een vervolgbehandeling met imatinib klinisch niet aangewezen is,</p> <p>- of die de T315I-mutatie heeft.</p>	<p>1. du traitement d'une leucémie myéloïde chronique en phase chronique, en phase accélérée ou en crise blastique, avec présence initiale d'un chromosome de Philadelphie (présence d'un gène BCR/ABL1, ou Breakpoint cluster region/Abelson gene)</p> <p>- qui présente une résistance au dasatinib ou au nilotinib ou une intolérance au dasatinib ou au nilotinib et pour qui un traitement ultérieur par imatinib n'est pas cliniquement approprié, et qui, selon le jugement clinique du médecin spécialiste décrit au point c) , justifie un arrêt de traitement par cet autre inhibiteur de la tyrosine kinase</p> <p>- ou qui exprime la mutation T315I</p> <p>2. ou du traitement d'une leucémie aiguë lymphoblastique avec présence initiale d'un chromosome de Philadelphie (présence d'un gène BCR/ABL1, ou Breakpoint cluster region/Abelson gene)</p> <p>- qui présente une résistance au dasatinib ou une intolérance au dasatinib et pour qui un traitement ultérieur par imatinib n'est pas cliniquement approprié,</p> <p>- ou qui exprime la mutation T315I.</p>



Appendix 2.3. Medical literature: search for evidence

Appendix 2.3.1. Search medical literature (systematic reviews)

The search for systematic reviews in MEDLINE, PreMedline and the Cochrane library of systematic reviews (inception to search date) specifically developed for this research question, yielded 84 records (Figure 63). After de-duplication, 84 (2020-1999) reviews were screened based on title and abstract, of which 50 were excluded. In total 34 full text articles were assessed for eligibility. Based on full text evaluation, 28 reviews were excluded (Figure 64).

Figure 39 – Chronic myeloid leukaemia – Selection of SRs - Study flow

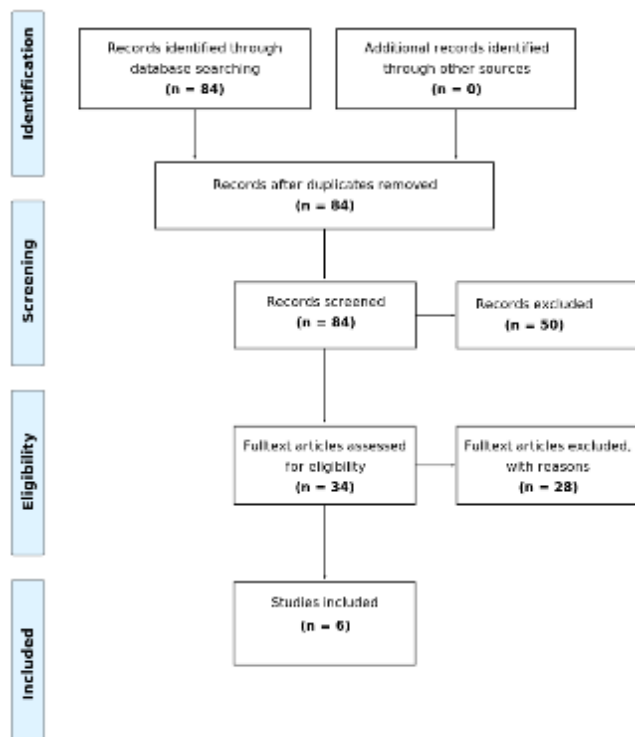


**Table 25 – CML: excluded reviews and reason for exclusion**

	Year	Publication	Reason for exclusion
1	2020	Efficace, F. Stagno, F. Iurlo, A. et al. Health-related quality of life of newly diagnosed chronic myeloid leukemia patients treated with first-line dasatinib versus imatinib therapy. <i>Leukemia</i> 2020; 34(2):488-498	Not a systematic review
2	2020	Warraich, Z. Tenneti, P. Thai, T. et al. Relapse Prevention with Tyrosine Kinase Inhibitors after Allogeneic Transplantation for Philadelphia Chromosome-Positive Acute Lymphoblast Leukemia: A Systematic Review. <i>Biol Blood Marrow Transplant</i> 2020;26(3):e55-e64	wrong patient group
3	2020	Vener, C. Banzi, R. Ambroggi, F. et al. First-line imatinib vs second- and third-generation TKIs for chronic-phase CML: a systematic review and meta-analysis. <i>Blood Adv</i> 2020;4(12):2723-2735	Included
4	2020	Pan, P. Wang, L. Wang, Y. et al. Systematic Review and Meta-Analysis of -New-Generation Tyrosine Kinase Inhibitors versus Imatinib for Newly Diagnosed Chronic Myeloid Leukemia. <i>Acta Haematol</i> 2020;143(3):204-216	No additional information
5	2020	Haguet, H. Graux, C. Mullier, F. et al. Long-Term Survival, Vascular Occlusive Events and Efficacy Biomarkers of First-Line Treatment of CML: A Meta-Analysis. <i>Cancers (Basel)</i> 2020;12(5):15	No additional information
6	2019	Tang, L. Zhang, H. Peng, Y. Z. et al. Comparative efficacy and tolerability of front-line treatments for newly diagnosed chronic-phase chronic myeloid leukemia: an update network meta-analysis. <i>BMC Cancer</i> 2019;19(1):849	Included (No OS or QoL as outcome)
7	2019	Pan, P. Wang, L. Wang, Y. et al. Systematic Review and Meta-Analysis of -New-Generation Tyrosine Kinase Inhibitors versus Imatinib for Newly Diagnosed Chronic Myeloid Leukemia. <i>Acta Haematol</i> 2019; Sep 12:1-13. doi:10.1159/000501537. [Epub ahead of print]	Review of reviews
8	2019	Kim, J. Park, J. Moon, Y. et al. Effect of study-level factors on treatment-free remission rate in patients with chronic myeloid leukemia: a systematic review and meta-analysis. <i>Int J Hematol</i> 2019;110(6):683-689	Wrong outcomes
9	2018	Fu, J. Liu, Y. Lin, H. Wu, B. Economic Evaluations of Tyrosine Kinase Inhibitors for Patients with Chronic Myeloid ;Leukemia in Middle- and High-Income Countries: A Systematic Review. <i>Clin Drug Invest</i> ; 38(12):1167-1178	No clinical outcomes. No original economic evaluation.
10	2018	Fachi, M. M. Tonin, F. S. Leonart, L. P. et al. Comparative efficacy and safety of tyrosine kinase inhibitors for chronic myeloid leukaemia: A systematic review and network meta-analysis. <i>Eur J Cancer</i> 2018; 104:9-20	All results included in Tang et al.
11	2018	Chen, K. K. Du, T. F. Wu, K. S. et al. First-line treatment strategies for newly diagnosed chronic myeloid leukemia: a network meta-analysis. <i>Cancer Manag Res</i> 2018; 10:3891-3910	results included in Tang et al, unclear which studies included for OS analysis
12	2017	Hoffmann, V. S. Hasford, J. Deininger, M. et al. Systematic review and meta-analysis of standard-dose imatinib vs. high-dose imatinib and second generation tyrosine kinase inhibitors for chronic myeloid leukemia. <i>J Cancer Res Clin Oncol</i> 2017; 143(7):1311-1318	Searched only 1 database
13	2017	Haguet, H. Dauxfils, J. Mullier, F. et al. Risk of arterial and venous occlusive events in chronic myeloid leukemia patients treated with new generation BCR-ABL tyrosine kinase inhibitors: a systematic review and meta-analysis. <i>Expert Opin Drug Saf</i> 2017; 16(1):5-12	No general results on SAEs
14	2016	Yun, S. Vincelette, N. D. Segar, J. M. et al. Comparative Effectiveness of Newer Tyrosine Kinase Inhibitors Versus Imatinib in the First-Line Treatment of Chronic-Phase Chronic Myeloid Leukemia Across Risk Groups: A Systematic Review and Meta-Analysis of Eight Randomized Trials.	No added information



Year	Publication	Reason for exclusion
15	2016 Gurion, R. Raanani, P. Vidal, L. et al. First line treatment with newer tyrosine kinase inhibitors in chronic myeloid leukemia associated with deep and durable molecular response - systematic review and meta-analysis. <i>Acta Oncol</i> 2016;55(9):1077-1083	Included for (OS)
16	2016 Firwana, B. Sonbol, M. B. Diab, M. et al. Tyrosine kinase inhibitors as a first-line treatment in patients with newly diagnosed chronic myeloid leukemia in chronic phase: A mixed-treatment comparison. <i>Int J Cancer</i> 2016; 138(6):1545-53	No added information
17	2016 Douchfils, J. Haguet, H. Mullier, F. et al. Association Between BCR-ABL Tyrosine Kinase Inhibitors for Chronic Myeloid Leukemia and Cardiovascular Events, Major Molecular Response, and Overall Survival: A Systematic Review and Meta-analysis.	Included (OS)
18	2016 Chai-Adisaksopha, C. Lam, W. Hillis, C. Major arterial events in patients with chronic myeloid leukemia treated with tyrosine kinase inhibitors: a meta-analysis. <i>Leuk Lymphoma</i> 2016; 57(6):1300-10	No added information
19	2015 Saret, C. J. Winn, A. N. Shah, G. et al. Value of innovation in hematologic malignancies: a systematic review of published cost-effectiveness analyses. <i>Blood</i> 2015; 125(12): 1866-9	No clinical outcomes. No original economic evaluation.
20	2015 Park, J. Kwon, H. Shin, M. et al. Comparative Efficacy Of Imatinib, Dasatinib And Nilotinib For Newly Diagnosed Chronic Myeloid Leukemia In Chronic Phase (Cml-Cp): A Meta-Analysis And Indirect Comparison. <i>Value Health</i> 2015; 18(7):A433	Abstract
21	2015 Lipton, J. H. Bryden, P. Sidhu, M. K. et al. Comparative efficacy of tyrosine kinase inhibitor treatments in the third-line setting, for chronic-phase chronic myelogenous leukemia after failure of second-generation tyrosine kinase inhibitors. <i>Leuk Res</i> 2015; 39(1):58-64	No critical appraisal (no RCTs identified)
22	2013 Mealing, S. Barcena, L. Hawkins, N. et al. The relative efficacy of imatinib, dasatinib and nilotinib for newly diagnosed chronic myeloid leukemia: a systematic review and network meta-analysis. <i>Experimental Hematology & Oncology</i> 2013, 2:5	No additional information
23	2013 Efficace, F. Cardoni, A. Cottone, F. et al. Tyrosine-kinase inhibitors and patient-reported outcomes in chronic myeloid leukemia: a systematic review. <i>Leuk Res</i> 2013; 37(2):206-213	Included
24	2013 Breccia, M. Salaroli, A. Molica, M. et al. Systematic review of dasatinib in chronic myeloid leukemia. <i>Onco Targets Ther</i> 2013; 6:257-65	searched only 1 database
25	2013 Gurion, R. Gafer-Gvili, A. Vidal, L. et al. Has the time for first-line treatment with second generation tyrosine kinase inhibitors in patients with chronic myelogenous leukemia already come? Systematic review and meta-analysis. <i>Haematologica</i> 2013; 98(1) :95-102	No additional information
26	2012 Rogers, G. Hoyle, M. Thompson Coon, J. et al. Dasatinib and nilotinib for imatinib-resistant or -intolerant chronic myeloid leukaemia: a systematic review and economic evaluation. <i>Health Technol Assess</i> 2012; 16(22):1-140	No additional information (included in HE summary)
27	2012 Pavey, T. Hoyle, M. Ciani, O. et al. Dasatinib, nilotinib and standard-dose imatinib for the first-line treatment of chronic myeloid leukaemia: systematic reviews and economic analyses. <i>Health Technol Assess</i> 2012; 16(42):1-277	No additional information (included in HE summary)
28	2012 Loveman, E. Cooper, K. Bryant, J. et al. Dasatinib, high-dose imatinib and nilotinib for the treatment of imatinib-resistant chronic myeloid leukaemia: a systematic review and economic evaluation. 2012; 16(23):1-137	Included



	Year	Publication	Reason for exclusion
29	2012	Efficace, F. Cocks, K. Breccia, M. et al. Time for a new era in the evaluation of targeted therapies for patients with chronic myeloid leukemia: inclusion of quality of life and other patient-reported outcomes Crit Rev Oncol Hematol 2012; 81(2):123-35	No additional information
30	2011	Li, J. Xu, G. Yu, S. et al. Dasatinib treatment for imatinib resistant or intolerant patients with chronic myeloid leukaemia. J Int Med Res 2011; 39(2):337-47	No additional information
31	2010	von Bubnoff, N. Duyster, J. Chronic myelogenous leukemia: treatment and monitoring. Dtsch Arztebl Int 2010; 107(7): 114–21	Narrative review
32	2008	Efficace, F. Kemmler, G. Vignetti, M. et al. Health-related quality of life assessment and reported outcomes in leukaemia randomised controlled trials - a systematic review to evaluate the added value in supporting clinical decision making. Eur J Cancer 2008; 44(11):1497-506	No additional information
33	2004	Dalziel, K. Round, A. Stein, K. et al. Effectiveness and cost-effectiveness of imatinib for first-line treatment of chronic myeloid leukaemia in chronic phase: a systematic review and economic analysis. Health Technol Assess 2004; 8(28):1-120	No additional information
34	2002	Garside, R. Round, A. Dalziel, K. et al. The effectiveness and cost-effectiveness of imatinib in chronic myeloid leukaemia: a systematic review. Health Technol Assess 2002; 6(33):1-162	No additional information



Appendix 2.3.2. Critical appraisal systematic reviews

	Tang 2019 ²⁸		Douxfls 2016 ²⁹	
	Score	Rationale/comment	score	Rationale/comment
1. PICO	Y		Y	
2. A priori study design	N		Y	
3. Inclusion study designs	N		N	
4. Comprehensive literature search	Partial Y	No search in grey literature, trial registries, no consultation of experts, search date unclear	Partial Y	No search in grey literature, no consultation of experts
5. Duplicate study selection	Y		Y	
6. Duplicate data extraction	Y		Y	
7. List of excluded studies and rationale	N		N	
8. Characteristics of included studies provided	partial Y		Partial Yes	No description of study setting and timeframe of follow-up
9. Assessment of risk of bias	Partial Yes	no explicit assessment of "selection of the reported result from among multiple measurements or analyses of s specified outcome (all other items assessed)	Partial Yes	used Jadad score
10. Sources of funding reported	No	NMA supported by grants from the National Natural Science Foundation of China. Sources of funding of the individual studies not reported.	No	
11. Appropriate methods to combine findings	N	appropriate methods to combine results but causes of any heterogeneity were only partly investigated (not for direct comparisons)	Y	Both fixed and random effects models are reported
12. Assessment of impact RoB in included studies on results MA	N		N	
13. RoB assessment used in interpretation of results and in conclusions	N		N	
14. Explanation for and discussion of any observed heterogeneity	Y	For NMA	Y	



Tang 2019 ²⁸		Douxflis 2016 ²⁹			
	Score	Rationale/comment		score	Rationale/comment
15. Adequate investigation of publication bias and its impact on the results	Y			Y	
16. Potential sources of conflict of interest reported	Y			Y	

Gurion 2016 ³⁰			Efficace 2013 ³¹	
	Score	Rationale/comment	score	Rationale/comment
1. PICO	Y		Y	
2. A priori study design	N		N	
3. Inclusion study designs	N		Y	
4. Comprehensive literature search	Partial Yes	No search in grey literature, no consultation of experts	Partial yes	no search of reference lists, grey literature and trial registries
5. Duplicate study selection	Y		Y	
6. Duplicate data extraction	Y		Y	
7. List of excluded studies and rationale	N		N	
8. Characteristics of included studies provided	Partial Yes	few details	Y	
9. Assessment of risk of bias	Y		N*	
10. Sources of funding reported	N	No funding received for MA, sources of funding of individual studies not reported	N	No funding received for MA, sources of funding of individual studies not reported
11. Appropriate methods to combine findings	Y		NA	
12. Assessment of impact RoB in included studies on results MA	N		N	
13. RoB assessment used in interpretation of results and in conclusions	N		Y	The paucity of high quality data is stressed
14. Explanation for and discussion of any observed heterogeneity	N		N	



	Gurion 2016 ³⁰		Efficace 2013 ³¹	
	Score	Rationale/comment	score	Rationale/comment
15. Adequate investigation of publication bias and its impact on the results	N		N	
16. Potential sources of conflict of interest reported	Y		Y	

*SR included in spite of not having performed risk of bias assessment of included studies, as no other SR on QoL available.

Loveman 2012 ³²		Vener 2020 ³³			
	Score	Rationale/comment		score	Rationale/comment
1.	PICO	Y		Y	
2.	A priori study design	Y		Y	
3.	Inclusion study designs	Y		Y	
4.	Comprehensive literature search	Y		Y	
5.	Duplicate study selection	Y		Y	
6.	Duplicate data extraction	Y		Y	
7.	List of excluded studies and rationale	Y		N	
8.	Characteristics of included studies provided	Y		Y	
9.	Assessment of risk of bias	Y		Y	
10.	Sources of funding reported	Y		N	
11.	Appropriate methods to combine findings	NA		Y	
12.	Assessment of impact RoB in included studies on results MA	Y		N	
13.	RoB assessment used in interpretation of results and in conclusions	Y		N	
14.	Explanation for and discussion of any observed heterogeneity	NA		N	
15.	Adequate investigation of publication bias and its impact on the results	N		Y	(unclear)



	Loveman 2012 ³²		Vener 2020 ³³	
	Score	Rationale/comment	score	Rationale/comment
16. Potential sources of conflict of interest reported	Y		Y	

Appendix 2.3.3. Search strategy

Appendix 2.3.3.1. Cochrane library of systematic reviews

Date	24/06/2020 13:20:06		
Database	Cochrane@Wiley.com		
Search strategy			
#1	[mh "Leukemia, Myelogenous, Chronic, BCR-ABL Positive"]		485
#2	"chronic granulocytic" NEAR/3 (leukemia or leukemias or leukaemia or leukaemias):ab,ti		30
#3	"chronic myelocytic" NEAR/3 (leukemia or leukemias or leukaemia or leukaemias):ab,ti		27
#4	"chronic myelogenous" NEAR/3 (leukemia or leukemias or leukaemia or leukaemias):ab,ti		336
#5	"chronic myeloid" NEAR/3 (leukemia or leukemias or leukaemia or leukaemias):ab,ti		1002
#6	"ph1-positive myelogenous" NEAR/3 (leukemia or leukemias or leukaemia or leukaemias):ab,ti		0
#7	"ph1-positive myeloid" NEAR/3 (leukemia or leukemias or leukaemia or leukaemias):ab,ti		0
#8	"ph1-positive myelocytic" NEAR/3 (leukemia or leukemias or leukaemia or leukaemias):ab,ti		0
#9	"ph1-positive granulocytic" NEAR/3 (leukemia or leukemias or leukaemia or leukaemias):ab,ti		0
#10	"philadelphia-positive myeloid" NEAR/3 (leukemia or leukemias or leukaemia or leukaemias):ab,ti		0
#11	"philadelphia-positive myelocytic" NEAR/3 (leukemia or leukemias or leukaemia or leukaemias):ab,ti		0
#12	"philadelphia-positive myelogenous" NEAR/3 (leukemia or leukemias or leukaemia or leukaemias):ab,ti		0
#13	"philadelphia-positive granulocytic" NEAR/3 (leukemia or leukemias or leukaemia or leukaemias):ab,ti		0
#14	chronic NEAR/3 (myeloleukemia or myeloleukaemia or myeloleukemias or myeloleukaemias):ab,ti		1
#15	"bcr-abl positive myelogenous" NEAR/3 (leukemia or leukemias or leukaemia or leukaemias):ab,ti		0
#16	"bcr-abl positive myelocytic" NEAR/3 (leukemia or leukemias or leukaemia or leukaemias):ab,ti		0



Date	24/06/2020 13:20:06	
#17	"bcr-abl positive myeloid" NEAR/3 (leukemia or leukemias or leukaemia or leukaemias):ab,ti	0
#18	"bcr-abl positive granulocytic" NEAR/3 (leukemia or leukemias or leukaemia or leukaemias):ab,ti	0
#19	(blast NEAR/2 crises):ab,ti	121
#20	(blast NEAR/2 crisis):ab,ti	121
#21	(blast NEAR/2 phase?):ab,ti	129
#22	(blastic NEAR/2 crises):ab,ti	16
#23	(blastic NEAR/2 crisis):ab,ti	16
#24	(blastic NEAR/2 phase?):ab,ti	43
#25	(leukemia or leukemias or leukaemia or leukaemias) NEAR/3 "myeloid accelerated-phase":ab,ti	0
#26	(leukemia or leukemias or leukaemia or leukaemias) NEAR/3 "myelocytic accelerated-phase":ab,ti	0
#27	(leukemia or leukemias or leukaemia or leukaemias) NEAR/3 "myelogenous accelerated-phase":ab,ti	0
#28	(leukemia or leukemias or leukaemia or leukaemias) NEAR/3 "granulocytic accelerated-phase":ab,ti	0
#29	(myeloid NEAR/3 (leukemia or leukemias or leukaemia or leukaemias) NEAR/3 aggressive-phase):ab,ti	0
#30	(myelocytic NEAR/3 (leukemia or leukemias or leukaemia or leukaemias) NEAR/3 aggressive-phase):ab,ti	0
#31	(myelogenous NEAR/3 (leukemia or leukemias or leukaemia or leukaemias) NEAR/3 aggressive-phase):ab,ti	0
#32	(granulocytic NEAR/3 (leukemia or leukemias or leukaemia or leukaemias) NEAR/3 aggressive-phase):ab,ti	0
#33	CML:ab,ti	1642
#34	(philadelphia NEAR/3 (leukemia or leukemias or leukaemia or leukaemias)):ab,ti	28
#35	granular NEAR/3 blast?:ab,ti	0
#36	myeloproliferative NEAR/3 neoplasm?:ab,ti	183
#37	myeloblastic NEAR/3 transformation?:ab,ti	2
#38	myeloid NEAR/3 neoplasm?:ab,ti	44
#39	(leukemic or leukaemic) NEAR/3 blast?:ab,ti	132
#40	#2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39	2422
#41	#1 or #40	2523



Date	24/06/2020 13:20:06	
#42	[mh ^"Imatinib Mesylate"]	393
#43	Imatinib:ab,ti	1344
#44	GLAMOX:ab,ti	1
#45	Gleevec:ab,ti	96
#46	Glivec:ab,ti	103
#47	Glivic:ab,ti	1
#48	Ruvise:ab,ti	0
#49	STI571:ab,ti	75
#50	"STI 571":ab,ti	12
#51	"ST 1571":ab,ti	0
#52	ST1571:ab,ti	8
#53	"signal transduction inhibitor 571":ab,ti	0
#54	"CGP 57148":ab,ti	0
#55	CGP57148:ab,ti	0
#56	"CGP 57148B":ab,ti	0
#57	CGP57148B:ab,ti	0
#58	BKJ8M8G5HI:ab,ti	0
#59	"152459-95-5":ab,ti	12
#60	"220127-57-1":ab,ti	11
#61	#43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60	1366
#62	#42 or #61	1376
#63	nilotinib:ab,ti	360
#64	Tasigna:ab,ti	34
#65	F41401512X:ab,ti	0
#66	"641571-10-0":ab,ti	11
#67	"AMN 107":ab,ti	3



Date	24/06/2020 13:20:06	
#68	AMN107:ab,ti	21
#69	#63 or #64 or #65 or #66 or #67 or #68	367
#70	[mh ^"Dasatinib"]	100
#71	dasatinib:ab,ti	407
#72	sprycel:ab,ti	48
#73	"bms 354825":ab,ti	31
#74	bms354825:ab,ti	0
#75	RBZ1571X5H:ab,ti	0
#76	#71 or #72 or #73 or #74 or #75	412
#77	#70 or #76	423
#78	bosutinib:ab,ti	105
#79	bosulif:ab,ti	5
#80	5018V4AEZ0:ab,ti	0
#81	"SK-606":ab,ti	0
#82	"SKI-606":ab,ti	19
#83	SK606:ab,ti	0
#84	SKI606:ab,ti	0
#85	"380843-75-4":ab,ti	6
#86	#78 OR #79 OR #80 OR #81 OR #82 OR #83 OR #84 OR #85	108
#87	ponatinib:ab,ti	69
#88	iclusig:ab,ti	3
#89	4340891KFS:ab,ti	0
#90	"AP-24534":ab,ti	0
#91	AP24534:ab,ti	6
#92	"1114544-31-8":ab,ti	2
#93	"943319-70-8":ab,ti	3



Date	24/06/2020 13:20:06	
#94	#87 OR #88 OR #89 OR #90 OR #91 OR #92 OR #93	69
#95	#62 or #77 or #86 or #94	1636
#96	#41 and #95	910
#97	(bcr-abl NEAR/5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)):ab,ti	101
#98	[mh ^"Fusion Proteins, bcr-abl"/AI]	14
#99	#97 or #98	106
#100	[mh ^"Protein Kinase Inhibitors"]	762
#101	[mh "Protein-Tyrosine Kinases"/AI]	640
#102	tki:ab,ti	1225
#103	(kinase? NEAR/3 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)):ab,ti	3959
#104	#100 or #101	1133
#105	#102 or #103	4506
#106	#104 or #105	5203
#107	#41 and #99	98
#108	#41 and #106	399
#109	((new class* or innovative or target*) NEAR/3 (drug? or therapy or therapies or therapeutic* or treatment? or chemotherap*)):ab,ti	34196
#110	#41 and #109	154
#111	#96 or #107 or #108 or #110	1074
#112	#111 in Cochrane Reviews	0
Comments		

Appendix 2.3.3.2. Medline + PreMedline

Date	June 22, 2020		
Database	Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946 to June 22, 2020>		
Search strategy			
1	exp Leukemia, Myelogenous, Chronic, BCR-ABL Positive/		19740



Date	June 22, 2020	
2	chronic granulocytic leuk?emia?.ab,ti,kw.	1242
3	chronic myelocytic leuk?emia?.ab,ti,kw.	1352
4	chronic myelogenous leuk?emia?.ab,ti,kw.	8641
5	chronic myeloid leuk?emia?.ab,ti,kw.	15469
6	ph1-positive myelogenous leuk?emia.ab,ti,kw.	0
7	ph1-positive myeloid leuk?emia.ab,ti,kw.	4
8	ph1-positive myelocytic leuk?emia.ab,ti,kw.	1
9	ph1-positive granulocytic leuk?emia.ab,ti,kw.	0
10	philadelphia-positive myeloid leuk?emia.ab,ti,kw.	1
11	philadelphia-positive myelocytic leuk?emia.ab,ti,kw.	0
12	philadelphia-positive myelogenous leuk?emia.ab,ti,kw.	0
13	philadelphia-positive granulocytic leuk?emia.ab,ti,kw.	0
14	chronic myeloleuk?emia.ab,ti,kw.	156
15	bcr-abl positive myelogenous leuk?emia.ab,ti,kw.	1
16	bcr-abl positive myelocytic leuk?emia?.ab,ti,kw.	0
17	bcr-abl positive myeloid leuk?emia?.ab,ti,kw.	1
18	bcr-abl positive granulocytic leuk?emia?.ab,ti,kw.	0
19	(blast adj2 crises).ab,ti,kw.	74
20	(blast adj2 crisis).ab,ti,kw.	2798
21	(blast adj2 phase?).ab,ti,kw.	967
22	(blastic adj2 crises).ab,ti,kw.	28
23	(blastic adj2 crisis).ab,ti,kw.	736
24	(blastic adj2 phase?).ab,ti,kw.	757
25	leuk?emia myeloid accelerated-phase.ab,ti,kw.	0
26	leuk?emia myelocytic accelerated-phase.ab,ti,kw.	0
27	leuk?emia myelogenous accelerated-phase.ab,ti,kw.	0



Date	June 22, 2020	
28	leuk?emia granulocytic accelerated-phase.ab,ti,kw.	0
29	(myeloid adj3 leuk?emia adj3 aggressive-phase).ab,ti,kw.	1
30	(myelocytic adj3 leuk?emia adj3 aggressive-phase).ab,ti,kw.	0
31	(myelogenous adj3 leuk?emia adj3 aggressive-phase).ab,ti,kw.	1
32	(granulocytic adj3 leuk?emia adj3 aggressive-phase).ab,ti,kw.	0
33	CML.ab,ti,kf.	17068
34	(philadelphia adj3 leuk?emia?).ab,ti,kf.	618
35	granular blast?.ab,ti,kf.	10
36	myeloproliferative neoplasm?.ab,ti,kf.	3967
37	myeloblastic transformation?.ab,ti,kf.	47
38	myeloid neoplasm?.ab,ti,kf.	1241
39	leukemic blast?.ab,ti,kf.	2255
40	2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39	37515
41	1 or 40	41516
42	Imatinib Mesylate/	10150
43	Imatinib.ab,ti,kf,rn.	15433
44	GLAMOX.ab,ti,kf,rn.	0
45	Gleevec.ab,ti,kf,rn.	983
46	Glivec.ab,ti,kf,rn.	436
47	Glivic.ab,ti,kf,rn.	1
48	Ruvise.ab,ti,kf,rn.	0
49	STI571.ab,ti,kf,rn.	897
50	STI 571.ab,ti,kf,rn.	348
51	ST 1571.ab,ti,kf,rn.	2
52	ST1571.ab,ti,kf,rn.	35
53	signal transduction inhibitor 571.ab,ti,kf,rn.	10



Date	June 22, 2020	
54	CGP 57148.ab,ti,kf,rn.	11
55	CGP57148.ab,ti,kf,rn.	8
56	CGP 57148B.ab,ti,kf,rn.	10
57	CGP57148B.ab,ti,kf,rn.	27
58	BKJ8M8G5HI.ab,ti,kf,rn.	1
59	152459-95-5.ab,ti,kf,rn.	1
60	220127-57-1.ab,ti,kf,rn.	0
61	43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60	15793
62	42 or 61	15793
63	nilotinib.ab,ti,kf,rn.	2024
64	Tasigna.ab,ti,kf,rn.	49
65	F41401512X.ab,ti,kf,rn.	1
66	641571-10-0.ab,ti,kf,rn.	1
67	AMN 107.ab,ti,kf,rn.	8
68	AMN107.ab,ti,kf,rn.	77
69	63 or 64 or 65 or 66 or 67 or 68	2064
70	Dasatinib/	2019
71	dasatinib.ab,ti,kf,rn.	3556
72	sprycel.ab,ti,kf,rn.	51
73	bms 354825.ab,ti,kf,rn.	94
74	bms354825.ab,ti,kf,rn.	5
75	RBZ1571X5H.ab,ti,kf,rn.	2019
76	71 or 72 or 73 or 74 or 75	3566
77	70 or 76	3566
78	bosutinib.ab,ti,kf,rn.	521
79	bosulif.ab,ti,kf,rn.	7



Date	June 22, 2020	
80	5018V4AEZ0.ab,ti,kf,rn.	236
81	SK-606.ab,ti,kf,rn.	0
82	SKI-606.ab,ti,kf,rn.	64
83	SK606.ab,ti,kf,rn.	0
84	SKI606.ab,ti,kf,rn.	9
85	380843-75-4.ab,ti,kf,rn.	1
86	78 or 79 or 80 or 81 or 82 or 83 or 84 or 85	538
87	ponatinib.ab,ti,kf,rn.	679
88	iclusig.ab,ti,kf,rn.	17
89	4340891KFS.ab,ti,kf,rn.	307
90	AP-24534.ab,ti,kf,rn.	2
91	AP24534.ab,ti,kf,rn.	34
92	1114544-31-8.ab,ti,kf,rn.	0
93	943319-70-8.ab,ti,kf,rn.	1
94	87 or 88 or 89 or 90 or 91 or 92 or 93	682
95	62 or 77 or 86 or 94	18126
96	41 and 95	8297
97	(bcr-abl adj5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)).ab,ti,kf.	2907
98	Fusion Proteins, bcr-abl/ai	1025
99	97 or 98	3409
100	Protein Kinase Inhibitors/	45220
101	exp Protein-Tyrosine Kinases/ai	38027
102	tki.ab,ti,kf.	7575
103	(kinase? adj3 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)).ab,ti,kf.	118086
104	100 or 101	70065
105	102 or 103	118925
106	104 or 105	157349



Date	June 22, 2020	
107	41 and 99	2760
108	41 and 106	7260
109	((new class* or innovative or target*) adj3 (drug? or therapy or therapies or therapeutic* or treatment? or chemotherap*)).ab,ti,kf.	330072
110	41 and 109	2450
111	96 or 107 or 108 or 110	11925
112	((systematic review or systematic literature review or systematic scoping review or systematic narrative review or systematic qualitative review or systematic evidence review or systematic quantitative review or systematic meta-review or systematic critical review or systematic mixed studies review or systematic mapping review or systematic cochrane review or "systematic search and review" or systematic integrative review).ti. not comment.pt. not (protocol or protocols).ti. not medline.st.) or (Cochrane Database Syst Rev.ja. and review.pt.) or systematic review.pt.	159328
113	meta-analys*.ti.	108916
114	meta-analysis.pt.	116279
115	exp Technology Assessment, Biomedical/	11062
116	health technology assessment.ti,kf.	1917
117	HtA.ti,kf.	593
118	112 or 113 or 114 or 115 or 116 or 117	252947
119	111 and 118	81
Comments		

Appendix 2.4. Economic literature

Appendix 2.4.1. Search economic literature (HTA reports)

The search strategy in CRD's HTA database identified 65 references (Table 26). In a first round, 13 references were selected based on a review of title, keywords and abstract. The 52 remaining references were excluded for the following reasons: intervention (33), design (14), language (3), population (1) or duplicate (1). In a second round, the full text of the 13 selected references was reviewed. Six references were excluded (design (3), update available (3)). Seven references were retained. These references are indicated in Table 27 with an asterix (*).

Furthermore, in May 2020, the website of the National Institute for Health Research (NIHR) was searched for relevant reports. The following search terms were used: imatinib nilotinib dasatinib bosutinib ponatinib lenalidomide (43 hits, 9 with a focus on CML, 3 not previously identified).



Finally, already in April 2020, the website of the National Institute for Health and Care Excellence (NICE) was searched. The following search term was used: chronic myeloid leukaemia (28 hits, 10 relevant Technology Assessments (TAs), 9 not previously identified).

An overview of the identified references is provided in Table 27.

No report on lenalidomide was identified in the above search strategy. In October 2020, an extra search was performed both on the NIHR and NICE website using the term 'Myelodysplastic syndromes' and identified twice an extra report on lenalidomide for treating myelodysplastic syndromes.^{34 35} However, because of the low uptake of lenalidomide in Belgium in this population, it was decided not to include information from these reports in our study.

Table 26 – Search strategy and results for CRD: HTA

Date			
Date covered	All		
Search Strategy	1	MeSH DESCRIPTOR Leukemia, Myeloid EXPLODE ALL TREES	176
	2	* IN HTA	17351
	3	#1 AND #2	65 references
Note	<p>The combination of the following MeSH terms (combined with 'OR') provides the same 176 references:</p> <ul style="list-style-type: none">- MeSH DESCRIPTOR Leukemia, Myelogenous, Chronic, BCR-ABL Positive EXPLODE ALL TREES (71 hits)- MeSH DESCRIPTOR Leukemia, Myeloid, Chronic-Phase EXPLODE ALL TREES (14 hits)- MeSH DESCRIPTOR Leukemia, Myeloid EXPLODE ALL TREES (176 hits)- MeSH DESCRIPTOR Leukemia, Myeloid, Accelerated Phase EXPLODE ALL TREES (1 hit)- MeSH DESCRIPTOR Leukemia, Myeloid, Chronic, Atypical, BCR-ABL Negative EXPLODE ALL TREES (0 hits)- MeSH DESCRIPTOR Leukemia, Myeloid, Chronic-Phase EXPLODE ALL TREES (14 hits) <p>The widest descriptor was used to avoid that relevant studies would be missed.</p>		

Table 27 – Chronic myeloid leukaemia – Identified HTA reports for the selected drugs

Selected reports
Imatinib
<ul style="list-style-type: none">• NICE, TA70. October 2003. Guidance on the use of imatinib for chronic myeloid leukaemia.^{36 * β}<ul style="list-style-type: none">○ Dalziel K, Round A, Stein K, Garside R, Price A. Jul-2004. Effectiveness and cost-effectiveness of imatinib for first-line treatment of chronic myeloid leukaemia in chronic phase: a systematic review and economic analysis. Health Technology Assessment Volume: 8 Issue: 28.^{37 * α}○ This guidance has been partially updated by NICE technology appraisal guidance 425³⁸ and NICE technology appraisal guidance 426.³⁹

**Selected reports****Dasatinib, nilotinib en imatinib**

- NICE, TA425. December 2016. Dasatinib, nilotinib and high-dose imatinib for treating imatinib-resistant or intolerant chronic myeloid leukaemia.^{38 β §}
- NICE, TA426. December 2016. Dasatinib, nilotinib and imatinib for untreated chronic myeloid leukaemia.^{39 β #}
 - Dasatinib and nilotinib and standard dose imatinib for 1st line chronic myeloid leukaemia (Rapid Review of TA251) (ID638) ^α → no link to a full report available.

Bosutinib

- NICE, TA401. August 2016. Bosutinib for previously treated chronic myeloid leukaemia.^{40 β ¥}
 - Bosutinib for previously treated chronic myeloid leukaemia (review of TA299) [ID1004] ^α → no link to a full report available.
- NICE, TA576. April 2019. Bosutinib for untreated chronic myeloid leukaemia (terminated appraisal).^{41 β}

Ponatinib

- NICE, TA451. June 2017. Ponatinib for treating chronic myeloid leukaemia and acute lymphoblastic leukaemia.^{42 β}
 - Ponatinib for treating chronic myeloid leukaemia [ID671] ^α → no link to a full report available.

Excluded reports

- NICE, TA50. October 2002. Imanitib for chronic myeloid leukaemia.^{43 β}
 - Garside R, Round A, Dalziel K, Stein K, Royle P. Mar-2003. The effectiveness and cost-effectiveness of imatinib in chronic myeloid leukaemia: a systematic review. Health Technology Assessment Volume: 6 Issue: 33.^{44 * α}
 - This guidance has been updated and replaced by NICE technology appraisal guidance 70.
 - → this guidance and the underlying report were excluded from our overview.
- NICE, TA241. January 2012. Dasatinib, high-dose imatinib and nilotinib for the treatment of imatinib-resistant chronic myeloid leukaemia (CML) (part review of NICE technology appraisal guidance 70), and dasatinib and nilotinib for people with CML for whom treatment with imatinib has failed because of intolerance.^{45 β}
 - Loveman E, Cooper K, Bryant J, Colquitt J, Frampton G. May-2012. Dasatinib, high-dose imatinib and nilotinib for the treatment of imatinib-resistant chronic myeloid leukaemia: a systematic review and economic evaluation. Health Technology Assessment Volume: 16 Issue: 23.^{32* α}
 - This guidance has been updated and replaced by NICE technology appraisal guidance 425.³⁸
 - → this guidance and the underlying report were excluded from our overview.
- NICE, TA251. April 2012. Dasatinib, nilotinib and standard-dose imatinib for the first-line treatment of chronic myeloid leukaemia.^{46 β}
 - Pavey T, Hoyle M, Ciani O, Crathorne L, Jones-Hughes T. Dec-2012. Dasatinib, nilotinib and standard-dose imatinib for the first-line treatment of chronic myeloid leukaemia: systematic reviews and economic analyses. Health Technology Assessment Volume: 16 Issue: 42.^{47 * α}

**Selected reports**

- Rogers G, Hoyle M, Thompson-Coon J, Moxham T, Liu Z. May-2012. Dasatinib and nilotinib for imatinib-resistant or -intolerant chronic myeloid Leukaemia: A systematic review and economic evaluation. Health Technology Assessment Volume: 16 Issue: 22.⁴⁸ * α
 - This guidance has been updated and replaced by NICE technology appraisal guidance 426.³⁹
 - → this guidance and the underlying report were excluded from our overview.
-
- NICE, TA299. November 2013. Bosutinib for previously treated chronic myeloid leukaemia.⁴⁹ β
 - Hoyle M, Snowsill T, Haasova M, Cooper C, Rudin C. Bosutinib for previously treated chronic myeloid leukaemia: A Single Technology Appraisal. PenTAG, University of Exeter, 2013.⁵⁰ * α
 - This guidance has been updated and replaced by NICE technology appraisal guidance 401.⁴⁰
 - → this guidance and the underlying report were excluded from our overview.

* These references were identified in CRD's HTA database. α References identified on NIHR's website. β References identified on NICE's website. § There was no information on quality of life in TA425,³⁸ and no underlying HTA report was identified. To obtain information on this topic, the HTA report of TA241⁴⁵ was consulted (Loveman et al., 2012³²). # There was no information on quality of life in TA426,³⁹ and no underlying HTA report was identified. To obtain information on this topic, the Committee Papers of TA251 were consulted.⁵¹ ¥ There was no information on quality of life in TA401,⁴⁰ and no underlying HTA report was identified. To obtain information on this topic, the Committee Papers of TA401 were consulted.⁵²

Appendix 2.4.2. Results economic literature (HTA reports)

Appendix 2.4.2.1. NICE, TA70 (2003): imatinib

- QoL:
 - "EQ-5D data were obtained from the Novartis study 0106 (IRIS trial, comparing imatinib with IFN- α plus Ara-C) to capture patient preferences for the treatment as well as for being in a particular health state."³⁷
 - "The small non-significant difference at baseline favours imatinib. Better quality of life scores were found with imatinib than IFN-plus Ara-C at each subsequent assessment point [i.e. from month 1 to month 12]."³⁷
- Results:
 - "The independent model estimated the ICER of imatinib compared with IFN- α to be around £26,000 per QALY gained (ranging from £13,500 to £52,000). Results were relatively robust when subjected to a number of sensitivity analyses."³⁶
 - "Using less conservative estimates of the relative effectiveness of imatinib, based on treatment completers, the present authors' estimates of the ICER compared to IFN- α were between £17,445 and £29,901 per QALY."³⁷
- Uncertainty and sensitivity:



- “The Committee considered the implications of high crossover rates in the IRIS trial, and the appropriateness of using intention-to-treat and per protocol analyses. The Committee thought that the degree of the benefit of imatinib treatment would have been underestimated because of the high crossover rate in the IFN- α and Ara-C combination group.”³⁶
- “However, the Committee’s deliberations were hampered by the absence of long-term survival data. Thus, the published supportive evidence from the RCT relied principally on the surrogate measures of efficacy such as the achievement of an HR [Haematological response] and/or a CR [cytogenetic response]. The extent to which CR (particularly) and HR, as surrogate measures, predict survival is central to the judgment about the clinical and cost effectiveness of imatinib. After reviewing the available data, the Committee considered it likely (...) that the relationship between CR and survival is sufficiently strong to support the use of CR, in particular, as a surrogate measure of survival in people with chronic-phase CML. The Committee was therefore persuaded (...) that the RCT reviewed for the first-line use of imatinib indicated that there was likely to be a significant survival advantage for imatinib over IFN- α in this clinical situation. However, the Committee did not believe it was possible, based on the current evidence, to determine precisely the absolute survival gain that would result from switching from IFN- α to imatinib as first-line treatment.”³⁶
- “One of the uncertainties with this assessment is around long-term outcomes with imatinib. Currently, 18-month data are available, whereas for IFN- α 10-year trial follow-up data have been published.”³⁷
- Modelling of survival and progression. “The Novartis models assume IFN- α plus Ara-C survival rates for imatinib after 12 months. The independent economic model applies a continuing relative risk of benefit (for the length of the chronic phase) for imatinib. There are no long-term empirical data to support or refute either technique.”³⁶
- “The highest ICER estimate was obtained when higher doses of imatinib were assumed (that is, 600 mg for the chronic and accelerated phases and 800 mg for the blast-crisis phase).”³⁶
- Conclusions:
 - “Compared with IFN- α , the Committee considered that imatinib was a cost-effective option.”³⁶
 - “The ICER for imatinib compared with IFN- α falls within the range considered by many decision-makers as cost-effective. This is due to a combination of markedly better utility values in the chronic phase and improved survival.”³⁷
- (Confidential) price:
 - No reference to confidential discounts is made in the ‘Summary of Appraisal Committee’s key conclusions’ of TA70.



Reference	Costs (list prices & remarks)	Population, Intervention & comparator IC, IE and ICERs	Remarks on use of generic utility instrument (e.g. EQ-5D) to measure impact on QoL in economic evaluations	Most uncertain variables or important variables in sensitivity analysis																		
Imatinib																						
NICE, TA70 (2003) ³⁶ Dalziel (2004) ³⁷		People with newly diagnosed chronic phase CML (first-line treatment of adults with CML) Imatinib compared with IFN-α																				
List price Imatinib costs £12.98 per 100 mg (excluding VAT) *		Results from the manufacturer model: £19 000 and £27 000 per QALY gained depending on the technique to estimate the survival benefit. Results from the ERG model (ITT analysis): £26 000 (£13 500 to £52 000) per QALY gained. Results from the ERG model (PP analysis): between £17 500 and £29 900 per QALY gained. Remark: the use of the surrogate endpoint CR (instead of OS) was considered appropriate by the ERG. Conclusion: imatinib is a cost-effective option.	QoL (EQ-5D) was measured in the underlying clinical trial (IRIS) <table><tr><th>Utility (SD)</th><th>Imatinib</th><th>IFN-α</th></tr><tr><td>Chronic phase</td><td>0.8539 (0.1925)</td><td>0.7104 (0.2658)</td></tr><tr><td>Chronic phase after loss of CR</td><td>0.8539 (0.1925)</td><td>0.7104 (0.2658)</td></tr><tr><td>CR</td><td>0.8539 (0.1925)</td><td>0.7104 (0.2658)</td></tr><tr><td>Accelerated phase</td><td>0.729 (0.204)</td><td>0.729 (0.204)</td></tr><tr><td>Blast phase</td><td>0.524 (0.424)</td><td>0.524 (0.424)</td></tr></table>	Utility (SD)	Imatinib	IFN-α	Chronic phase	0.8539 (0.1925)	0.7104 (0.2658)	Chronic phase after loss of CR	0.8539 (0.1925)	0.7104 (0.2658)	CR	0.8539 (0.1925)	0.7104 (0.2658)	Accelerated phase	0.729 (0.204)	0.729 (0.204)	Blast phase	0.524 (0.424)	0.524 (0.424)	Uncertainties: - Impact on OS - Long-term modelling of OS (extrapolation). Results most sensitive to: - Imatinib dosage (400mg, 600mg, 800mg)
Utility (SD)	Imatinib	IFN-α																				
Chronic phase	0.8539 (0.1925)	0.7104 (0.2658)																				
Chronic phase after loss of CR	0.8539 (0.1925)	0.7104 (0.2658)																				
CR	0.8539 (0.1925)	0.7104 (0.2658)																				
Accelerated phase	0.729 (0.204)	0.729 (0.204)																				
Blast phase	0.524 (0.424)	0.524 (0.424)																				

CR: cytogenetic response, ITT: intention-to-treat, OS: overall survival, PP: per protocol, SD: standard deviation. * The approximate annual cost of imatinib is between £19 000 and £28 500 for a person in the chronic phase, and between £28 500 and £38 000 for a person in the accelerated phase or in blast crisis, depending on the dose.



Appendix 2.4.2.2. NICE, TA425 (2016): dasatinib, nilotinib and high-dose imatinib

- QoL:
 - No information was found in TA425³⁸ and no underlying HTA report with further details on QoL was identified. To obtain information on this topic, the HTA report of TA241⁴⁵ was consulted (Loveman et al., 2012³²).
 - “Utilities selected for the ERG model: “The PenTAG AR2 reviewed QoL studies to use in the economic model. From these data, the authors chose the IRIS study by Reed and colleagues, which was also used by Dalziel and colleagues in a previous assessment of imatinib for CML, as the most appropriate. These data were drawn from a large sample of patients and reported EQ-5D values. The utility values used for the health states are chronic phase (treatment or no treatment) 0.85; accelerated phase 0.73; and blast crisis 0.52.”³²
- Results:
 - Nilotinib**
 - Novartis model: “The committee considered the economic model developed by Novartis for chronic-phase CML that is resistant to standard-dose imatinib. It noted that in the base-case analysis, nilotinib dominated (that is, it was less expensive and more effective than) high-dose imatinib (...). The committee noted that when the modifications and the discount were applied, the ICERs for nilotinib compared with hydroxycarbamide decreased to £22,800 per QALY gained when a treatment duration of 6.5 years was assumed, and £25,000 per QALY gained when a treatment duration of 10 years was assumed.”³⁸
 - ERG model and committee’s appraisal: “However, the committee accepted that with the patient access scheme in place and its earlier conclusion that some of the adjustments to the model were plausible, the ICER for nilotinib is likely to be less than the SHTAC replicated ICER of £31,300 per QALY gained.”³⁸
 - Imatinib**
 - “It [The committee] noted that high-dose imatinib was dominated (that is, more expensive and less effective than another treatment) in all models.”³⁸
 - Dasatinib**
 - Without revised PAS for dasatinib (= results of TA241): “Therefore the committee concluded that dasatinib could not be recommended as a cost effective use of NHS resources for the treatment of adults with chronic-phase CML that is resistant to standard-dose imatinib, or who have imatinib intolerance. Furthermore, the committee noted that, given the patient access scheme for nilotinib and the assumed equivalence of effectiveness of dasatinib and nilotinib, dasatinib is considerably more expensive but no more effective than nilotinib.”³⁸
 - “The evidence review group (ERG) highlighted that the use of a cost-minimisation analysis assumes that all health outcomes and treatment costs (other than drug acquisition) are equivalent. (...) Therefore, the committee considered that it was plausible that cost-minimisation analysis was appropriate to inform its decision-making because treatment with dasatinib is sufficiently similar to nilotinib.”³⁸
 - “The committee discussed the results of the ERG’s cost-minimisation analysis which took into account the patient access schemes of both nilotinib and dasatinib. It concluded that, with the revised patient access scheme, it was likely that dasatinib was a cost-effective use of NHS resources and so



should be recommended for Philadelphia-chromosome-positive CML in the chronic or accelerated phase in adults who cannot have imatinib, or when their disease is imatinib-resistant.”³⁸

- Uncertainty and sensitivity:
 - “The committee discussed the clinical-effectiveness evidence for dasatinib, highdose imatinib and nilotinib for the treatment of chronic-phase CML that is resistant to standard-dose imatinib. It was aware of only 1 comparative trial, which compared dasatinib with high-dose imatinib [START-R], but noted the restricted comparison (only with high-dose imatinib) and the comments from the assessment groups on the interpretation of this trial. The committee noted that the clinical trials available were non-comparative, of short duration and had used surrogate outcomes to predict overall survival.”³⁸
 - “The committee concluded that it is clear that dasatinib, high-dose imatinib and nilotinib provide clinical benefit for people with imatinib-resistant CML. However, the committee agreed that the limited evidence base means that the magnitude of the benefit (for people with imatinib-resistant CML) is uncertain. The committee also agreed that there was no good evidence to distinguish between dasatinib and nilotinib; a conclusion supported by the clinical experts.”³⁸
 - “The committee did not consider that a conclusive ICER had been presented in any of the economic models.”³⁸
 - No underlying HTA report with further details on the results (IE, IC) was identified.
- Conclusions:
 - “The committee accepted that, with the patient access scheme in place, the use of nilotinib for the treatment of imatinib-resistant CML could be regarded as a cost-effective use of NHS resources.”³⁸
 - “Cancer Drugs Fund reconsideration: the committee concluded that, with the revised patient access scheme, it was likely that dasatinib was a cost-effective use of NHS resources and so should be recommended.”³⁸
 - “High-dose imatinib (that is, 600 mg in the chronic phase or 800 mg in the accelerated and blast-crisis phases) is not recommended for treating Philadelphia-chromosome-positive chronic myeloid leukaemia in adults whose disease is imatinib-resistant.”³⁸
 - TA425 (2016) is a CDF rapid reconsideration of TA70³⁶ and TA241.⁴⁵ “The committee considered the company's (Bristol-Myers Squibb) submission for the Cancer Drugs Fund reconsideration that included: a revised patient access scheme that provides a simple discount to the list price of dasatinib, an updated systematic literature review which provided a naive comparison of clinical outcomes of dasatinib compared with nilotinib, a cost-minimisation analysis of dasatinib compared with nilotinib and high-dose imatinib.”³⁸
- (Confidential) price:
 - “Cancer Drugs Fund reconsideration: the committee noted that the company of dasatinib had agreed a patient access scheme with the Department of Health. (...) The size of the discount is commercial in confidence.”³⁸
 - “The Department of Health and Novartis Pharmaceuticals have agreed that nilotinib will be available to the NHS with a patient access scheme which makes it available with a discount. The size of the discount is commercial in confidence.”³⁸



Reference Costs (list prices & remarks)	Population, Intervention & comparator IC, IE and ICERs	Remarks on use of generic utility instrument (e.g. EQ- 5D) to measure impact on QoL in economic evaluations	Most uncertain variables or important variables in sensitivity analysis
Dasatinib, nilotinib and high-dose imatinib			
NICE, TA425 (2016) ³⁸	Adults with only chronic- or accelerated-phase Philadelphia-chromosome-positive CML who are resistant or intolerant to imatinib Nilotinib versus high-dose imatinib; nilotinib versus hydroxycarbamide; dasatinib versus nilotinib		
List prices, negotiated discounts (PAS) are hidden. Dasatinib: £2 505 for both a pack of 30 100-mg or 140-mg tablets* Imatinib: £1 836 for a 400-mg 30-tablet pack* Nilotinib: £2 433 for a 200-mg 112-tablet pack*	Results (with PAS for nilotinib and revised PAS for dasatinib): - nilotinib vs high-dose imatinib: nilotinib dominant - nilotinib vs hydroxycarbamide: o Company: £22 800 - £25 000 per QALY gained o ERG: £31 300 per QALY gained o Committee's conclusion: nilotinib is cost-effective - dasatinib vs nilotinib: o Results not reported in TA425. o Committee's conclusion: based on a cost-minimisation analysis of dasatinib compared to nilotinib, the ERG considered it likely that dasatinib was a cost-effective use of NHS resources. Remark: TA425 is a CDF rapid reconsideration of TA241 ⁴⁵ that includes a revised PAS for dasatinib.	There was no head-to-head trials comparing the interventions under consideration. EQ-5D utilities (per disease stage) were obtained from the imatinib arm of the IRIS trial (imatinib vs IFN-α) Remark: The comparison between dasatinib and nilotinib is based on a cost-minimisation analysis.	The magnitude of the benefit is uncertain.

* The cost of dasatinib treatment is £30 477 per year, assuming a treatment regimen of 100 mg once daily or 140 mg once daily. The cost of imatinib treatment is £44 718 per year assuming a treatment regimen of 400 mg twice daily. The cost of nilotinib treatment is £31 736 per year, assuming a treatment regimen of 400 mg twice daily.



Appendix 2.4.2.3. NICE, TA426 (2016): dasatinib, nilotinib and standard-dose imatinib

- QoL:
 - No information was found in TA426³⁹ and no underlying HTA report with further details on QoL was identified.
 - “Health-related quality of life was not reported in the DASISION or ENESTnd trials. (...) Utility values were based on EQ-5D responses from people receiving standard-dose imatinib in the IRIS study.”⁵¹
- Results:
 - Nilotinib vs imatinib: “The committee noted that the ICER for first-line nilotinib followed by imatinib compared with first-line imatinib followed by nilotinib was £11,000 per QALY gained for both scenarios and that this was in the range normally considered a cost-effective use of NHS resources.”³⁹
 - Dasatinib (with PAS) vs imatinib (= results of TA251): “The committee noted that the ICERs for first-line treatment with dasatinib followed either by nilotinib or imatinib compared with first-line treatment with standard-dose imatinib followed by nilotinib exceeded £300,000 per QALY gained.”³⁹
 - Dasatinib (with PAS) vs nilotinib (= results of TA251): “The committee noted that dasatinib was associated with fewer QALYs and was more costly than nilotinib in all scenarios.”³⁹
 - Dasatinib (with revised PAS) vs imatinib/nilotinib: “The committee discussed the appropriateness of the company's cost-minimisation analysis for dasatinib compared with nilotinib. (...) Furthermore, it is plausible that a cost-minimisation analysis is appropriate because treatment with dasatinib is sufficiently similar to nilotinib. (...) The committee discussed the results of the ERG's cost-minimisation analysis, which took into account the list price of imatinib and the patient access schemes of both nilotinib and dasatinib. It concluded that, with the revised patient access scheme, it was likely that dasatinib was a cost-effective use of NHS resources and so should be recommended for untreated Philadelphia-chromosome-positive CML.”³⁹
- Uncertainty and sensitivity:
 - “The committee was aware of 2 comparative clinical trials, 1 that compared dasatinib with imatinib (DASISION) and 1 that compared nilotinib with imatinib (ENESTnd). It also noted that no trials directly comparing dasatinib and nilotinib were available. (...) However, it was also noted that both the clinical trials were of short duration and provided only short-term data on progression-free and overall survival and that surrogate outcome measures were used.”³⁹
 - “The committee considered the results of the indirect comparison of dasatinib and nilotinib conducted by the assessment group, which showed no statistically significant differences in rates of complete cytogenetic response and major molecular response by 12 months between the 2 treatments.”³⁹
 - “The committee noted that the assessment group's modelling included a range of scenarios because of uncertainty about the impact of dasatinib and nilotinib on long-term survival and about subsequent lines of treatment.”³⁹
 - “The committee was aware that the ICERs for first-line nilotinib followed by imatinib compared with first-line imatinib followed by nilotinib were sensitive to a number of parameters, including assumptions about the dose intensity of nilotinib and the average time spent on second-line nilotinib or imatinib treatment.”³⁹
- Conclusions:



- Dasatinib and nilotinib: “The drugs are recommended only if the companies provide them with the discounts agreed in the relevant patient access schemes.”³⁹
- “The committee (...) concluded that the results of the assessment group's analyses indicated that nilotinib represented a cost-effective first-line treatment for people with chronic-phase CML.”³⁹
- Dasatinib (with PAS): “The committee concluded that the ICERs for dasatinib were substantially outside the range normally considered a cost-effective use of NHS resources and that dasatinib could not be recommended as a cost-effective use of NHS resources for the first-line treatment of adults with chronic-phase CML.”³⁹
- Dasatinib (with revised PAS): “Therefore, the committee considered that, if drug acquisition costs of dasatinib were shown to be less than those of imatinib, it was likely that dasatinib would dominate imatinib (that is, be both more effective and less costly). Furthermore, it is plausible that a cost minimisation analysis is appropriate because treatment with dasatinib is sufficiently similar to nilotinib.”³⁹
- “Cancer Drugs Fund reconsideration: the committee concluded that, with the revised patient access scheme, it was likely that dasatinib was a cost-effective use of NHS resources and so should be recommended for untreated Philadelphia-chromosome-positive CML.”³⁹
- TA426 (2016) is a CDF rapid reconsideration of TA251⁴⁶. “The committee considered the company's (Bristol-Myers Squibb) submission for the Cancer Drugs Fund reconsideration that included: a revised patient access scheme that provides a simple discount to the list price of dasatinib, longer follow-up data from the DASISION study, an updated systematic literature review the results of which were used to inform a network meta-analysis of dasatinib, nilotinib and imatinib, a cost-minimisation analysis of dasatinib compared with nilotinib and imatinib.”³⁹
- (Confidential) price:
 - “The committee noted that the Department of Health had approved a patient access scheme for nilotinib, which makes it available with a discount applied to all invoices. The size of the discount is commercial in confidence.”³⁹
 - “Cancer Drugs Fund reconsideration: the committee noted that the Department of Health had approved a patient access scheme for dasatinib, which makes it available with a discount on the list price. The size of the discount is commercial in confidence.”³⁹



Reference Costs (list prices & remarks)	Population, Intervention & comparator IC, IE and ICERs	Remarks on use of generic utility instrument (e.g. EQ- 5D) to measure impact on QoL in economic evaluations	Most uncertain variables or important variables in sensitivity analysis
Dasatinib, nilotinib and standard-dose imatinib			
NICE, TA426 (2016) ³⁹	Adults with untreated, chronic-phase Philadelphia-chromosome-positive CML (first-line treatment of adults with CML)		
NICE, TA251 committee papers (2016) ⁵¹	Nilotinib vs standard-dose imatinib, dasatinib vs standard-dose imatinib, dasatinib vs nilotinib		
<p>List prices, negotiated discounts (PAS) are hidden.</p> <p>Dasatinib: £2 505 for a 100-mg 30-tablets pack*</p> <p>Imatinib: £1 836 for a 400-mg 30-tablets pack*</p> <p>Nilotinib: £2 433 for a 150-mg 112-tablets pack*</p>	<p>Results of the ERG economic model:</p> <ul style="list-style-type: none"> - nilotinib (with PAS) vs standard-dose imatinib (list price): £11 000 per QALY gained - dasatinib (with PAS) vs standard-dose imatinib (list price): over £300 000 per QALY gained. - dasatinib (with PAS) vs nilotinib: dasatinib is not cost-effective - dasatinib (with revised PAS) vs nilotinib (with PAS) / imatinib (list price): "it is likely that dasatinib is a cost-effective use of NHS resources and so should be recommended". <p>Remark: TA426 is a CDF rapid reconsideration of TA251⁴⁶ that includes a revised PAS for dasatinib.</p> <p>Conclusion: Based on a cost-minimisation analysis of dasatinib compared to nilotinib, the ERG considered it likely that dasatinib was a cost-effective use of NHS resources.</p>	<p>EQ-5D was not measured in the DASISION (dasatinib vs imatinib) and ENESTnd (nilotinib vs imatinib) trials.</p> <p>There was no head-to-head trials comparing nilotinib to dasatinib.</p> <p>EQ-5D utilities (per disease stage) were obtained from the imatinib arm of the IRIS trial (imatinib vs IFN-α)</p> <p>Remark: The comparison between dasatinib and nilotinib is based on a cost-minimisation analysis.</p>	<p>Results for nilotinib vs imatinib sensitive to:</p> <ul style="list-style-type: none"> - dose intensity of first-line nilotinib - average time spent on second-line nilotinib or imatinib treatment <p>Uncertainties:</p> <ul style="list-style-type: none"> - impact on OS - Long-term modelling of OS (extrapolation)

OS: overall survival. * The cost of dasatinib treatment is £30 477 per year, assuming a treatment regimen of 100 mg once daily. The cost of imatinib treatment is £44 718 per year assuming a treatment regimen of 400 mg twice daily. The cost of nilotinib treatment is £31 715 per year, assuming a treatment regimen of 300 mg twice daily.



Appendix 2.4.2.4. NICE, TA401 (2016): bosutinib

- QoL:
 - “Utility values derived directly from the bosutinib pivotal study (Study 200) are used as the base case in this resubmission. EQ-5D-3L utilities from Study 200 (scored using the UK tariff) became available during the original NICE appraisal (TA299), and were only incorporated in the final models submitted to NICE at the ACD response stage.”⁵² There was no head-to-head trial. The Study 200 is a single-arm trial.
 - The utilities were reported as commercial in confidence.
- Results:
 - Bosutinib (with PAS) versus hydroxycarbamide (= results of TA299⁴⁹)
 - “For chronic phase CML the most plausible available ICER was £43,000 per QALY gained but taking into account the limited potential for post-bosutinib benefit and a proportion of people taking bosutinib after loss of complete cytogenetic response an estimated range of £40,000 to £50,000 per QALY gained was appropriate for the purposes of its decision-making.”⁴⁰
 - “For accelerated phase CML and blast phase CML, the most plausible ICERs were £58,000 per QALY gained and £60,000 per QALY gained respectively.”⁴⁰
 - Bosutinib (with revised PAS) versus hydroxycarbamide (Cancer Drug Fund reconsideration of TA299⁴⁹)
 - The ICER, IE and IC are reported as commercial-in-confidence.⁵² No underlying HTA report was identified with further details on the results (ICER, IE, IC).
- Uncertainty and sensitivity:
 - “It [the committee] also concluded that, although there were indicative data on the survival of patients receiving bosutinib and the comparator treatments, the relative treatment effect between bosutinib and the comparators was subject to uncertainty.”⁴⁰
 - “The committee discussed the surrogate approach that the company had used to estimate overall survival with bosutinib in the chronic phase. It accepted that the overall survival estimates from Study 200 for this population were immature. The committee discussed whether a surrogate relationship was plausible. It noted a comment received during consultation from the CML Support Group (CMLSG) stating that the European Leukaemia Net guidelines are testament to the existence of a surrogate relationship between major cytogenetic response and overall survival.”⁴⁰
 - “The committee considered that there were 2 key assumptions that influenced the ICER. The first was the presence or absence of, and the magnitude of, any post-treatment benefit. (...)The second factor affecting the ICER was the duration of overall survival associated with best supportive care (hydroxycarbamide).”⁴⁰



- Conclusions:
 - “Cancer Drugs Fund reconsideration. Because the life expectancy of people with chronic phase CML is longer than 24 months the committee concluded that the end-of-life criteria did not apply to chronic phase CML. However the short life expectancy and the extension-to-life criteria were met for bosutinib in the accelerated and blast phases of CML.”⁴⁰
 - “Cancer Drugs Fund reconsideration. There is a significant unmet need for patients who have first-line imatinib treatment but are known to have CML unlikely to respond to nilotinib. (...) Bosutinib offers an alternative treatment option for people who are intolerant of other Bcr-Abl tyrosine kinase inhibitors.”⁴⁰
 - Bosutinib with PAS: “The committee concluded that, even allowing for the supplementary advice for committee for life-extending treatments, the magnitude of additional weight that would need to be applied to the QALY gains for bosutinib taken in accelerated phase and blast phase CML would be too great for bosutinib to be considered a cost-effective use of NHS resources.”⁴⁰
 - Bosutinib with revised PAS: “On balance, given the cost-effectiveness analyses including the revised patient access scheme and taking into account the unmet need in this patient population, the committee recommended bosutinib as a cost-effective use of NHS resources for treating Philadelphia chromosome positive CML.”⁴⁰
 - TA401 is a CDF rapid reconsideration of TA299.⁴⁹ “This appraisal was a Cancer Drugs Fund reconsideration of the published NICE technology appraisal guidance on bosutinib for previously treated chronic myeloid leukaemia. It focused on cost-effectiveness analyses using a revised patient access scheme, which provides a simple discount to the list price of bosutinib.”⁴⁰
- (Confidential) price: PAS (bosutinib)
 - “Cancer Drugs Fund reconsideration. The company for bosutinib has agreed a revised patient access scheme with the Department of Health. The size of the discount is commercial in confidence.”⁴⁰



Reference Costs (list prices & remarks)	Population, Intervention & comparator IC, IE and ICERs	Remarks on use of generic utility instrument (e.g. EQ- 5D) to measure impact on QoL in economic evaluations	Most uncertain variables or important variables in sensitivity analysis
Bosutinib			
NICE, TA401 (2016) ⁴⁰ NICE, Committee Papers TA401 (2016) ⁵²	Previously treated chronic myeloid leukaemia, i.e. adults with chronic phase (CP), accelerated phase (AP), and blast phase (BP) Philadelphia chromosome positive chronic myelogenous leukaemia (Ph+ CML) previously treated with one or more tyrosine kinase inhibitor(s) and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options. Bosutinib compared with hydroxycarbamide (considered here as best supportive care)		
List prices, negotiated discounts (PAS) are hidden. Bosutinib: £3 436.67 for a 500-mg 28-tablets pack*	Results from the ERG for bosutinib versus hydroxycarbamide. With PAS for bosutinib: - Chronic phase: £40 000 to £50 000 per QALY gained - Accelerated phase: £58 000 per QALY gained - Blast phase: £60 000 per QALY gained - Conclusion: bosutinib is not cost-effective With revised PAS for bosutinib (Cancer Drug Fund reconsideration): - IC, IE and ICER are reported as commercial-in-confidence. - Conclusion: on balance, given the cost-effectiveness analyses including the revised patient access scheme and taking into account the <i>unmet need</i> in this patient population, the committee recommended bosutinib as a cost-effective use of NHS resources. Remak: TA401 is a CDF rapid reconsideration of TA299 ⁴⁹ that includes a revised PAS for bosutinib.	There was no head-to-head trial comparing the interventions under consideration. EQ-5D utilities (per disease stage) were obtained from the bosutinib pivotal Study 200 (single arm).	Gain in OS uncertain ICER sensitive to: - presence or absence of, and the magnitude of, any post-treatment benefit - the overall survival estimates for bosutinib and hydroxycarbamide

* The average cost is £122.74 for 500 mg/day. The annual cost of bosutinib at this dose is £44 799 per patient.



Appendix 2.4.2.5. NICE, TA576 (2019): bosutinib

- “NICE is unable to make a recommendation about the use in the NHS of bosutinib for untreated chronic myeloid leukaemia because Pfizer did not provide an evidence submission.”⁴¹

Appendix 2.4.2.6. NICE, TA451 (2017): ponatinib

- QoL:
 - “The PACE trial did not collect quality-of-life data. The company therefore used the values reported in Szabo et al. (2010), and applied utility decrements to set them to the UK population norm.”⁴²
 - No further information on QoL was identified TA451 and no underlying HTA report of TA451 was identified. Utility elicitation in Szabo et al. was performed with the time trade-off technique for standardized CML-related health states.⁵³
- Results:
 - “For the cost-effectiveness results, the end-of-life criteria were met for people with accelerated and blast-phase CML. For these populations the most plausible ICERs were below £50,000 per QALY gained. For people with chronic-phase CML, even though some of the ICERs in the ERG's analyses for ponatinib compared with bosutinib were above £20,000 per QALY gained, the range did contain values below £20,000 per QALY gained. The precise ICERs could not be reported because of a confidential patient access scheme for the comparators.”⁴²
 - “The end-of-life criteria were met for people with Ph+ ALL regardless of allogeneic stem cell transplantation suitability. For people with Ph+ ALL for whom allogeneic stem cell transplant is suitable, the ICER for ponatinib compared with best supportive care ranged between £7,156 and £29,995 per QALY gained, and for ponatinib compared with induction was likely to be below £5,000 per QALY gained (dominant to £4,138 per QALY gained). The committee noted that in people with Ph+ ALL for whom allogeneic stem cell transplant was unsuitable, ponatinib dominated best supportive care.”⁴²
- Uncertainty and sensitivity:
 - “The clinical evidence was the PACE trial. The committee noted that this was a non-comparative study, and that, without comparative evidence, the company had made an indirect comparison with bosutinib. (...) The evidence was limited and had the potential for biases. In the Ph+ ALL group, and in some of the CML subgroups, patient numbers were small, and lacked statistical power. The main uncertainties in the evidence related to optimal dosing, duration of treatment, and in the results from the matching adjusted indirect comparison.”⁴²
 - “The key driver of cost effectiveness in all the models was the choice of distribution for measures of survival and treatment response. (...) The committee noted that because of limited data there was considerable parameter uncertainty and no curve provided a definitive fit (...).”⁴²
 - “The committee recognised that there was considerable uncertainty in the value of the ICERs, and therefore their most likely value fell within a range. It noted that the value of the ICER could fall anywhere within that range.”⁴²



- Conclusions:
 - “The committee concluded that ponatinib was cost effective compared with best supportive care and potentially cost effective compared with bosutinib, so recommended ponatinib for chronic-phase CML as a cost-effective use of NHS resources.”⁴²
 - “The committee concluded that the end-of-life criteria had been met in people with accelerated and blast-phase CML, and Ph+ ALL.”⁴²
 - “The committee concluded that in those groups in whom the end-of-life criteria were met, the ICERs for ponatinib compared with its relevant comparator were less than £50,000 per QALY gained, so it recommended ponatinib for chronic-, accelerated- and blast-phase CML, and Ph+ ALL, as a cost-effective use of NHS resources.”⁴²
 - “Ponatinib is recommended only if the company provides the drug with the discount agreed in the patient access scheme.”⁴²
- (Confidential) price:
 - “The Department of Health and Incyte have agreed that ponatinib will be available to the NHS with a patient access scheme which makes it available with a discount. The size of the discount is commercial in confidence.”⁴²



Reference Costs (list prices & remarks)	Population, Intervention & comparator IC, IE and ICERs	Remarks on use of generic utility instrument (e.g. EQ- 5D) to measure impact on QoL in economic evaluations	Most uncertain variables or important variables in sensitivity analysis
Ponatinib			
NICE, TA451 (2017) ⁴²	<p>Adult patients with:</p> <ul style="list-style-type: none"> - chronic-phase (CP), accelerated-phase (AP), or blast-phase (BP) <u>chronic myeloid leukaemia</u> (CML) who are resistant to dasatinib or nilotinib; or who are intolerant to dasatinib or nilotinib and for whom subsequent treatment with imatinib is not clinically appropriate; or who have the T315I mutation - Philadelphia-chromosome-positive <u>acute lymphoblastic leukaemia</u> (ALL) who are resistant to dasatinib; or who are intolerant to dasatinib and for whom subsequent treatment with imatinib is not clinically appropriate; or who have the T315I mutation <p>CML: ponatinib compared to bosutinib and to best supportive care (BSC) (best supportive care is not defined)</p> <p>ALL: ponatinib compared to best supportive care (BSC) and to induction chemotherapy</p>		
<p>List prices, negotiated discounts (PAS) are hidden.</p> <p>Ponatinib: £5 050 for a 15-mg 60-tablets pack, or a 45-mg 30-tablets pack</p>	<p>Results from the ERG analyses:</p> <p>For CML (with PAS for ponatinib and the comparators):</p> <ul style="list-style-type: none"> - CP CML: the range contains values of less than £20 000 per QALY gained. - AP and BP CML: < £50 000 per QALY gained (EOL criteria) <p>For Ph+ ALL (with PAS for ponatinib):</p> <ul style="list-style-type: none"> - Ph+ ALL in whom SCT is suitable: <ul style="list-style-type: none"> o Ponatinib vs. BSC: £7 156 to £29 995 per QALY gained o Ponatinib vs induction chemotherapy: dominant to £4 138 per QALY gained - Ph+ ALL in which SCT is unsuitable: ponatinib dominates BSC <p>Conclusion: ponatinib is recommended as a cost-effective use of NHS resources for CML and Ph+ ALL patients</p> <p>Remark 1: the ICERs for CML are reported as commercial in confidential because of a PAS for the comparator</p> <p>Remark 2: EOL criteria are met for AC and BP CML, and for Ph+ ALL irrespective of SCT suitability</p>	<p>There was no head-to-head trials comparing the interventions under consideration.</p> <p>The PACE trial (a single-arm, open-label, non-comparative study of ponatinib) did not collect quality-of-life data.</p> <p>TTO utilities were obtained from Szabo et al. (2010)⁵³</p>	<p>High parameters uncertainty</p> <p>Results sensitive to:</p> <ul style="list-style-type: none"> - the choice of curves of best fit for survival functions - the duration of treatment response

EOL: end-of-life, SCT: stem cell transplant, TTO: time trade-off.



APPENDIX 3. COLORECTAL CANCER

Appendix 3.1. BCR data

Appendix 3.1.1. Descriptive statistics

Appendix 3.1.1.1. Colorectal cancer, exploration

Table 28 – Colorectal cancer (2004-2017): Frequency table of patient and tumour characteristics

Characteristic	Total	Incidence period		
		2004-2008	2009-2013	2014-2017
Overall	111,623	37,568	40,597	33,458
Gender				
Male	62,018 (55.6)	20,506 (54.6)	22,543 (55.5)	18,969 (56.7)
Female	49,605 (44.4)	17,062 (45.4)	18,054 (44.5)	14,489 (43.3)
Age at diagnosis (year)				
<50 years	5,288 (4.7)	1,885 (5.0)	1,901 (4.7)	1,502 (4.5)
50-59 years	13,659 (12.2)	4,678 (12.5)	4,861 (12.0)	4,120 (12.3)
60-69 years	27,318 (24.5)	8,438 (22.5)	9,901 (24.4)	8,979 (26.8)
70-79 years	35,962 (32.2)	13,230 (35.2)	12,794 (31.5)	9,938 (29.7)
80+ years	29,396 (26.3)	9,337 (24.9)	11,140 (27.4)	8,919 (26.7)
WHO - Performance Status				
0 – Asymptomatic	15,607 (14.0)	3,551 (9.5)	5,487 (13.5)	6,569 (19.6)
1 – Symptomatic but completely ambulatory	58,126 (52.1)	15,691 (41.8)	23,292 (57.4)	19,143 (57.2)
2 – Symptomatic, <50% in bed during the day	7,671 (6.9)	2,946 (7.8)	2,535 (6.2)	2,190 (6.5)
3 – Symptomatic, >50% in bed, but not bedbound	1,967 (1.8)	697 (1.9)	675 (1.7)	595 (1.8)
4 – Bedbound	651 (0.6)	192 (0.5)	195 (0.5)	264 (0.8)
Not reported	27,601 (24.7)	14,491 (38.6)	8,413 (20.7)	4,697 (14.0)
Combined stage				



0	863 (0.8)	197 (0.5)	323 (0.8)	343 (1.0)
is	152 (0.1)	17 (0.0)	66 (0.2)	69 (0.2)
I	22,249 (19.9)	5,899 (15.7)	7,733 (19.0)	8,617 (25.8)
II	30,706 (27.5)	10,604 (28.2)	11,373 (28.0)	8,729 (26.1)
III	28,598 (25.6)	9,837 (26.2)	10,554 (26.0)	8,207 (24.5)
IV	19,635 (17.6)	6,263 (16.7)	7,469 (18.4)	5,903 (17.6)
X	9,420 (8.4)	4,751 (12.6)	3,079 (7.6)	1,590 (4.8)

Note: the values between parentheses are column percentages.

**Table 29 – Colorectal cancer (2004-2017), Combined stage I, Frequency table of patient and tumour characteristics**

Characteristic	Total	Incidence period		
		2004-2008	2009-2013	2014-2017
Overall	22,249	5,899	7,733	8,617
Gender				
Male	13,076 (58.8)	3,374 (57.2)	4,481 (57.9)	5,221 (60.6)
Female	9,173 (41.2)	2,525 (42.8)	3,252 (42.1)	3,396 (39.4)
Age at diagnosis (year)				
<50 years	859 (3.9)	275 (4.7)	320 (4.1)	264 (3.1)
50-59 years	2,895 (13.0)	771 (13.1)	1,002 (13.0)	1,122 (13.0)
60-69 years	6,183 (27.8)	1,415 (24.0)	1,996 (25.8)	2,772 (32.2)
70-79 years	7,482 (33.6)	2,171 (36.8)	2,621 (33.9)	2,690 (31.2)
80+ years	4,830 (21.7)	1,267 (21.5)	1,794 (23.2)	1,769 (20.5)
WHO - Performance Status				
0 – Asymptomatic	5,078 (22.8)	899 (15.2)	1,525 (19.7)	2,654 (30.8)
1 – Symptomatic but completely ambulatory	11,184 (50.3)	2,565 (43.5)	4,249 (54.9)	4,370 (50.7)
2 – Symptomatic, <50% in bed during the day	812 (3.6)	307 (5.2)	247 (3.2)	258 (3.0)
3 – Symptomatic, >50% in bed, but not bedbound	147 (0.7)	37 (0.6)	54 (0.7)	56 (0.6)
4 – Bedbound	54 (0.2)	15 (0.3)	14 (0.2)	25 (0.3)
Not reported	4,974 (22.4)	2,076 (35.2)	1,644 (21.3)	1,254 (14.6)

Note: the values between parentheses are column percentages.



Table 30 – Colorectal cancer (2004-2017), Combined stage II, Frequency table of patient and tumour characteristics

Characteristic	Total	Incidence period		
		2004-2008	2009-2013	2014-2017
Overall	30,706	10,604	11,373	8,729
Gender				
Male	16,459 (53.6)	5,599 (52.8)	6,150 (54.1)	4,710 (54.0)
Female	14,247 (46.4)	5,005 (47.2)	5,223 (45.9)	4,019 (46.0)
Age at diagnosis (year)				
<50 years	1,170 (3.8)	427 (4.0)	423 (3.7)	320 (3.7)
50-59 years	3,089 (10.1)	1,120 (10.6)	1,143 (10.1)	826 (9.5)
60-69 years	6,825 (22.2)	2,247 (21.2)	2,529 (22.2)	2,049 (23.5)
70-79 years	10,219 (33.3)	3,880 (36.6)	3,617 (31.8)	2,722 (31.2)
80+ years	9,403 (30.6)	2,930 (27.6)	3,661 (32.2)	2,812 (32.2)
WHO - Performance Status				
0 – Asymptomatic	3,934 (12.8)	973 (9.2)	1,457 (12.8)	1,504 (17.2)
1 – Symptomatic but completely ambulatory	17,031 (55.5)	4,842 (45.7)	6,867 (60.4)	5,322 (61.0)
2 – Symptomatic, <50% in bed during the day	2,194 (7.1)	868 (8.2)	736 (6.5)	590 (6.8)
3 – Symptomatic, >50% in bed, but not bedbound	491 (1.6)	165 (1.6)	170 (1.5)	156 (1.8)
4 – Bedbound	180 (0.6)	57 (0.5)	55 (0.5)	68 (0.8)
Not reported	6,876 (22.4)	3,699 (34.9)	2,088 (18.4)	1,089 (12.5)

Note: the values between parentheses are column percentages.

**Table 31 – Colorectal cancer (2004-2017), Combined stage III, Frequency table of patient and tumour characteristics**

Characteristic	Total	Incidence period		
		2004-2008	2009-2013	2014-2017
Overall	28,598	9,837	10,554	8,207
Gender				
Male	15,485 (54.1)	5,227 (53.1)	5,714 (54.1)	4,544 (55.4)
Female	13,113 (45.9)	4,610 (46.9)	4,840 (45.9)	3,663 (44.6)
Age at diagnosis (year)				
<50 years	1,546 (5.4)	532 (5.4)	572 (5.4)	442 (5.4)
50-59 years	3,684 (12.9)	1,290 (13.1)	1,298 (12.3)	1,096 (13.4)
60-69 years	7,022 (24.6)	2,229 (22.7)	2,632 (24.9)	2,161 (26.3)
70-79 years	8,945 (31.3)	3,390 (34.5)	3,254 (30.8)	2,301 (28.0)
80+ years	7,401 (25.9)	2,396 (24.4)	2,798 (26.5)	2,207 (26.9)
WHO - Performance Status				
0 – Asymptomatic	3,677 (12.9)	890 (9.0)	1,335 (12.6)	1,452 (17.7)
1 – Symptomatic but completely ambulatory	15,876 (55.5)	4,435 (45.1)	6,449 (61.1)	4,992 (60.8)
2 – Symptomatic, <50% in bed during the day	2,032 (7.1)	826 (8.4)	648 (6.1)	558 (6.8)
3 – Symptomatic, >50% in bed, but not bedbound	466 (1.6)	179 (1.8)	153 (1.4)	134 (1.6)
4 – Bedbound	154 (0.5)	43 (0.4)	48 (0.5)	63 (0.8)
Not reported	6,393 (22.4)	3,464 (35.2)	1,921 (18.2)	1,008 (12.3)

Note: the values between parentheses are column percentages.



Table 32 – Colorectal cancer (2004-2017), Combined stage IV, Frequency table of patient and tumour characteristics

Characteristic	Total	Incidence period		
		2004-2008	2009-2013	2014-2017
Overall	19,635	6,263	7,469	5,903
Gender				
Male	11,204 (57.1)	3,571 (57.0)	4,256 (57.0)	3,377 (57.2)
Female	8,431 (42.9)	2,692 (43.0)	3,213 (43.0)	2,526 (42.8)
Age at diagnosis (year)				
<50 years	1,260 (6.4)	420 (6.7)	450 (6.0)	390 (6.6)
50-59 years	2,924 (14.9)	1,004 (16.0)	1,065 (14.3)	855 (14.5)
60-69 years	5,154 (26.2)	1,603 (25.6)	2,021 (27.1)	1,530 (25.9)
70-79 years	6,152 (31.3)	2,112 (33.7)	2,310 (30.9)	1,730 (29.3)
80+ years	4,145 (21.1)	1,124 (17.9)	1,623 (21.7)	1,398 (23.7)
WHO - Performance Status				
0 – Asymptomatic	2,256 (11.5)	641 (10.2)	885 (11.8)	730 (12.4)
1 – Symptomatic but completely ambulatory	11,833 (60.3)	3,380 (54.0)	4,766 (63.8)	3,687 (62.5)
2 – Symptomatic, <50% in bed during the day	2,286 (11.6)	835 (13.3)	774 (10.4)	677 (11.5)
3 – Symptomatic, >50% in bed, but not bedbound	684 (3.5)	265 (4.2)	225 (3.0)	194 (3.3)
4 – Bedbound	211 (1.1)	64 (1.0)	61 (0.8)	86 (1.5)
Not reported	2,365 (12.0)	1,078 (17.2)	758 (10.1)	529 (9.0)

Note: the values between parentheses are column percentages.



Appendix 3.1.1.2. Colorectal cancer (2004-2017), Observed and Relative Survival graphs

Colorectal cancer (2004-2017)

Figure 40 – Colorectal cancer (2004-2017), Kaplan-Meier graphs observed survival by incidence period

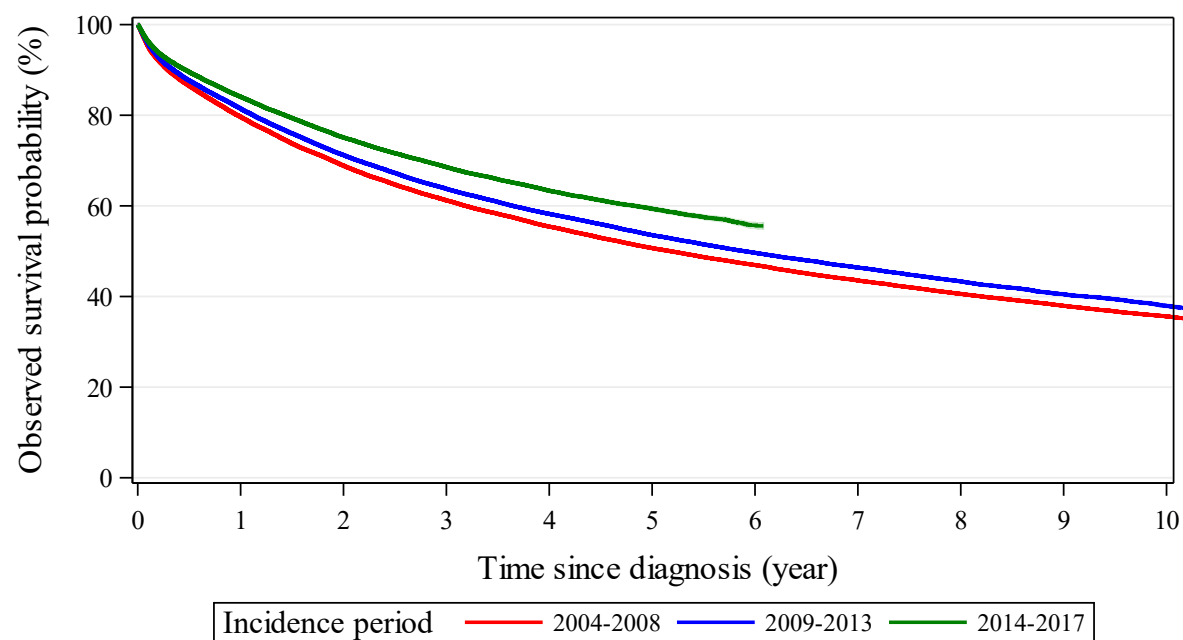
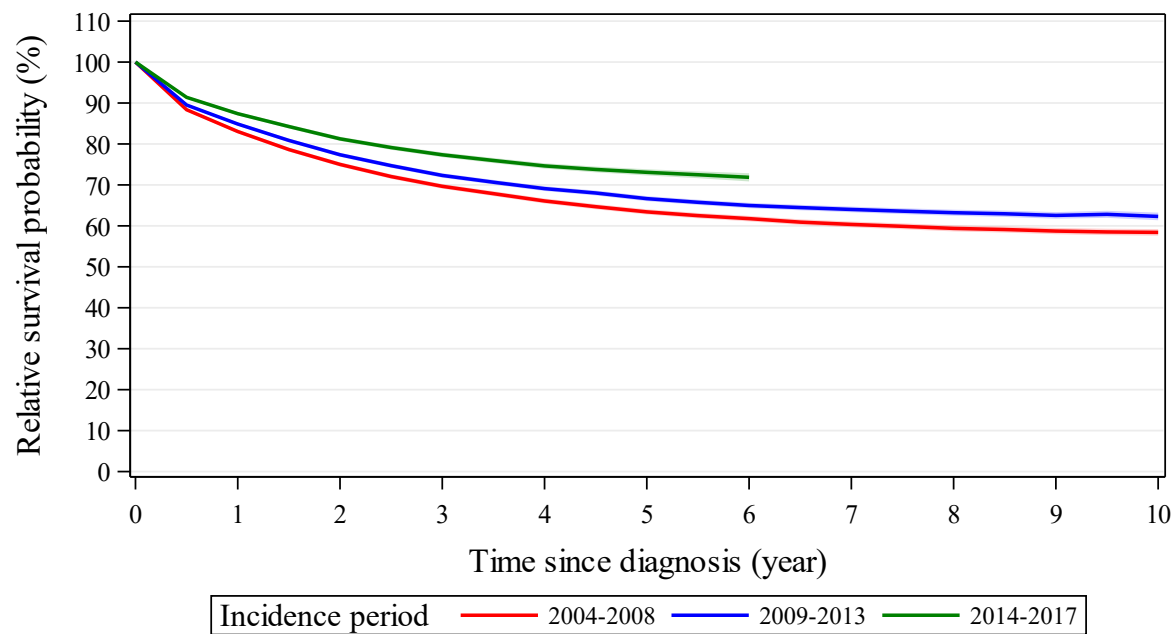




Figure 41 – Colorectal cancer (2004-2017), relative survival graphs by incidence period



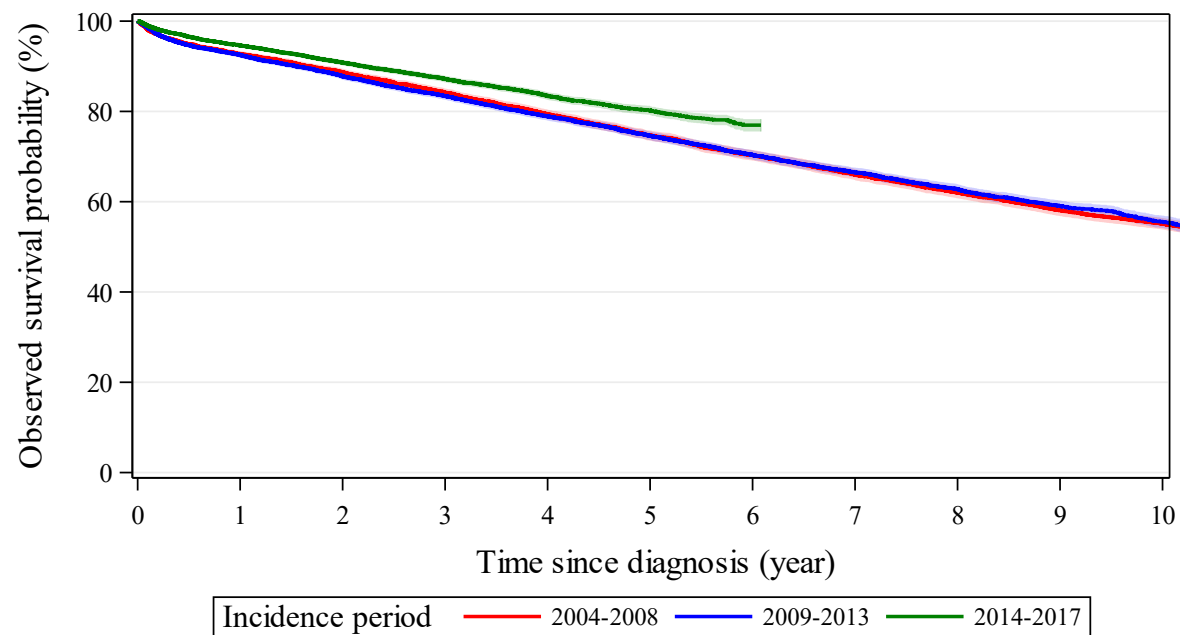
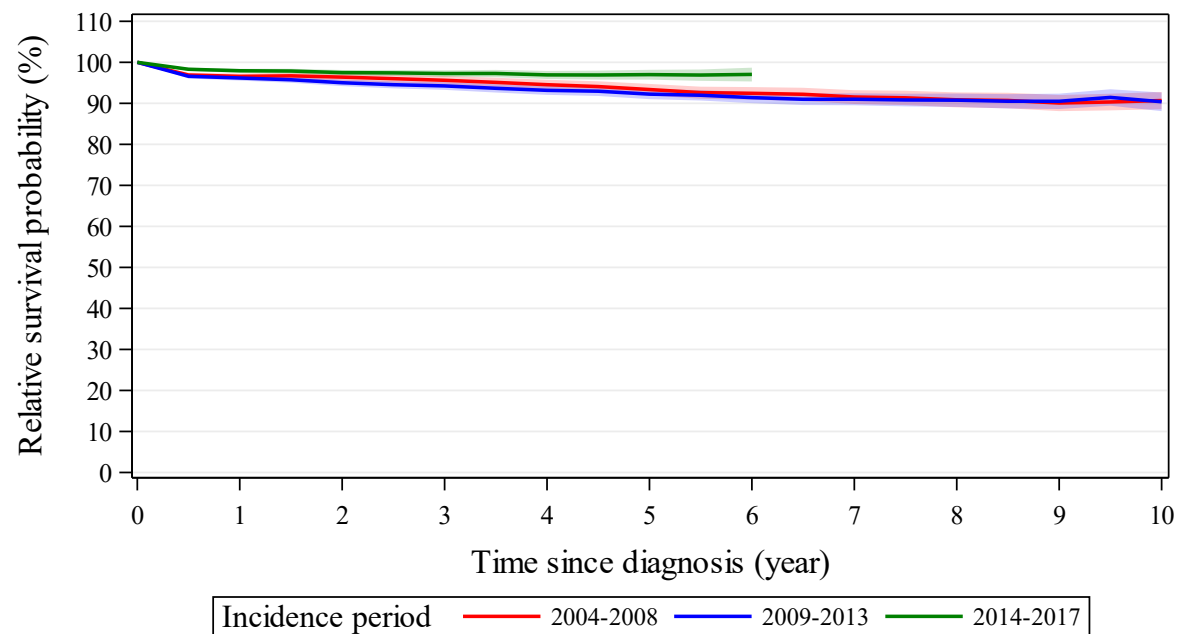
**Colorectal cancer, combined stage I (2004-2017)****Figure 42 – Colorectal cancer (2004-2017), combined stage I, Kaplan-Meier graphs observed survival by incidence period**



Figure 43 – Colorectal cancer (2004-2017), combined stage I, relative survival graphs by incidence period



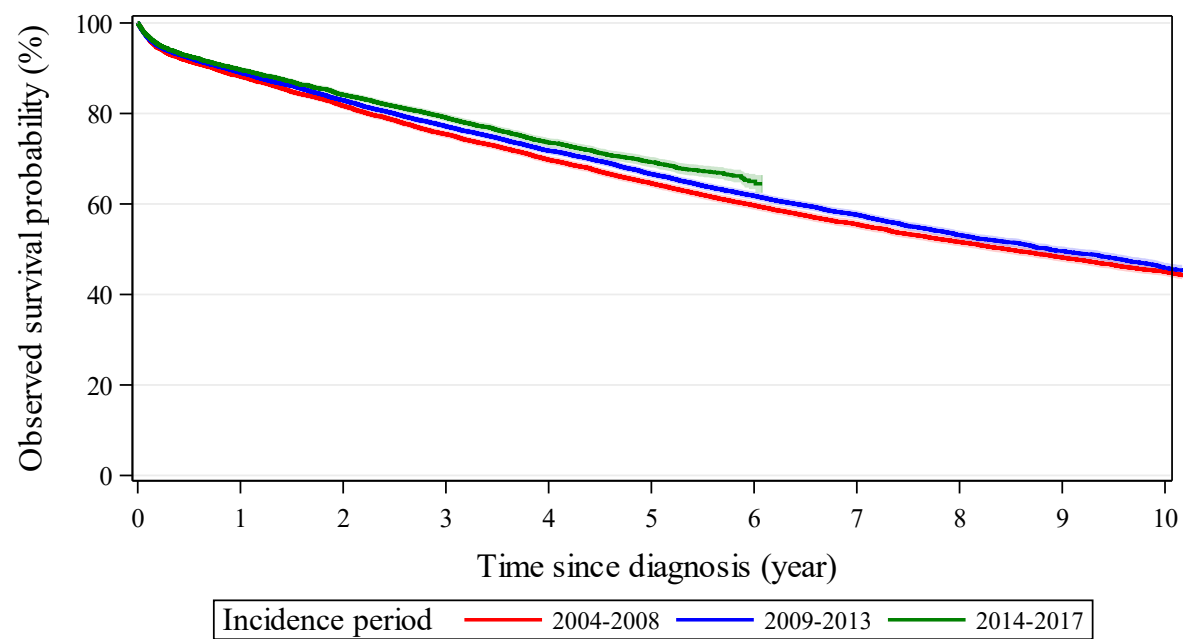
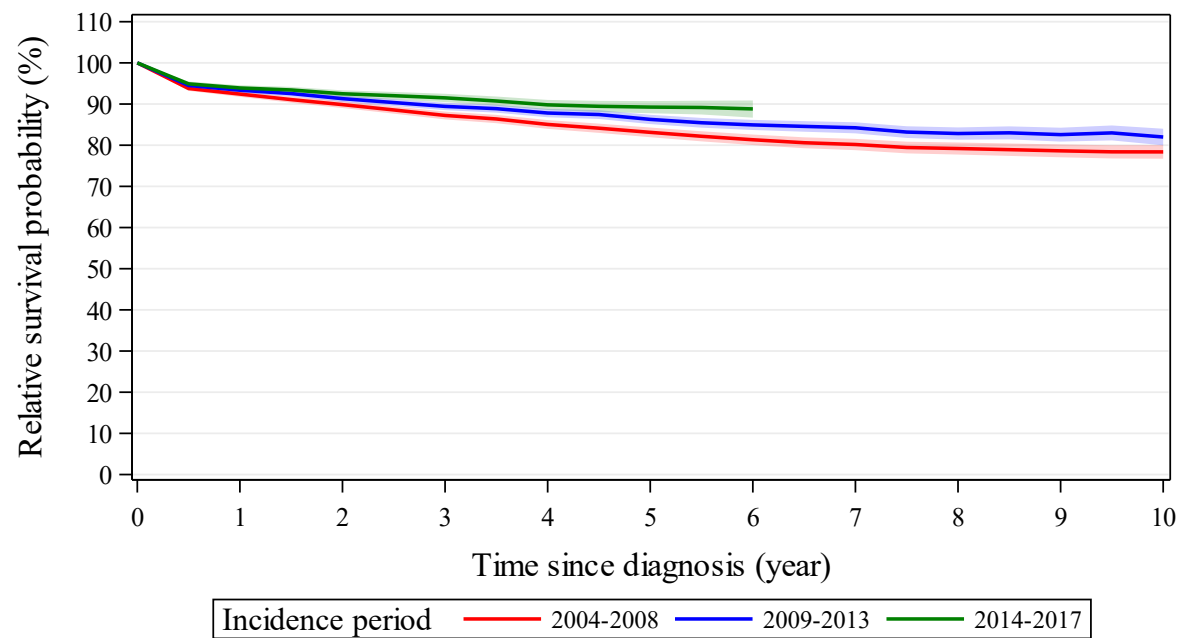
**Colorectal cancer, combined stage II (2004-2017)****Figure 44 – Colorectal cancer (2004-2017), combined stage II, Kaplan-Meier graphs observed survival by incidence period**



Figure 45 – Colorectal cancer (2004-2017), combined stage II, relative survival graphs by incidence period



Colorectal cancer, combined stage III (2004-2017)

Figure 46 – Colorectal cancer (2004-2017), combined stage III, Kaplan-Meier graphs observed survival by incidence period

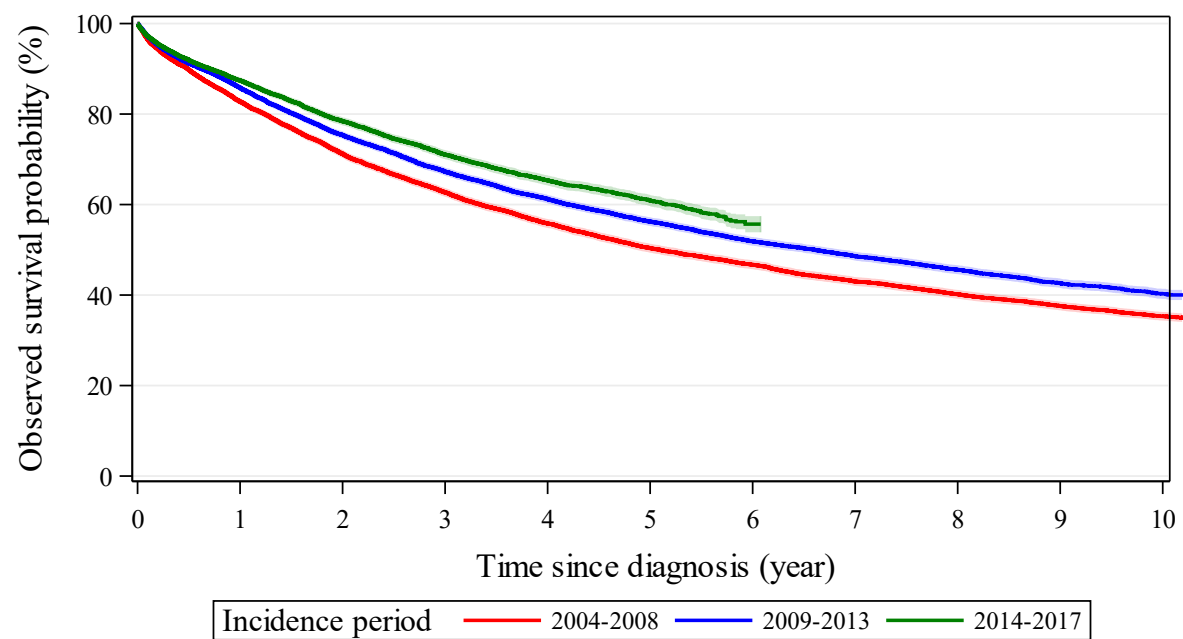
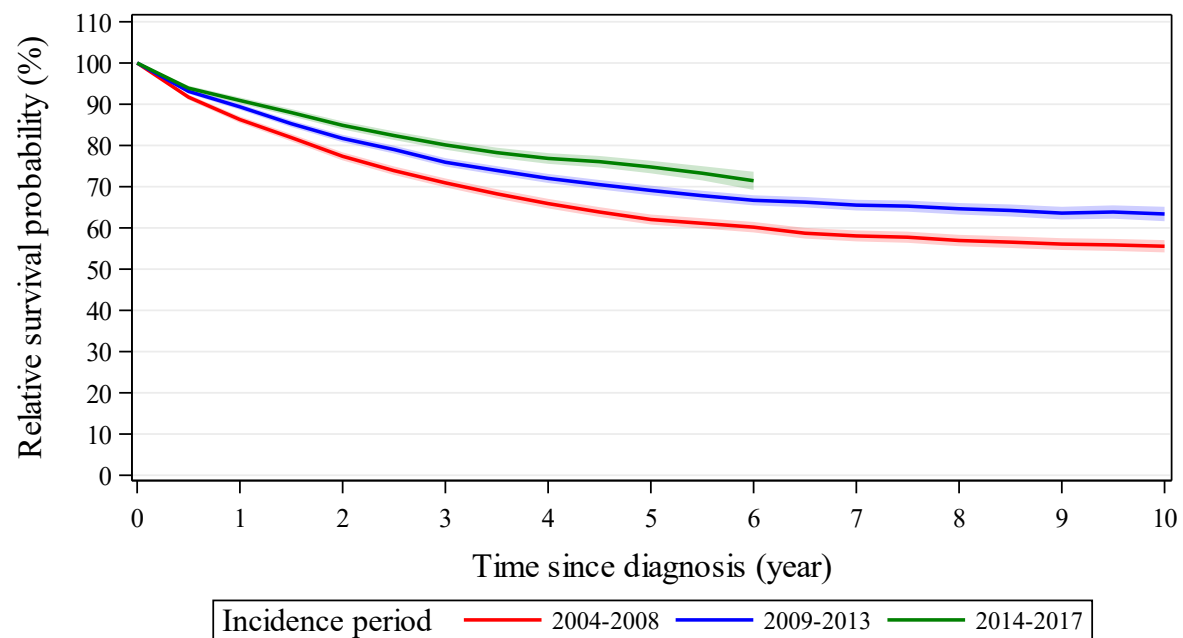




Figure 47 – Colorectal cancer (2004-2017), combined stage III, relative survival graphs by incidence period



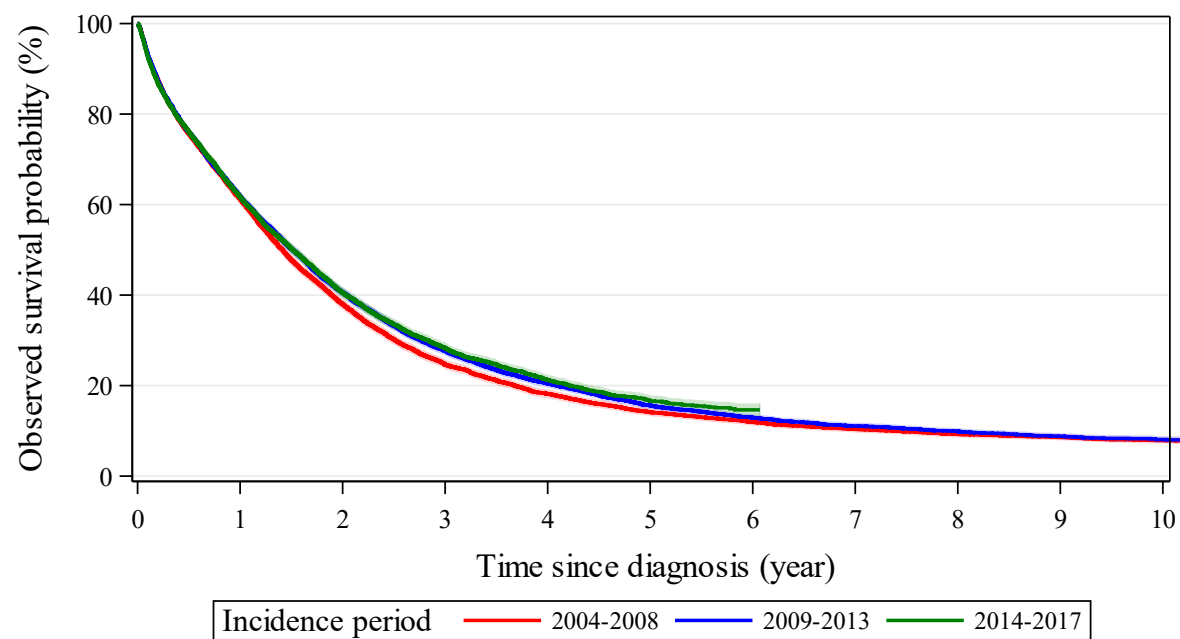
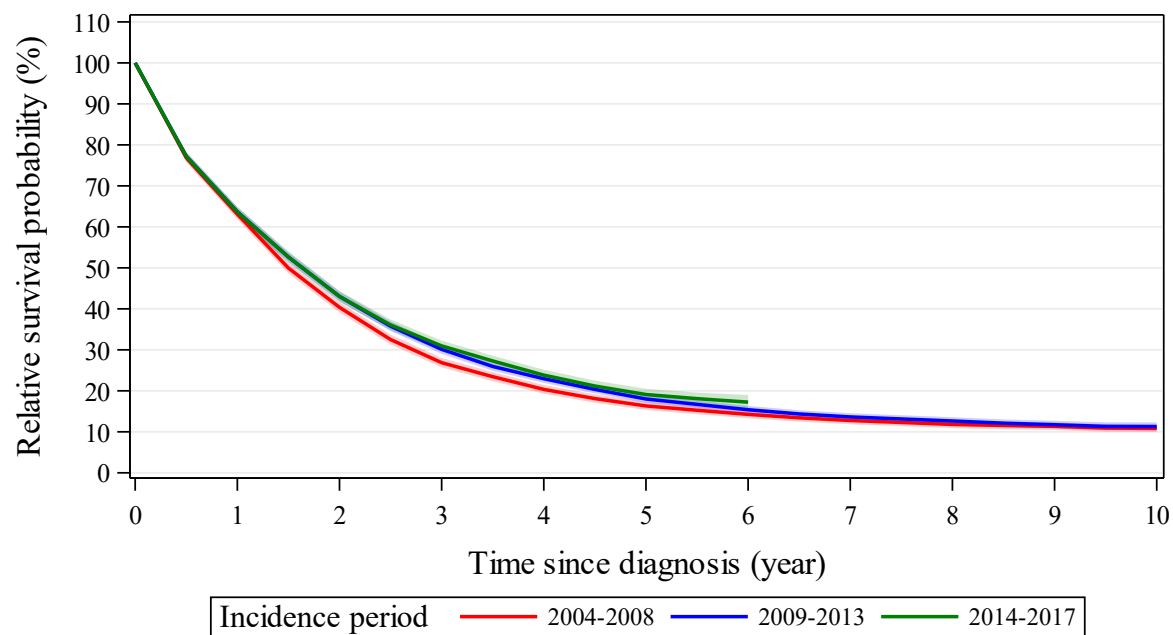
**Colorectal cancer, combined stage IV (2004-2017)****Figure 48 – Colorectal cancer (2004-2017), combined stage IV, Kaplan-Meier graphs observed survival by incidence period**



Figure 49 – Colorectal cancer (2004-2017), combined stage IV, relative survival graphs by incidence period

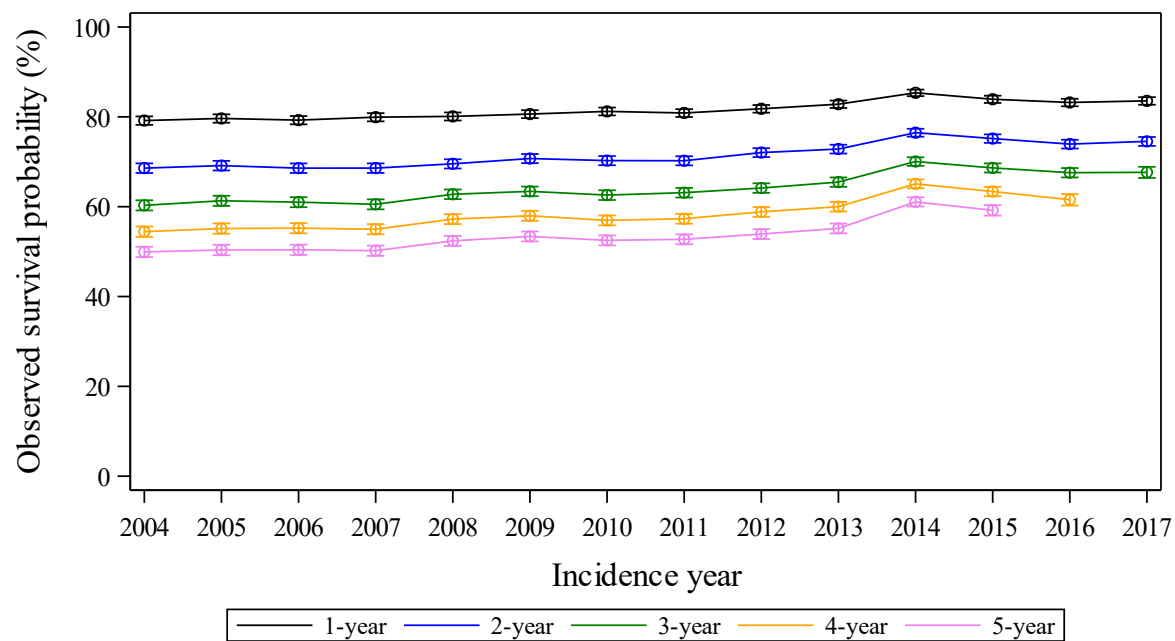




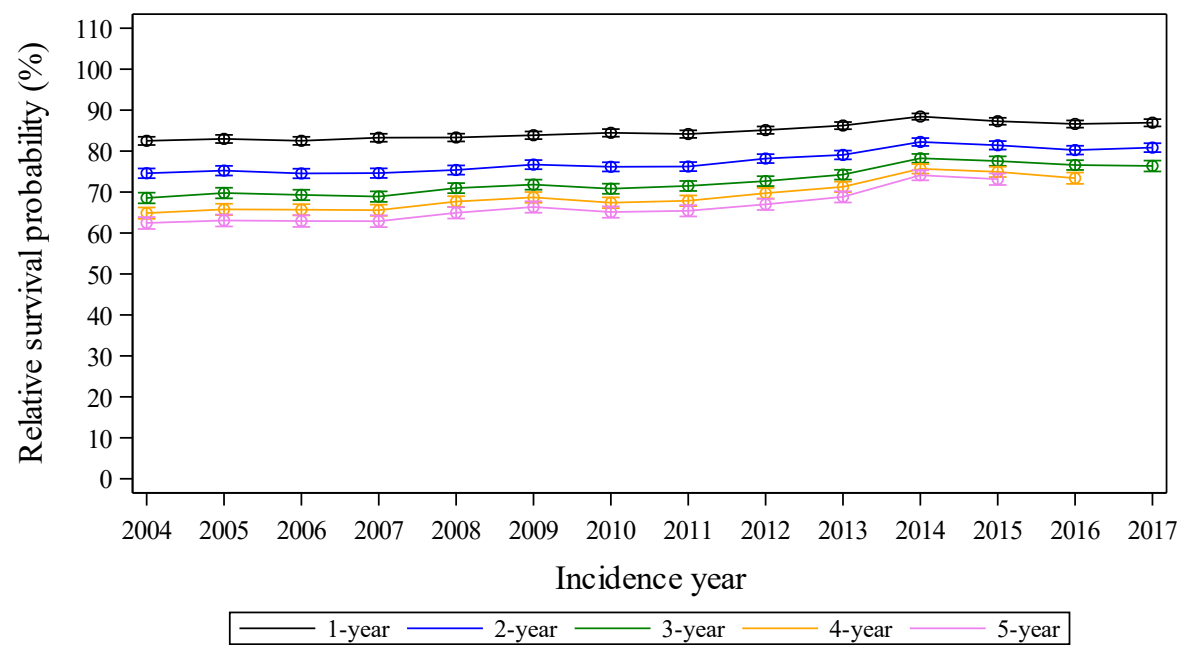
Appendix 3.1.1.3. Colorectal cancer, time trend Observed and Relative Survival

Colorectal cancer (2004-2017)

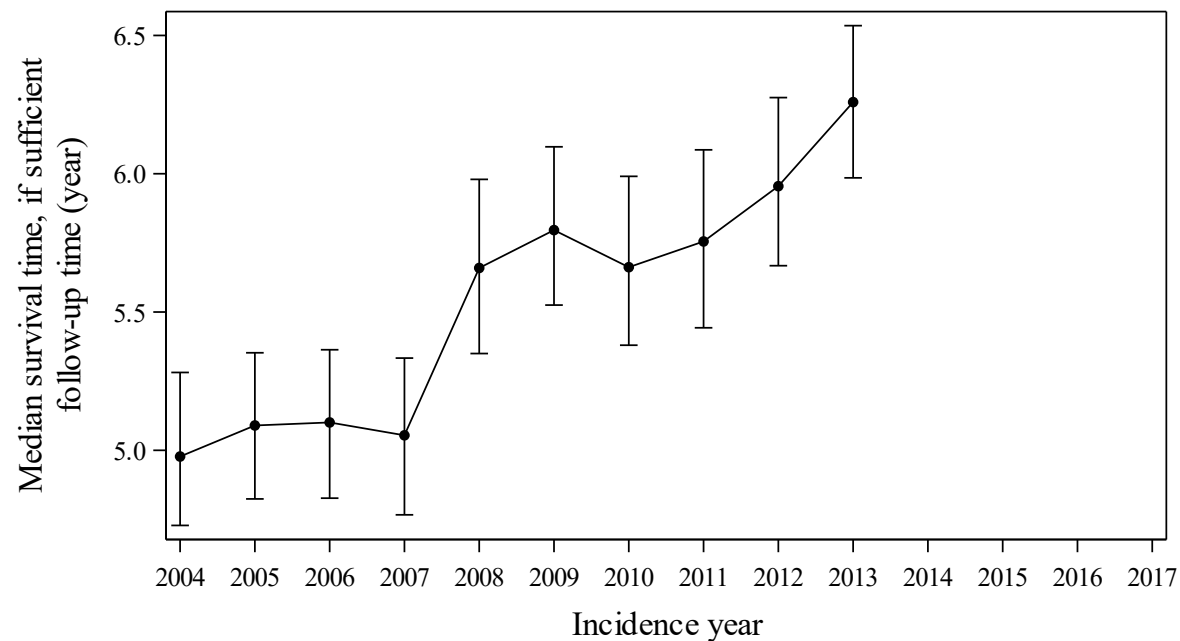
Figure 50 – Colorectal cancer (2004-2017), time trend observed survival with incidence year



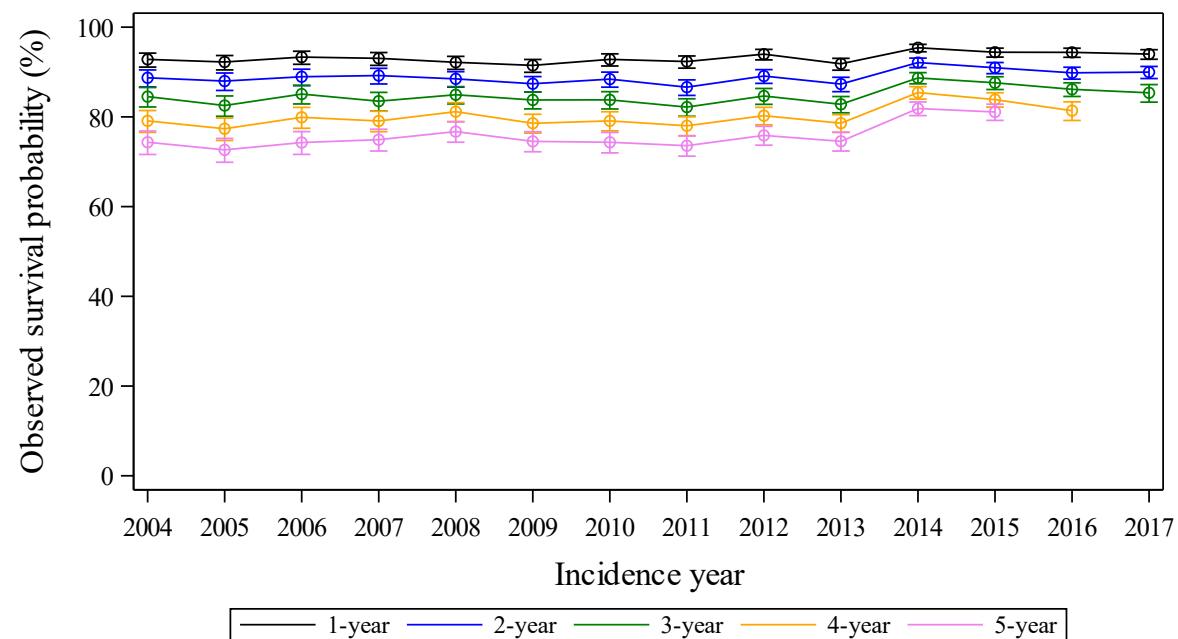
Note: the error bars represent the 95% CI.

**Figure 51 – Colorectal cancer (2004-2017), time trend relative survival with incidence year**

Note: the error bars represent the 95% CI.

**Figure 52 – Colorectal cancer (2004-2017), Median time observed survival**

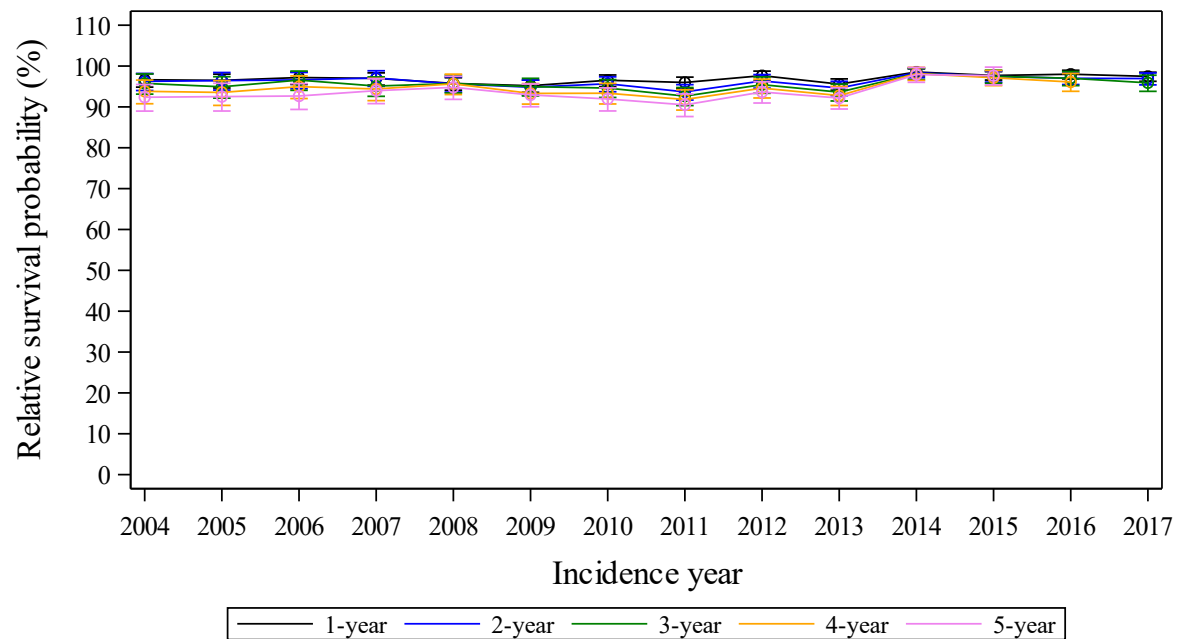
Note: the error bars represent the 95% CI. When the upper error is not plotted, the upper limit could not be determined with the follow-up available.

**Colorectal cancer, combined stage I (2004-2017)****Figure 53 – Colorectal cancer (2004-2017), combined stage I, time trend observed survival with incidence year**

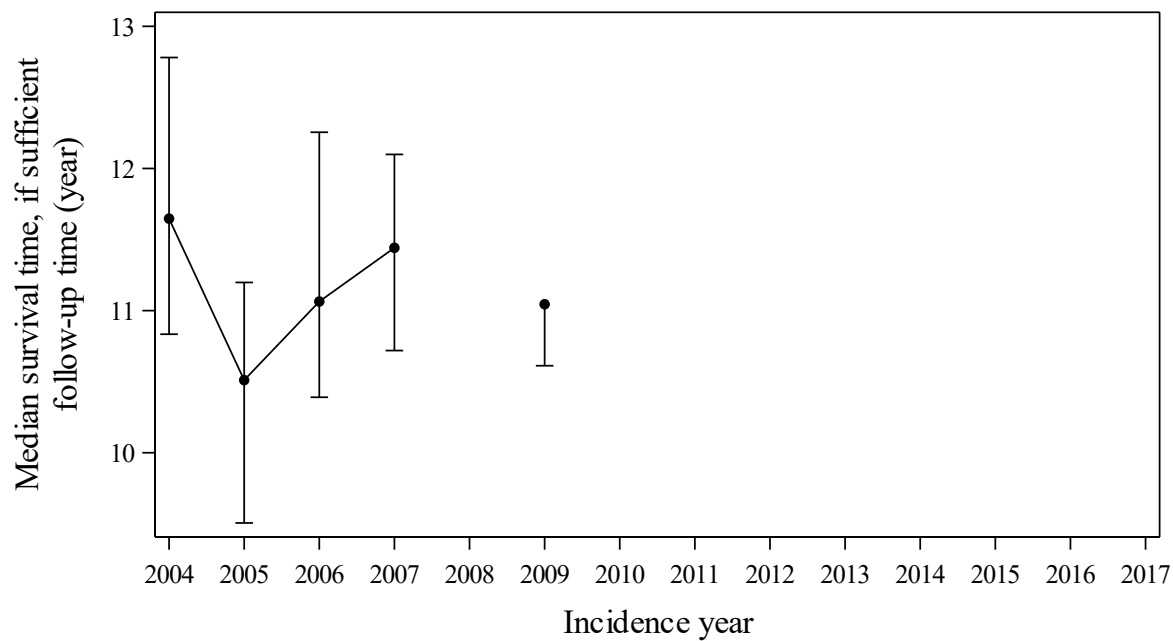
Note: the error bars represent the 95% CI.



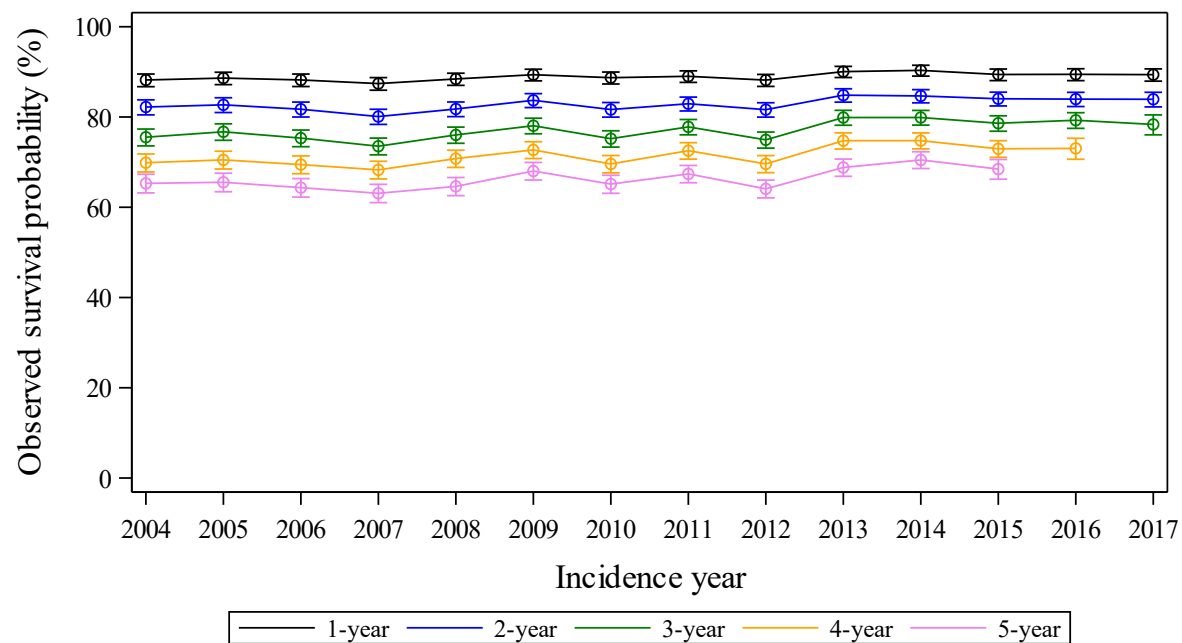
Figure 54 – Colorectal cancer (2004-2017), combined stage I, time trend relative survival with incidence year



Note: the error bars represent the 95% CI.

**Figure 55 – Colorectal cancer (2004-2017), combined stage I, median time observed survival**

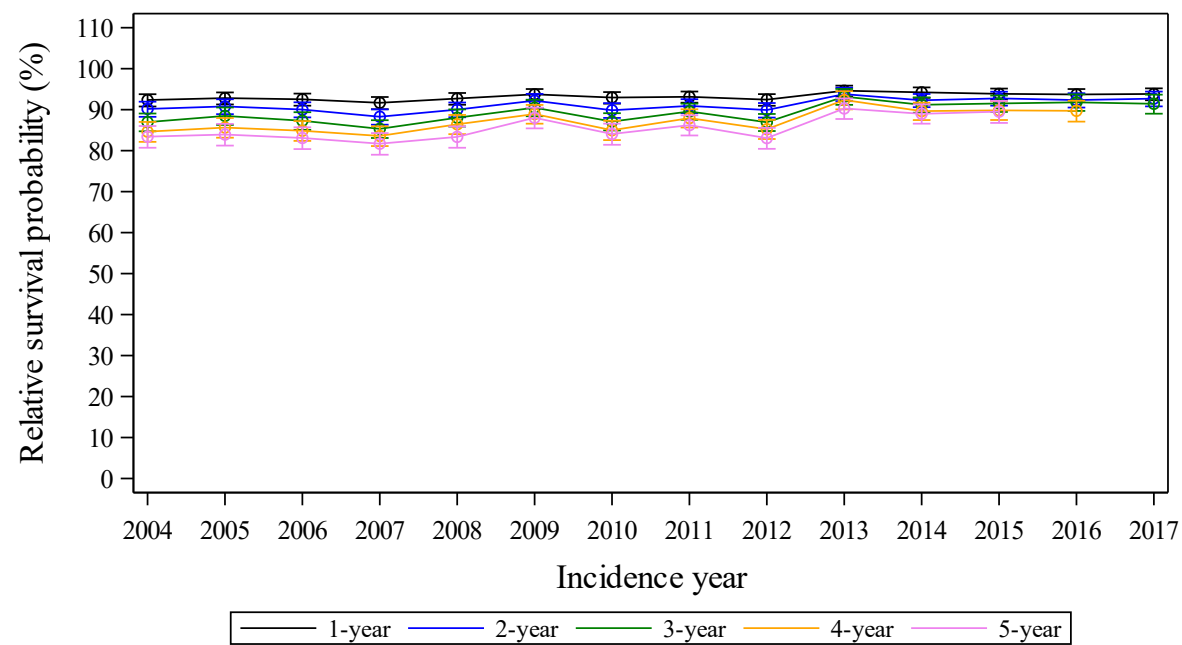
Note: the error bars represent the 95% CI. When the upper error is not plotted, the upper limit could not be determined with the follow-up available.

**Colorectal cancer, combined stage II (2004-2017)****Figure 56 – Colorectal cancer (2004-2017), combined stage II, time trend observed survival with incidence year**

Note: the error bars represent the 95% CI.

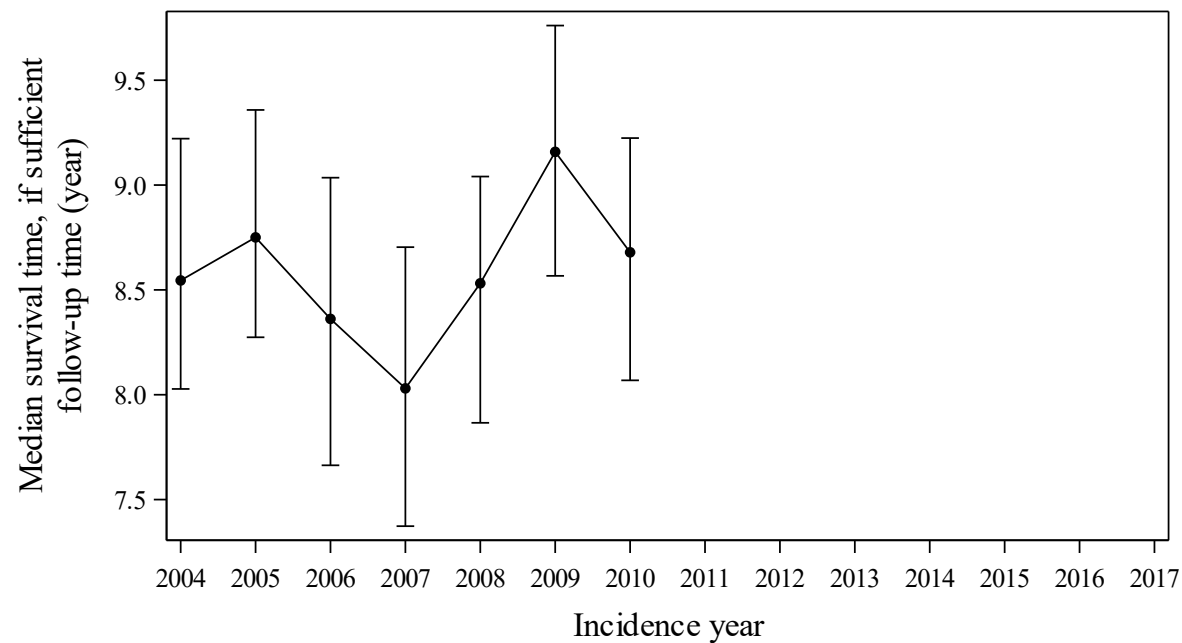


Figure 57 – Colorectal cancer (2004-2017), combined stage II, time trend relative survival with incidence year

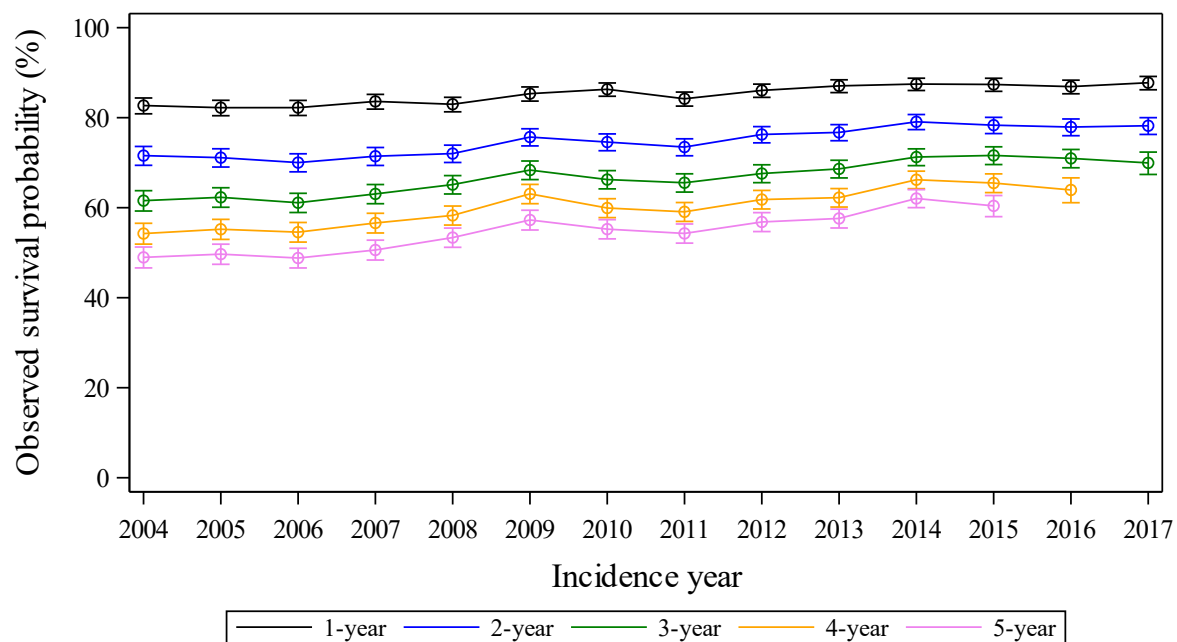


Note: the error bars represent the 95% CI.

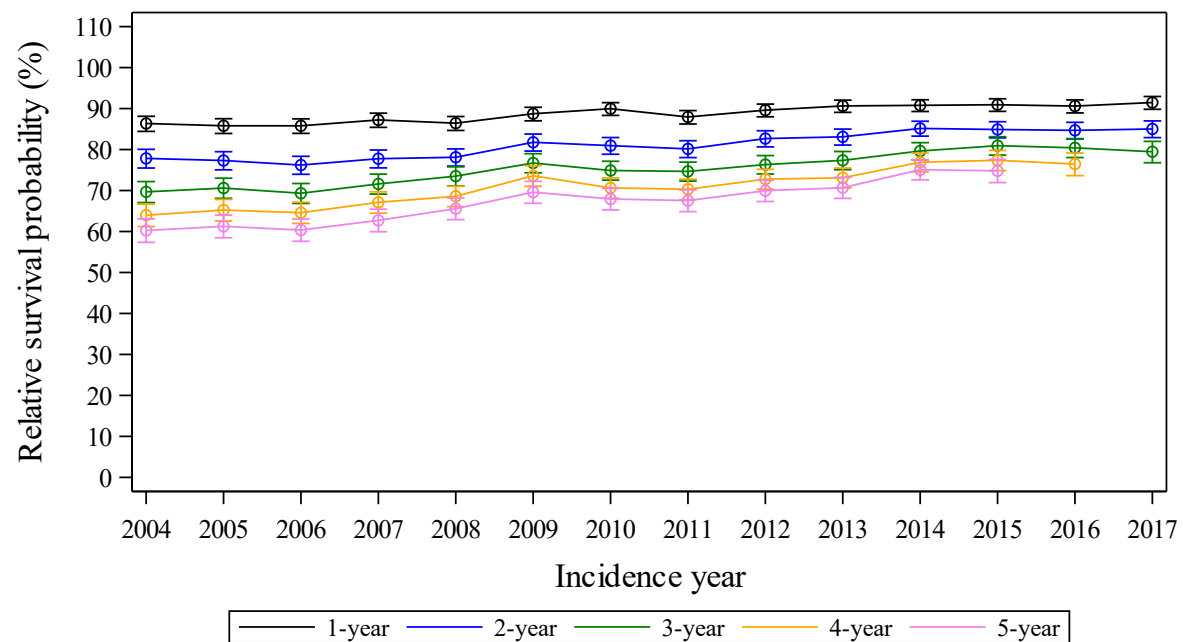
Figure 58 – Colorectal cancer (2004-2017), combined stage II, median time observed survival



Note: the error bars represent the 95% CI. When the upper error is not plotted, the upper limit could not be determined with the follow-up available.

**Colorectal cancer, combined stage III (2004-2017)****Figure 59 – Colorectal cancer (2004-2017), combined stage III, time trend observed survival with incidence year**

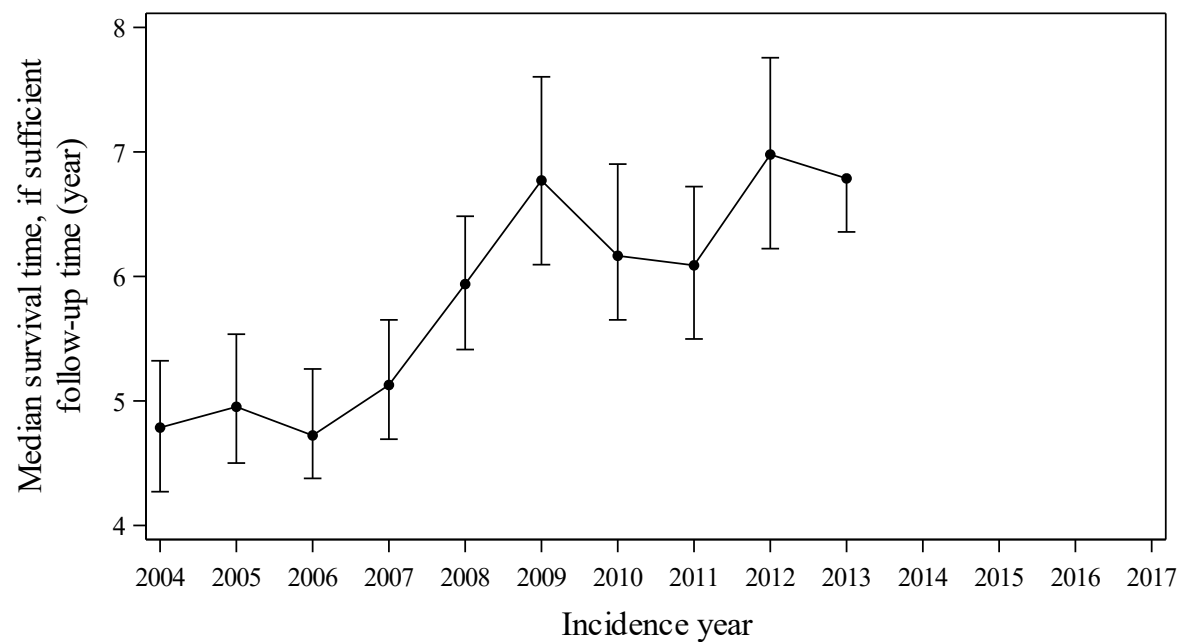
Note: the error bars represent the 95% CI.

**Figure 60 – Colorectal cancer (2004-2017), combined stage III, time trend relative survival with incidence year**

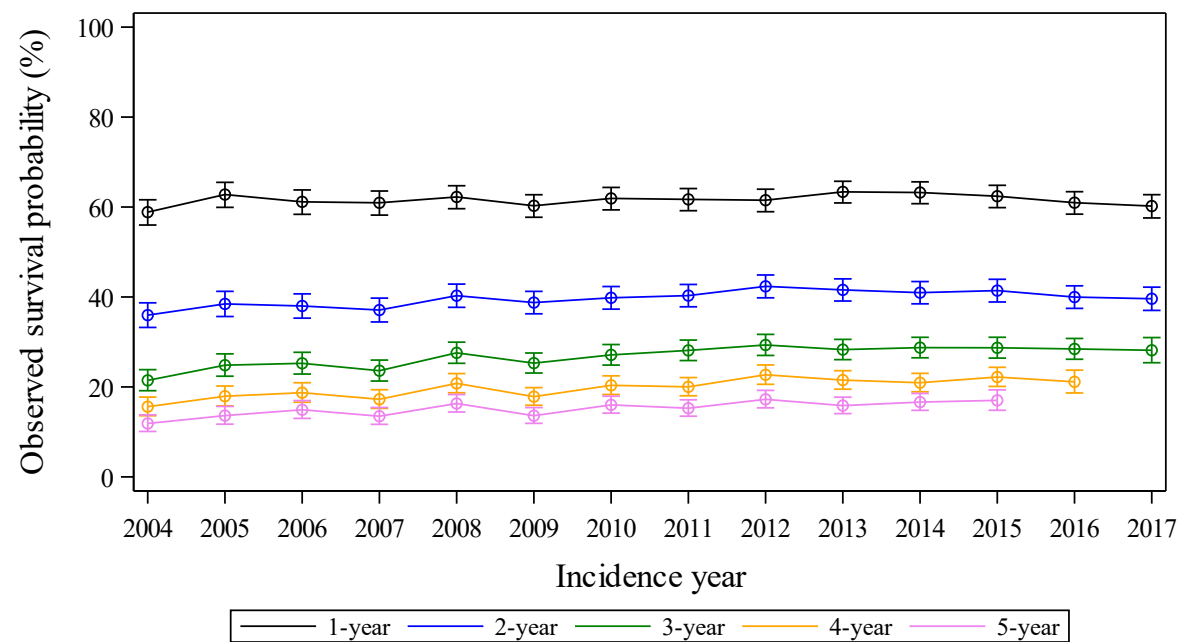
Note: the error bars represent the 95% CI.



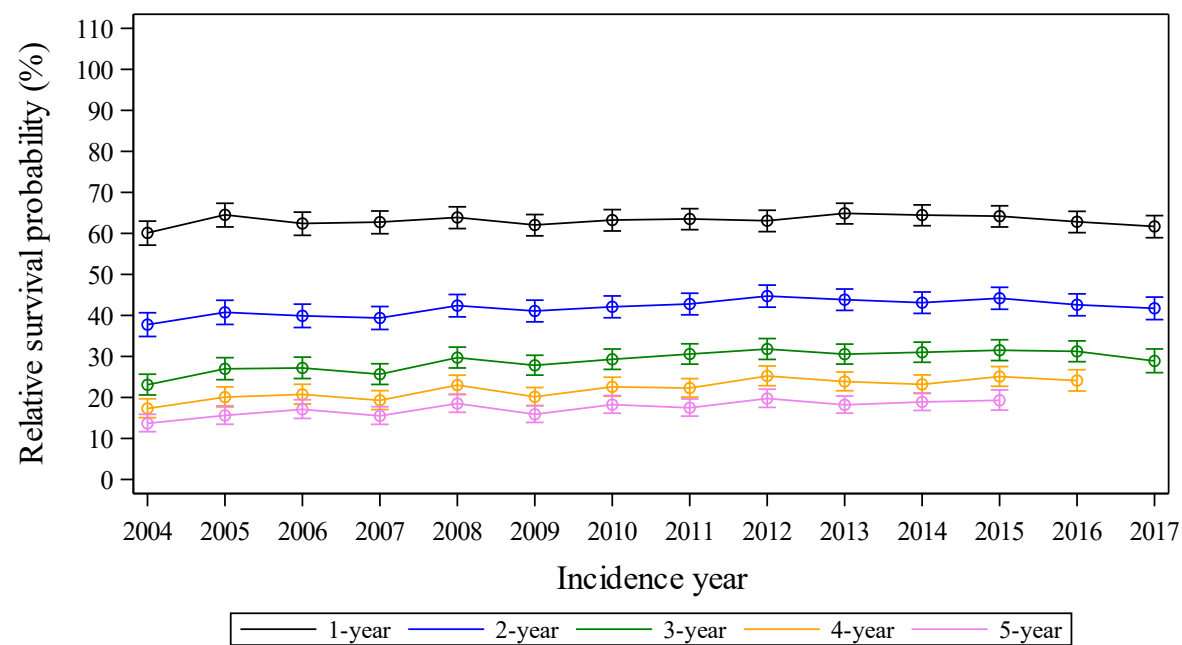
Figure 61 – Colorectal cancer (2004-2017), combined stage III, median time observed survival



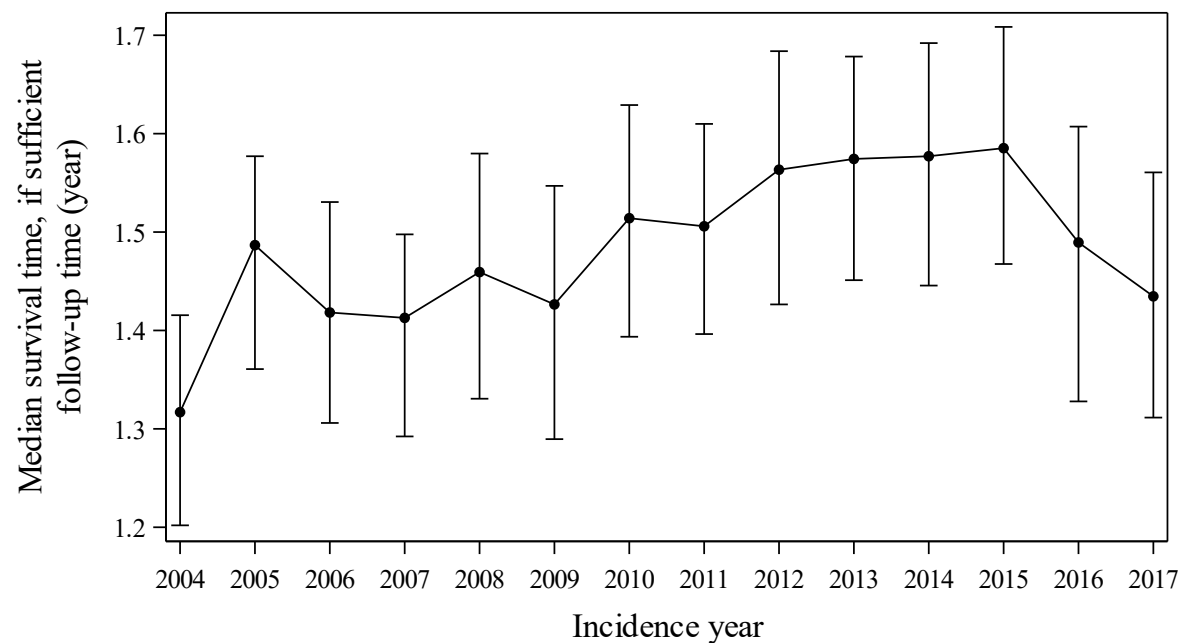
Note: the error bars represent the 95% CI. When the upper error is not plotted, the upper limit could not be determined with the follow-up available.

**Colorectal cancer, combined stage IV (2004-2017)****Figure 62 – Colorectal cancer (2004-2017), combined stage IV, time trend observed survival with incidence year**

Note: the error bars represent the 95% CI.

**Figure 63 – Colorectal cancer (2004-2017), combined stage IV, time trend relative survival with incidence year**

Note: the error bars represent the 95% CI.

**Figure 64 – Colorectal cancer (2004-2017), combined stage IV, median time observed survival**

Note: the error bars represent the 95% CI. When the upper error is not plotted, the upper limit could not be determined with the follow-up available.



Appendix 3.1.1.4. Colorectal cancer, time trend tables Observed and Relative Survival

Table 33 – Colorectal cancer (2004-2017), time trend observed survival with incidence year

Unadjusted observed survival, %													
Characteristic	N at risk	1 year		2 year		3 year		4 year		5 year		Median survival time (year)	
		%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI	T	95% CI
All													
2004	7,181	79.2	[78.2, 80.1]	68.6	[67.5, 69.6]	60.3	[59.2, 61.4]	54.4	[53.3, 55.6]	49.9	[48.8, 51.1]	5.0	[4.7, 5.3]
2005	7,167	79.6	[78.7, 80.6]	69.1	[68.1, 70.2]	61.3	[60.2, 62.4]	55.1	[54.0, 56.3]	50.4	[49.2, 51.5]	5.1	[4.8, 5.4]
2006	7,391	79.3	[78.3, 80.2]	68.6	[67.5, 69.6]	61.0	[59.9, 62.1]	55.2	[54.1, 56.3]	50.4	[49.2, 51.5]	5.1	[4.8, 5.4]
2007	7,402	79.9	[79.0, 80.8]	68.6	[67.5, 69.6]	60.5	[59.4, 61.6]	55.0	[53.8, 56.1]	50.2	[49.1, 51.3]	5.1	[4.8, 5.3]
2008	7,756	80.1	[79.2, 81.0]	69.5	[68.5, 70.5]	62.8	[61.7, 63.8]	57.2	[56.1, 58.3]	52.4	[51.3, 53.5]	5.7	[5.3, 6.0]
2009	7,751	80.6	[79.7, 81.5]	70.7	[69.7, 71.7]	63.4	[62.3, 64.5]	58.0	[56.9, 59.1]	53.4	[52.3, 54.5]	5.8	[5.5, 6.1]
2010	7,733	81.2	[80.3, 82.1]	70.3	[69.2, 71.3]	62.6	[61.5, 63.6]	57.0	[55.8, 58.0]	52.5	[51.4, 53.6]	5.7	[5.4, 6.0]
2011	7,893	80.8	[80.0, 81.7]	70.2	[69.2, 71.2]	63.1	[62.0, 64.2]	57.3	[56.2, 58.4]	52.7	[51.6, 53.8]	5.8	[5.4, 6.1]
2012	7,936	81.8	[80.9, 82.6]	72.0	[71.0, 73.0]	64.1	[63.1, 65.2]	58.8	[57.7, 59.9]	53.9	[52.8, 55.0]	6.0	[5.7, 6.3]
2013	7,991	82.8	[82.0, 83.6]	72.8	[71.8, 73.8]	65.5	[64.4, 66.5]	60.0	[58.9, 61.1]	55.2	[54.1, 56.3]	6.3	[6.0, 6.5]
2014	8,963	85.3	[84.6, 86.1]	76.5	[75.6, 77.3]	70.0	[69.1, 71.0]	65.1	[64.1, 66.1]	61.1	[60.1, 62.1]	>6	
2015	8,039	83.9	[83.1, 84.7]	75.2	[74.2, 76.1]	68.6	[67.6, 69.6]	63.4	[62.3, 64.4]	59.2	[58.0, 60.3]	>5	
2016	7,775	83.2	[82.3, 84.0]	73.9	[72.9, 74.9]	67.6	[66.5, 68.6]	61.6	[60.2, 62.8]	no FU	—	>4	
2017	7,469	83.5	[82.7, 84.4]	74.5	[73.5, 75.5]	67.6	[66.4, 68.9]	no FU	—	no FU	—	>3	
Combined Stage I													
2004	1,074	92.8	[91.1, 94.2]	88.7	[86.7, 90.5]	84.5	[82.2, 86.6]	79.1	[76.5, 81.4]	74.3	[71.6, 76.9]	11.6	[10.8, 12.8]
2005	1,082	92.2	[90.5, 93.7]	88.0	[85.9, 89.8]	82.5	[80.1, 84.7]	77.4	[74.7, 79.7]	72.6	[69.9, 75.2]	10.5	[9.5, 11.2]
2006	1,140	93.3	[91.7, 94.6]	88.9	[87.0, 90.6]	85.1	[82.9, 87.0]	79.9	[77.5, 82.1]	74.3	[71.6, 76.7]	11.1	[10.4, 12.3]
2007	1,224	93.1	[91.5, 94.3]	89.2	[87.3, 90.8]	83.5	[81.3, 85.5]	79.1	[76.7, 81.3]	74.9	[72.4, 77.3]	11.4	[10.7, 12.1]
2008	1,328	92.2	[90.6, 93.5]	88.5	[86.6, 90.1]	84.9	[82.9, 86.7]	81.2	[79.0, 83.2]	76.7	[74.4, 78.9]	>12	
2009	1,469	91.5	[89.9, 92.8]	87.4	[85.6, 89.0]	83.8	[81.8, 85.6]	78.6	[76.4, 80.6]	74.5	[72.2, 76.7]	11.0	[10.6, 11.4]



2010	1,408	92.8	[91.3, 94.1]	88.4	[86.6, 90.0]	83.8	[81.8, 85.6]	79.1	[76.9, 81.1]	74.3	[72.0, 76.5]	>10
2011	1,489	92.3	[90.9, 93.6]	86.6	[84.8, 88.3]	82.2	[80.1, 84.0]	78.0	[75.8, 80.0]	73.6	[71.3, 75.7]	>9
2012	1,597	94.0	[92.7, 95.1]	89.1	[87.5, 90.5]	84.7	[82.8, 86.3]	80.3	[78.2, 82.1]	75.9	[73.7, 77.9]	>8
2013	1,666	91.8	[90.4, 93.1]	87.3	[85.6, 88.8]	82.8	[80.9, 84.5]	78.6	[76.5, 80.5]	74.6	[72.4, 76.6]	>7
2014	2,487	95.4	[94.5, 96.2]	92.1	[91.0, 93.1]	88.7	[87.4, 89.9]	85.4	[84.0, 86.7]	81.9	[80.3, 83.3]	>6
2015	2,058	94.4	[93.3, 95.3]	91.0	[89.6, 92.1]	87.6	[86.1, 89.0]	83.8	[82.2, 85.4]	81.1	[79.2, 82.8]	>5
2016	1,997	94.4	[93.3, 95.3]	89.8	[88.4, 91.1]	86.1	[84.6, 87.6]	81.4	[79.2, 83.4]	no FU	—	>4
2017	1,919	94.0	[92.8, 95.0]	90.0	[88.5, 91.2]	85.4	[83.3, 87.2]	no FU	—	no FU	—	>3
Combined Stage II												
2004	2,035	88.2	[86.7, 89.5]	82.2	[80.5, 83.8]	75.5	[73.6, 77.3]	69.9	[67.8, 71.8]	65.3	[63.2, 67.3]	8.5 [8.0, 9.2]
2005	2,058	88.6	[87.2, 89.9]	82.7	[81.0, 84.3]	76.7	[74.8, 78.5]	70.5	[68.5, 72.4]	65.5	[63.4, 67.5]	8.8 [8.3, 9.4]
2006	2,097	88.2	[86.8, 89.5]	81.7	[80.0, 83.3]	75.3	[73.4, 77.1]	69.5	[67.4, 71.4]	64.3	[62.3, 66.4]	8.4 [7.7, 9.0]
2007	2,177	87.4	[85.9, 88.7]	80.1	[78.4, 81.7]	73.5	[71.6, 75.3]	68.3	[66.3, 70.2]	63.1	[61.0, 65.1]	8.0 [7.4, 8.7]
2008	2,180	88.4	[87.0, 89.7]	81.8	[80.1, 83.3]	76.0	[74.2, 77.8]	70.8	[68.8, 72.6]	64.6	[62.6, 66.6]	8.5 [7.9, 9.0]
2009	2,204	89.4	[88.0, 90.6]	83.7	[82.1, 85.2]	78.1	[76.3, 79.7]	72.7	[70.8, 74.5]	68.0	[66.0, 69.9]	9.2 [8.6, 9.8]
2010	2,198	88.7	[87.3, 90.0]	81.7	[80.0, 83.2]	75.2	[73.3, 76.9]	69.6	[67.6, 71.5]	65.1	[63.1, 67.1]	8.7 [8.1, 9.2]
2011	2,305	89.0	[87.7, 90.2]	82.9	[81.3, 84.4]	77.8	[76.1, 79.5]	72.5	[70.7, 74.3]	67.4	[65.4, 69.3]	>9
2012	2,276	88.2	[86.8, 89.4]	81.6	[80.0, 83.2]	74.9	[73.1, 76.7]	69.6	[67.7, 71.5]	64.1	[62.1, 66.0]	>8
2013	2,264	90.1	[88.8, 91.2]	84.8	[83.3, 86.3]	79.9	[78.2, 81.5]	74.7	[72.9, 76.5]	68.8	[66.9, 70.7]	>7
2014	2,330	90.3	[89.1, 91.5]	84.7	[83.1, 86.1]	79.9	[78.2, 81.5]	74.8	[72.9, 76.5]	70.5	[68.6, 72.3]	>6
2015	2,213	89.4	[88.1, 90.6]	84.0	[82.5, 85.5]	78.6	[76.8, 80.3]	73.0	[71.1, 74.8]	68.5	[66.2, 70.6]	>5
2016	2,097	89.5	[88.1, 90.7]	84.0	[82.3, 85.5]	79.3	[77.5, 81.0]	73.0	[70.6, 75.3]	no FU	—	>4
2017	1,982	89.4	[88.0, 90.7]	83.9	[82.2, 85.5]	78.4	[76.0, 80.5]	no FU	—	no FU	—	>3
Combined Stage III												
2004	1,780	82.7	[80.9, 84.4]	71.6	[69.4, 73.6]	61.6	[59.3, 63.8]	54.3	[51.9, 56.5]	49.0	[46.6, 51.3]	4.8 [4.3, 5.3]
2005	1,920	82.2	[80.4, 83.9]	71.1	[69.0, 73.1]	62.3	[60.1, 64.4]	55.2	[53.0, 57.4]	49.7	[47.4, 51.9]	5.0 [4.5, 5.5]
2006	2,011	82.2	[80.5, 83.8]	70.0	[68.0, 72.0]	61.1	[58.9, 63.2]	54.6	[52.4, 56.7]	48.8	[46.6, 51.0]	4.7 [4.4, 5.3]
2007	1,971	83.6	[81.9, 85.2]	71.4	[69.4, 73.4]	63.1	[60.9, 65.1]	56.6	[54.4, 58.8]	50.6	[48.4, 52.8]	5.1 [4.7, 5.7]



2008	2,092	83.0	[81.3, 84.5]	72.0	[70.0, 73.9]	65.1	[63.0, 67.1]	58.3	[56.1, 60.4]	53.4	[51.2, 55.5]	5.9	[5.4, 6.5]
2009	1,950	85.3	[83.7, 86.8]	75.7	[73.7, 77.5]	68.4	[66.2, 70.4]	63.1	[60.9, 65.2]	57.3	[55.0, 59.4]	6.8	[6.1, 7.6]
2010	2,091	86.3	[84.8, 87.7]	74.6	[72.7, 76.4]	66.3	[64.2, 68.2]	59.9	[57.8, 62.0]	55.2	[53.1, 57.3]	6.2	[5.7, 6.9]
2011	2,108	84.2	[82.6, 85.7]	73.5	[71.5, 75.3]	65.5	[63.5, 67.5]	59.1	[56.9, 61.1]	54.3	[52.1, 56.4]	6.1	[5.5, 6.7]
2012	2,139	86.1	[84.5, 87.5]	76.3	[74.4, 78.0]	67.6	[65.6, 69.5]	61.8	[59.7, 63.8]	56.8	[54.7, 58.9]	7.0	[6.2, 7.8]
2013	2,152	87.1	[85.6, 88.4]	76.7	[74.9, 78.5]	68.6	[66.6, 70.5]	62.2	[60.1, 64.2]	57.6	[55.5, 59.7]	6.8	[6.4, .]
2014	2,270	87.5	[86.0, 88.8]	79.1	[77.3, 80.7]	71.3	[69.3, 73.1]	66.2	[64.2, 68.1]	62.0	[60.0, 64.0]	>6	
2015	2,014	87.4	[85.9, 88.8]	78.3	[76.5, 80.1]	71.6	[69.6, 73.5]	65.5	[63.4, 67.5]	60.4	[58.0, 62.7]	>5	
2016	1,918	86.9	[85.3, 88.3]	77.9	[76.0, 79.7]	71.0	[68.9, 72.9]	63.9	[61.1, 66.6]	no FU	—	>4	
2017	1,888	87.8	[86.2, 89.2]	78.2	[76.3, 80.0]	69.9	[67.4, 72.4]	no FU	—	no FU	—	>3	
Combined Stage IV													
2004	1,179	58.9	[56.0, 61.6]	36.0	[33.2, 38.7]	21.5	[19.2, 23.8]	15.6	[13.6, 17.7]	11.9	[10.1, 13.8]	1.3	[1.2, 1.4]
2005	1,161	62.8	[59.9, 65.5]	38.5	[35.7, 41.3]	24.8	[22.4, 27.4]	17.9	[15.8, 20.2]	13.6	[11.7, 15.7]	1.5	[1.4, 1.6]
2006	1,242	61.2	[58.4, 63.8]	38.0	[35.3, 40.7]	25.3	[22.9, 27.7]	18.7	[16.6, 20.9]	14.9	[13.0, 17.0]	1.4	[1.3, 1.5]
2007	1,275	60.9	[58.2, 63.6]	37.1	[34.4, 39.7]	23.6	[21.3, 26.0]	17.3	[15.2, 19.4]	13.5	[11.7, 15.4]	1.4	[1.3, 1.5]
2008	1,385	62.2	[59.6, 64.7]	40.3	[37.7, 42.9]	27.6	[25.3, 30.0]	20.8	[18.7, 23.0]	16.3	[14.4, 18.3]	1.5	[1.3, 1.6]
2009	1,467	60.3	[57.7, 62.7]	38.8	[36.3, 41.2]	25.3	[23.1, 27.5]	17.8	[15.9, 19.8]	13.6	[11.9, 15.4]	1.4	[1.3, 1.5]
2010	1,455	61.9	[59.4, 64.4]	39.8	[37.3, 42.3]	27.1	[24.9, 29.4]	20.4	[18.3, 22.5]	16.0	[14.2, 17.9]	1.5	[1.4, 1.6]
2011	1,497	61.7	[59.2, 64.1]	40.3	[37.8, 42.8]	28.1	[25.9, 30.4]	20.0	[18.0, 22.1]	15.3	[13.5, 17.1]	1.5	[1.4, 1.6]
2012	1,453	61.5	[59.0, 64.0]	42.4	[39.8, 44.9]	29.3	[27.0, 31.7]	22.7	[20.6, 24.9]	17.2	[15.4, 19.2]	1.6	[1.4, 1.7]
2013	1,537	63.4	[60.9, 65.7]	41.6	[39.1, 44.0]	28.3	[26.1, 30.6]	21.5	[19.5, 23.6]	15.8	[14.1, 17.7]	1.6	[1.5, 1.7]
2014	1,515	63.2	[60.7, 65.6]	41.0	[38.5, 43.4]	28.7	[26.5, 31.0]	20.9	[18.9, 23.0]	16.6	[14.8, 18.6]	1.6	[1.4, 1.7]
2015	1,466	62.4	[59.9, 64.8]	41.4	[38.9, 43.9]	28.7	[26.4, 31.0]	22.2	[20.1, 24.4]	17.0	[14.8, 19.4]	1.6	[1.5, 1.7]
2016	1,466	61.0	[58.4, 63.4]	40.0	[37.5, 42.5]	28.4	[26.2, 30.8]	21.1	[18.7, 23.7]	no FU	—	1.5	[1.3, 1.6]
2017	1,375	60.2	[57.6, 62.7]	39.6	[37.0, 42.2]	28.2	[25.4, 31.0]	no FU	—	no FU	—	1.4	[1.3, 1.6]


Table 34 – Colorectal cancer (2004-2017), time trend relative survival with incidence year

Characteristic	N at risk	Unadjusted relative survival, %									
		1 year		2 year		3 year		4 year		5 year	
		%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI
All											
2004	7,181	82.5	[81.5, 83.5]	74.6	[73.4, 75.8]	68.6	[67.2, 69.8]	64.9	[63.5, 66.2]	62.4	[61.0, 63.9]
2005	7,167	83.0	[82.0, 84.0]	75.2	[74.0, 76.4]	69.8	[68.5, 71.1]	65.8	[64.4, 67.1]	63.1	[61.6, 64.5]
2006	7,391	82.5	[81.5, 83.5]	74.5	[73.4, 75.7]	69.3	[68.0, 70.6]	65.7	[64.3, 67.0]	62.9	[61.5, 64.3]
2007	7,402	83.3	[82.3, 84.2]	74.6	[73.4, 75.8]	68.9	[67.6, 70.2]	65.6	[64.2, 66.9]	62.9	[61.4, 64.3]
2008	7,756	83.3	[82.4, 84.2]	75.4	[74.2, 76.5]	71.0	[69.7, 72.2]	67.7	[66.4, 69.0]	64.9	[63.5, 66.3]
2009	7,751	83.9	[82.9, 84.8]	76.7	[75.6, 77.8]	71.8	[70.6, 73.0]	68.7	[67.4, 70.0]	66.4	[65.0, 67.7]
2010	7,733	84.5	[83.5, 85.4]	76.2	[75.0, 77.3]	70.8	[69.6, 72.0]	67.4	[66.1, 68.7]	65.1	[63.7, 66.5]
2011	7,893	84.2	[83.2, 85.1]	76.2	[75.1, 77.3]	71.5	[70.3, 72.7]	67.9	[66.6, 69.2]	65.4	[64.0, 66.8]
2012	7,936	85.1	[84.2, 86.0]	78.2	[77.1, 79.2]	72.7	[71.5, 73.9]	69.7	[68.4, 71.0]	67.0	[65.6, 68.4]
2013	7,991	86.2	[85.3, 87.1]	79.1	[78.0, 80.1]	74.3	[73.0, 75.4]	71.3	[70.0, 72.5]	68.8	[67.4, 70.2]
2014	8,963	88.4	[87.6, 89.2]	82.2	[81.3, 83.2]	78.2	[77.2, 79.3]	75.7	[74.5, 76.8]	74.1	[72.9, 75.3]
2015	8,039	87.3	[86.4, 88.1]	81.4	[80.4, 82.4]	77.6	[76.4, 78.7]	74.9	[73.7, 76.2]	73.1	[71.7, 74.5]
2016	7,775	86.6	[85.7, 87.5]	80.2	[79.2, 81.3]	76.6	[75.4, 77.8]	73.4	[72.0, 74.8]	no FU	—
2017	7,469	86.9	[86.0, 87.8]	80.9	[79.8, 81.9]	76.4	[75.0, 77.7]	no FU	—	no FU	—
Combined Stage I											
2004	1,074	96.7	[94.8, 98.1]	96.3	[94.0, 98.2]	95.8	[93.1, 98.1]	93.8	[90.8, 96.6]	92.4	[89.0, 95.5]
2005	1,082	96.5	[94.6, 98.0]	96.4	[94.1, 98.4]	94.9	[92.2, 97.4]	93.5	[90.4, 96.4]	92.5	[89.0, 95.8]
2006	1,140	97.2	[95.5, 98.6]	96.6	[94.5, 98.4]	96.6	[94.1, 98.8]	95.0	[92.1, 97.6]	92.7	[89.4, 95.7]
2007	1,224	97.0	[95.3, 98.3]	97.1	[95.0, 98.9]	95.1	[92.6, 97.3]	94.4	[91.5, 97.0]	94.0	[90.8, 96.9]
2008	1,328	95.8	[94.1, 97.1]	95.6	[93.6, 97.4]	95.7	[93.4, 97.8]	95.6	[93.0, 98.0]	94.8	[91.8, 97.5]
2009	1,469	95.2	[93.6, 96.6]	94.8	[92.9, 96.6]	95.0	[92.7, 97.0]	93.3	[90.7, 95.7]	92.9	[90.0, 95.6]
2010	1,408	96.5	[95.0, 97.8]	95.7	[93.7, 97.4]	94.6	[92.3, 96.7]	93.3	[90.7, 95.8]	91.9	[89.0, 94.7]
2011	1,489	96.0	[94.4, 97.3]	93.7	[91.7, 95.5]	92.6	[90.3, 94.7]	91.8	[89.2, 94.2]	90.5	[87.6, 93.2]



Characteristic	N at risk	Unadjusted relative survival, %									
		1 year		2 year		3 year		4 year		5 year	
		%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI
2012	1,597	97.7	[96.3, 98.8]	96.4	[94.6, 97.9]	95.4	[93.3, 97.3]	94.6	[92.2, 96.8]	93.6	[91.0, 96.2]
2013	1,666	95.6	[94.1, 96.9]	94.6	[92.8, 96.3]	93.6	[91.5, 95.6]	92.8	[90.3, 95.0]	92.2	[89.5, 94.7]
2014	2,487	98.5	[97.6, 99.3]	98.4	[97.2, 99.4]	98.1	[96.7, 99.4]	98.2	[96.5, 99.7]	97.9	[96.0, 99.7]
2015	2,058	97.7	[96.6, 98.6]	97.5	[96.1, 98.7]	97.5	[95.8, 99.0]	97.1	[95.2, 98.9]	97.6	[95.4, 99.7]
2016	1,997	98.0	[96.9, 99.0]	97.0	[95.5, 98.4]	97.0	[95.2, 98.6]	96.1	[93.8, 98.2]	no FU	—
2017	1,919	97.5	[96.3, 98.5]	96.9	[95.4, 98.3]	95.9	[93.8, 97.8]	no FU	—	no FU	—
Combined Stage II											
2004	2,035	92.4	[90.8, 93.8]	90.2	[88.3, 91.9]	87.0	[84.7, 89.1]	84.6	[82.1, 87.0]	83.4	[80.7, 86.0]
2005	2,058	92.8	[91.3, 94.2]	90.8	[88.9, 92.5]	88.5	[86.3, 90.5]	85.6	[83.2, 88.0]	83.9	[81.2, 86.5]
2006	2,097	92.5	[91.0, 93.9]	90.0	[88.1, 91.8]	87.3	[85.1, 89.4]	84.9	[82.4, 87.2]	83.1	[80.4, 85.7]
2007	2,177	91.7	[90.1, 93.1]	88.3	[86.3, 90.1]	85.3	[83.1, 87.4]	83.6	[81.1, 85.9]	81.7	[79.0, 84.3]
2008	2,180	92.7	[91.2, 94.1]	90.0	[88.1, 91.7]	88.0	[85.9, 90.1]	86.4	[84.0, 88.7]	83.4	[80.7, 85.9]
2009	2,204	93.7	[92.3, 95.0]	92.2	[90.4, 93.8]	90.5	[88.4, 92.4]	88.9	[86.6, 91.2]	88.0	[85.4, 90.5]
2010	2,198	93.0	[91.5, 94.3]	89.9	[88.0, 91.6]	87.1	[84.9, 89.1]	85.0	[82.6, 87.3]	84.1	[81.4, 86.6]
2011	2,305	93.1	[91.7, 94.4]	90.9	[89.1, 92.6]	89.6	[87.5, 91.5]	87.9	[85.6, 90.1]	86.2	[83.7, 88.6]
2012	2,276	92.4	[90.9, 93.8]	89.9	[88.1, 91.6]	86.9	[84.8, 88.9]	85.2	[82.8, 87.5]	83.1	[80.4, 85.6]
2013	2,264	94.6	[93.2, 95.9]	93.8	[92.1, 95.4]	93.2	[91.2, 95.0]	92.4	[90.1, 94.5]	90.3	[87.7, 92.7]
2014	2,330	94.2	[92.9, 95.4]	92.3	[90.6, 93.8]	91.2	[89.3, 93.0]	89.6	[87.5, 91.7]	89.0	[86.6, 91.3]
2015	2,213	93.9	[92.4, 95.1]	92.8	[91.0, 94.4]	91.5	[89.4, 93.4]	89.8	[87.5, 92.1]	89.5	[86.8, 92.1]
2016	2,097	93.7	[92.2, 95.0]	92.3	[90.5, 94.0]	91.8	[89.7, 93.7]	89.7	[87.1, 92.2]	no FU	—
2017	1,982	93.8	[92.3, 95.2]	92.7	[90.8, 94.4]	91.4	[89.0, 93.7]	no FU	—	no FU	—
Combined Stage III											
2004	1,780	86.3	[84.4, 88.1]	77.8	[75.5, 80.0]	69.7	[67.1, 72.2]	64.0	[61.2, 66.7]	60.2	[57.4, 63.1]
2005	1,920	85.8	[83.9, 87.5]	77.3	[75.0, 79.5]	70.6	[68.1, 73.0]	65.2	[62.6, 67.8]	61.3	[58.5, 64.0]
2006	2,011	85.8	[83.9, 87.5]	76.2	[74.0, 78.3]	69.3	[66.9, 71.7]	64.6	[62.0, 67.1]	60.3	[57.6, 63.0]



Characteristic	N at risk	Unadjusted relative survival, %									
		1 year		2 year		3 year		4 year		5 year	
		%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI
2007	1,971	87.2	[85.4, 88.9]	77.8	[75.5, 79.9]	71.6	[69.1, 74.0]	67.1	[64.5, 69.7]	62.7	[59.9, 65.4]
2008	2,092	86.4	[84.7, 88.1]	78.1	[76.0, 80.2]	73.5	[71.1, 75.8]	68.6	[66.1, 71.0]	65.6	[62.9, 68.2]
2009	1,950	88.7	[87.0, 90.3]	81.8	[79.6, 83.8]	76.7	[74.3, 79.0]	73.6	[71.0, 76.1]	69.6	[66.9, 72.2]
2010	2,091	90.0	[88.3, 91.4]	80.9	[78.8, 82.9]	74.9	[72.5, 77.1]	70.6	[68.1, 73.1]	67.9	[65.3, 70.5]
2011	2,108	87.9	[86.2, 89.5]	80.2	[78.0, 82.2]	74.7	[72.3, 76.9]	70.3	[67.8, 72.8]	67.5	[64.9, 70.2]
2012	2,139	89.6	[88.0, 91.1]	82.7	[80.6, 84.6]	76.3	[74.0, 78.5]	72.8	[70.3, 75.2]	70.0	[67.3, 72.5]
2013	2,152	90.6	[89.1, 92.1]	83.1	[81.1, 85.0]	77.4	[75.1, 79.5]	73.1	[70.6, 75.5]	70.7	[68.1, 73.2]
2014	2,270	90.8	[89.3, 92.1]	85.1	[83.3, 86.9]	79.6	[77.5, 81.7]	76.9	[74.6, 79.1]	75.1	[72.6, 77.5]
2015	2,014	90.9	[89.3, 92.4]	84.9	[82.8, 86.8]	80.9	[78.6, 83.1]	77.4	[74.9, 79.8]	74.8	[71.9, 77.6]
2016	1,918	90.6	[88.9, 92.1]	84.7	[82.6, 86.6]	80.4	[78.0, 82.7]	76.5	[73.6, 79.2]	no FU	—
2017	1,888	91.5	[89.8, 92.9]	85.0	[82.9, 87.0]	79.5	[76.8, 82.0]	no FU	—	no FU	—
Combined Stage IV											
2004	1,179	60.1	[57.1, 63.0]	37.8	[34.9, 40.7]	23.1	[20.6, 25.7]	17.3	[15.1, 19.7]	13.7	[11.7, 15.9]
2005	1,161	64.5	[61.6, 67.3]	40.8	[37.8, 43.7]	27.0	[24.3, 29.7]	20.1	[17.7, 22.6]	15.6	[13.5, 18.0]
2006	1,242	62.4	[59.5, 65.2]	39.9	[37.1, 42.8]	27.2	[24.6, 29.8]	20.7	[18.4, 23.2]	17.1	[14.9, 19.4]
2007	1,275	62.8	[59.9, 65.5]	39.4	[36.6, 42.2]	25.7	[23.2, 28.2]	19.3	[17.0, 21.7]	15.5	[13.4, 17.7]
2008	1,385	63.9	[61.2, 66.5]	42.4	[39.7, 45.1]	29.7	[27.2, 32.3]	23.0	[20.7, 25.4]	18.5	[16.4, 20.8]
2009	1,467	62.1	[59.4, 64.6]	41.1	[38.4, 43.7]	27.8	[25.4, 30.3]	20.2	[18.0, 22.4]	15.9	[13.9, 18.0]
2010	1,455	63.3	[60.6, 65.8]	42.1	[39.4, 44.8]	29.3	[26.8, 31.8]	22.6	[20.3, 24.9]	18.2	[16.1, 20.5]
2011	1,497	63.5	[60.9, 66.0]	42.8	[40.1, 45.4]	30.6	[28.1, 33.1]	22.3	[20.1, 24.6]	17.5	[15.4, 19.6]
2012	1,453	63.1	[60.4, 65.6]	44.7	[42.0, 47.4]	31.8	[29.3, 34.4]	25.2	[22.9, 27.7]	19.7	[17.6, 22.0]
2013	1,537	64.9	[62.3, 67.4]	43.8	[41.2, 46.4]	30.6	[28.1, 33.0]	23.9	[21.6, 26.2]	18.2	[16.2, 20.3]
2014	1,515	64.5	[61.9, 67.0]	43.1	[40.5, 45.7]	31.0	[28.6, 33.5]	23.2	[21.0, 25.5]	18.9	[16.8, 21.1]
2015	1,466	64.2	[61.6, 66.7]	44.2	[41.5, 46.9]	31.5	[29.0, 34.1]	25.1	[22.7, 27.5]	19.3	[16.9, 21.8]
2016	1,466	62.8	[60.2, 65.4]	42.6	[39.9, 45.3]	31.2	[28.7, 33.8]	24.1	[21.6, 26.8]	no FU	—



Characteristic	N at risk	Unadjusted relative survival, %									
		1 year		2 year		3 year		4 year		5 year	
		%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI
2017	1,375	61.7	[59.0, 64.3]	41.7	[39.0, 44.5]	28.9	[26.0, 31.8]	no FU	—	no FU	—

Appendix 3.1.2. Uptake of selected drugs

Table 35 – Colorectal cancer stage I: proportion of patients who received at least one dose during 5-year period after diagnosis

Drug/incidence year (n)	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
	1087	1088	1150	1235	1343	1486	1424	1510	1625	1688	2535	2088	2038	1957
Bevacizumab	0.3%	0.4%	1.3%	1.8%	2.2%	3.0%	2.9%	3.1%	2.6%	2.2%	2.0%	1.4%	1.1%	1.1%
Panitumumab	0.3%	0.3%	0.7%	0.3%	0.4%	0.8%	0.8%	0.7%	0.5%	0.7%	0.5%	0.2%	0.2%	0.1%
Cetuximab	1.4%	1.0%	1.3%	0.7%	1.0%	1.0%	0.9%	0.6%	0.8%	0.2%	0.4%	0.3%	0.1%	0.1%
Aflibercept														
Regorafenib														

Source: BCR-IMA.

Table 36 – Colorectal cancer stage II: proportion of patients who received at least one dose during 5-year period after diagnosis

Drug/incidence year (n)	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
	2043	2068	2116	2196	2197	2229	2217	2337	2307	2298	2366	2238	2125	2005
Bevacizumab	0.5%	1.1%	1.9%	3.6%	4.3%	4.6%	5.5%	4.9%	6.2%	4.9%	4.3%	3.9%	3.4%	2.2%
Panitumumab	0.3%	0.6%	1.0%	1.2%	1.5%	0.9%	1.1%	1.2%	1.1%	1.2%	1.3%	1.1%	1.1%	0.5%
Cetuximab	1.8%	2.8%	2.4%	1.4%	2.0%	1.5%	1.4%	1.5%	1.3%	1.0%	1.1%	0.6%	0.6%	0.1%
Aflibercept							0.1%	0.4%	0.8%	0.8%	0.7%	0.7%	0.4%	0.2%
Regorafenib							0.1%	0.3%	0.9%	0.7%	0.6%	0.4%	0.1%	

Source: BCR-IMA.

**Table 37 – Colorectal cancer stage III: proportion of patients who received at least one dose during 5-year period after diagnosis**

Drug/incidence year (n)	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
	1788	1940	2032	1984	2112	1966	2111	2141	2171	2179	2300	2051	1947	1912
Bevacizumab	1.2%	3.0%	4.0%	7.2%	10.7%	13.1%	14.1%	14.3%	14.0%	14.0%	12.3%	11.0%	9.2%	5.7%
Panitumumab	0.7%	1.4%	1.9%	2.8%	4.1%	4.1%	3.1%	3.1%	3.8%	3.7%	2.7%	2.6%	2.6%	2.5%
Cetuximab	5.4%	7.1%	7.0%	5.5%	5.8%	4.7%	4.7%	5.1%	4.1%	4.1%	2.2%	2.0%	2.2%	1.0%
Aflibercept							0.3%	0.7%	1.3%	2.1%	1.9%	2.0%	1.4%	0.6%
Regorafenib							0.5%	1.0%	1.8%	2.8%	2.2%	2.0%	0.9%	0.2%

Source: BCR-IMA.

Table 38 – Colorectal cancer stage IV: proportion of patients who received at least one dose during 5-year period after diagnosis

Drug/incidence year (n)	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
	1185	1166	1249	1280	1391	1476	1466	1511	1466	1557	1543	1486	1485	1393
bevacizumab	1.3%	3.3%	4.9%	7.4%	23.9%	39.6%	44.9%	46.3%	47.7%	47.5%	47.4%	43.6%	43.2%	40.3%
panitumumab	0.9%	3.1%	4.3%	7.6%	10.8%	10.2%	12.4%	11.9%	10.4%	11.6%	11.7%	11.6%	11.2%	9.8%
cetuximab	5.4%	7.1%	7.0%	5.5%	5.8%	4.7%	4.7%	5.1%	4.1%	4.1%	2.2%	2.0%	2.2%	1.0%
aflibercept							0.3%	0.7%	1.3%	2.1%	1.9%	2.0%	1.4%	0.6%
regorafenib							0.2%	0.7%	1.5%	2.5%	2.8%	2.3%	1.5%	0.6%

* Numbers in yellow indicate the first calendar year of reimbursement. For example, bevacizumab was first reimbursed in 2008. The columns in this table indicate the incidence year. For example, for incidence year 2009, 39.6% of patients received reimbursed bevacizumab during the five years after diagnosis. Source: BCR-IMA.



Appendix 3.2. Reimbursement criteria for selected drugs

Table 39 – targeted therapy in colorectal cancer

Drug	Trade name	Date start reimbursement	Indication NI	Indication Fr
Bevacizumab	Avastin	1/12/2008 1 st line with irinotecan 1/10/2010 1 st line with oxliplatin 1/9/2014 2 nd line	De specialiteit komt voor vergoeding in aanmerking indien ze wordt toegediend in associatie met een schema dat 5-fluorouracil of capecitabine omvat, voor de behandeling van een patiënt met gemetastaseerde colorectaal carcinoom met een ECOG PS (Eastern Cooperative Oncology Group performance status) ≤ 1 , en voor zover deze behandeling in strikte overeenkomst met elke bepaling vermeld in de Samenvatting van de Productkenmerken (SKP) van AVASTIN wordt voorgeschreven.	La spécialité fait l'objet d'un remboursement si elle est utilisée en association avec un schéma qui contient le 5-fluorouracil ou la capécitabine, pour le traitement de patients atteints d'un carcinome colorectal métastaté, avec un ECOG PS (Eastern Cooperative Oncology Group performance status) ≤ 1 , et pour autant que ce traitement soit prescrit en stricte conformité avec chacune des dispositions mentionnées dans le Résumé des Caractéristiques du Produit (RCP) d'AVASTIN.
Panitumumab	Vectibix	1/9/2008	De specialiteit komt in aanmerking voor vergoeding indien zij wordt toegediend in het kader van de behandeling van een gemetastaseerd colorectaal carcinoom waarvan de RAS genen (KRAS en NRAS) niet-gemuteerd zijn. De vergoeding kan worden toegestaan in het kader van: 1. de behandeling in eerste lijn indien de specialiteit samen met de combinatie FOLFOX of FOLFIRI wordt toegediend. De patiënt moet bij aanvang een Karnofsky performance status $> \text{ of } = 80$ hebben; 2. de behandeling in tweede lijn indien de specialiteit samen met de combinatie FOLFIRI wordt toegediend bij patiënten die in eerste lijn een fluoropyrimidine-bevattende chemotherapieregime hebben ontvangen (zonder irinotecan); 3. de behandeling in monotherapie van patiënten bij wie eerdere behandelingen met 5	La spécialité fait l'objet d'un remboursement si elle est administrée dans le cadre du traitement d'un cancer colorectal métastaté dont les gènes RAS (du KRAS et du NRAS) sont non mutés. Le peut être accordé dans le cadre : 1. du traitement en première ligne si la spécialité est administrée en association avec la combinaison FOLFOX ou FOLFIRI. Le patient doit avoir un Karnofsky performance status $> \text{ ou } = 80$ à l'instauration du traitement; 2. du traitement en deuxième ligne si la spécialité est administrée en association avec la combinaison FOLFIRI chez des patients qui ont reçu en première ligne un protocole de chimiothérapie à base de



Drug	Trade name	Date start reimbursement	Indication NI	Indication Fr
			FU, oxaliplatin en irinotecan bevattende chemotherapieregimes gefaald hebben.	fluoropyrimidine (excluant l'irinotecan); 3. du traitement en monothérapie de patients chez qui des traitements antérieurs par des protocoles de chimiothérapie à base de 5-FU, d'oxaliplatine et d'irinotecan ont échoué.
Cetuximab	Erbitux	1/2/2010	<p>De specialiteit komt voor vergoeding in aanmerking indien zij wordt toegediend in het kader van de behandeling van een gemetastaseerd colorectaal carcinoom waarvan de RAS genen (KRAS en NRAS) niet-gemuteerd zijn. De vergoeding kan worden toegekend:</p> <ol style="list-style-type: none"> 1. voor de behandeling in eerste lijn indien de specialiteit samen met de combinatie FOLFIRI of FOLFOX wordt toegediend; 2. voor de behandeling in tweede lijn indien de specialiteit samen met irinotecan wordt toegediend na falen van een behandeling met de combinatie FOLFOX; 3. voor de behandeling in associatie met irinotecan van patiënten die eerder al werden behandeld met oxaliplatin en irinotecan en van wie de tumor refractair of resistent aan irinotecan is gebleken (resistent wordt gedefinieerd als recidief binnen de maand na stopzetting van de behandeling). De patiënt moet bij aanvang van de behandeling met cetuximab aan de volgende criteria voldoen: <ul style="list-style-type: none"> - totale bilirubine < of = 1.5 x ULN (Upper Limit of Normal); - goede tolerantie op irinotecan met een minimumdosis van 110mg/m² (om de 2 weken) tijdens de vorige behandeling; - Karnofsky performance status > of = 80; 	<p>La spécialité fait l'objet d'un remboursement si elle est administrée dans le cadre du traitement du cancer colorectal métastasé dont les gènes RAS (du KRAS et du NRAS) sont non mutés. Le remboursement peut être accordé :</p> <ol style="list-style-type: none"> 1. pour le traitement en première ligne si la spécialité est administrée en association avec la combinaison FOLFIRI ou FOLFOX ; 2. pour le traitement en deuxième ligne si la spécialité est administrée en association avec l'irinotécan après échec d'un traitement avec la combinaison FOLFOX ; 3. pour le traitement en association avec l'irinotécan des patients qui ont déjà été traités, et avec de l'oxaliplatine et avec de l'irinotecan, et dont la tumeur s'est avérée réfractaire ou résistante à l'irinotecan (résistant étant défini comme une reprise de la progression dans le mois qui a suivi l'arrêt du traitement). Le patient à l'instauration du traitement par cetuximab doit répondre aux critères suivants : <ul style="list-style-type: none"> - bilirubine totale < ou = 1.5 x ULN (Upper Limit of Normal);



Drug	Trade name	Date start reimbursement	Indication NI	Indication Fr
			4. voor de behandeling in monotherapie van patiënten die eerder al werden behandeld met oxaliplatin en irinotecan en die niet meer met irinotecan behandeld kunnen worden.	<p>- bonne tolérance à l'irinotecan à une dose minimum de 110mg/m² (toutes les 2 semaines) pendant le traitement précédent;</p> <p>- Karnofsky performance status > ou = 80;</p> <p>4. pour le traitement en monothérapie de patients qui ont déjà été traités, et avec de l'oxaliplatine et avec de l'irinotecan, et qui ne peuvent plus être traités avec de l'irinotécan.</p>
Aflibercept	Zaltrap	1-11-2014	in associatie met irinotecan voor de behandeling van een gemetastaseerd colorectaal carcinoom na falen van een behandeling op basis van oxaliplatin bij een patiënt met een ECOG (Eastern Cooperative Oncology Group performance status) van 0 of 1 en die geen progressie had vertoond binnen de 6 maanden na adjuvante therapie, en voor zover deze behandeling in strikte overeenkomst met elke bepaling vermeld in de Samenvatting van de Productkenmerken (SKP) van ZALTRAP wordt voorgeschreven.	e traitement du cancer colorectal métastasé et si elle est administrée en association avec l'irinotécan après échec d'un traitement à base d'oxaliplatine chez un patient avec un ECOG (Eastern Cooperative Oncology Group performance status) de 0 ou 1 et qui n'avait pas progressé endéans les 6 mois du traitement adjuvant, et pour autant que ce traitement soit prescrit en stricte conformité avec chacune des dispositions mentionnées dans le Résumé des Caractéristiques du Produit (RCP) du ZALTRAP
Regorafenib	Stivarga	1/7/2015	gemetastaseerd colorectaal carcinoom (CRC) dat progressie vertoont onder of na enige andere beschikbare therapie, bestaande uit chemotherapie op basis van fluoropyrimidine, een anti VEGF behandeling en/of een anti EGFR behandeling, of indien dergelijke behandelingen niet in aanmerking komen omwille van objectiveerbare medische redenen	carcinome colorectal métastasé (CRC) qui montre une progression après ou sous traitement avec un autre traitement disponible, consistant en une chimiothérapie à base de fluoropyrimidine, un traitement anti-VEGF et/ou un traitement anti-EGFR, ou si de tels traitements ne sont pas envisageables pour des raisons médicales objectivables
		1/7/2015	niet-reseceerbare of gemetastaseerde gastro-intestinale stromale tumor (GIST) die progressie	une tumeur stromale gastro-intestinale (GIST) non-résécable ou



Drug	Trade name	Date start reimbursement	Indication NI	Indication Fr
			vertoonde op of intolerant is voor eerdere behandeling met zowel imatinib als sunitinib.	métastasée qui a montré une progression ou une intolérance à un traitement antérieur aussi bien par imatinib que sunitinib

Appendix 3.3. Medical literature: search for evidence

Appendix 3.3.1. Search medical literature (systematic reviews)

The search for systematic reviews in MEDLINE, PreMedline and the Cochrane library of systematic reviews (inception to search date) specifically developed for this research question, yielded 425 records (Figure 104). After de-duplication, 231 reviews (2016-2020) of the 425 remaining records were screened based on title and abstract, of which 166 were excluded. In total 65 full text articles were assessed for eligibility. Based on full text evaluation, 60 reviews were excluded (Figure 105).



Figure 65 – Colorectal cancer – Selection of SRs - Study flow

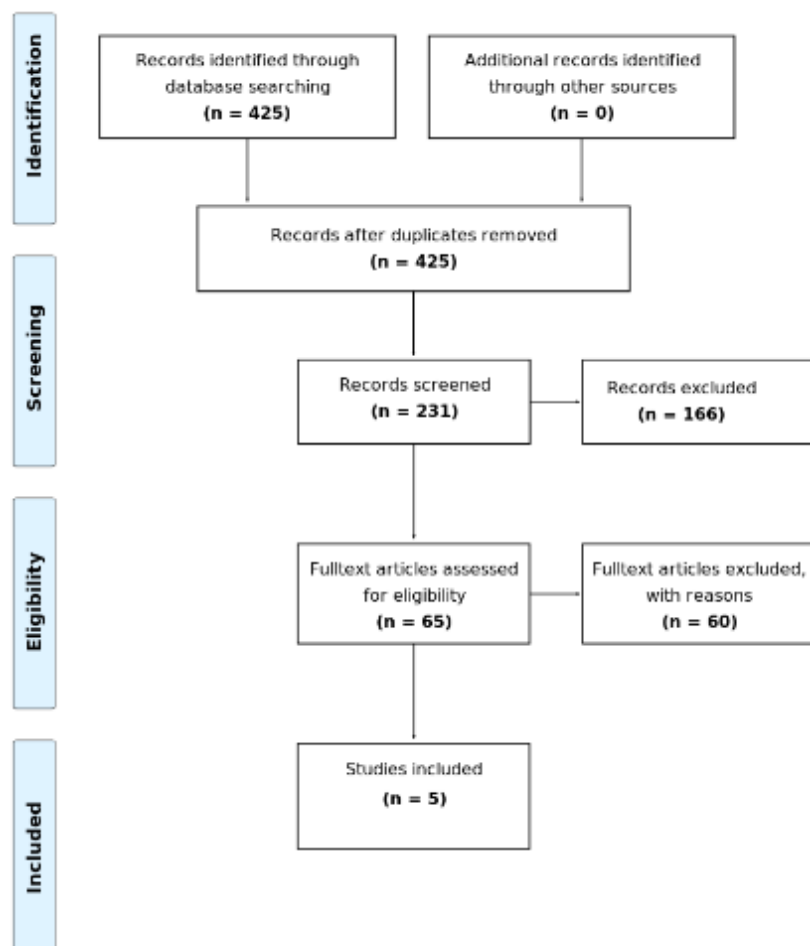


**Table 40 – Colorectal cancer: excluded reviews and reason for exclusion**

	Year	Publication	Reason for exclusion
1	2020	Zhong, X. Zhou, Y. Cui, W. et al. The Addition of EGFR Inhibitors in Neoadjuvant Therapy for KRAS-Wild Type Locally Advanced Rectal Cancer Patients: A Systematic Review and Meta-Analysis. <i>Front Pharmacol</i> 2020; 11:706	Indication not reimbursed in Belgium
2	2020	You, X. H. Jiang, Y. H. Fang, Z. et al. Chemotherapy plus bevacizumab as an optimal first-line therapeutic treatment for patients with right-sided metastatic colon cancer: a meta-analysis of first-line clinical trials. <i>ESMO open</i> 2020;4:03	No critical appraisal
3	2020	Wang, J. X. Wu, H. L. Zhu, M. Zhou, R. Role of Anti-Epidermal Growth Factor Receptor Therapy Compared with Anti-Vascular Endothelial Growth Factor Therapy for Metastatic Colorectal Cancer: an Update Meta-Analysis of Randomized Clinical Trials. <i>Pathol Oncol Res</i> 2020; 26(1):159-166	wrong comparison
4	2020	Wang, C. Tan, C. Chen, X. Chen, S. The efficacy and safety of panitumumab supplementation for colorectal cancer: A meta-analysis of randomized controlled studies. <i>Medicine (Baltimore)</i> 2020;99(11):e19210	no additional information
5	2020	Unim, B. Pitini, E. De Vito, C. et al. Cost-Effectiveness of RAS Genetic Testing Strategies in Patients With Metastatic Colorectal Cancer: A Systematic Review. <i>Value Health</i> 2020;23(1):114-126	wrong research question
6	2020	Petrelli, F. Perego, G. Ghidini, A. et al. A systematic review of salvage therapies in refractory metastatic colorectal cancer. <i>Int J Colorectal Dis</i> 2020;35(5):783-794	no results for separate drugs reported
7	2020	Li, R. Liang, M. Liang, X. et al. Chemotherapeutic Effectiveness of Combining Cetuximab for Metastatic Colorectal Cancer Treatment: A System Review and Meta-Analysis. <i>Front</i> 2020;10:868	No separate results for 1 st and 2 nd line
8	2020	Fan, Q. Lv, H. Xu, Y. et al. Selective vascular endothelial growth factor receptor inhibitors provide limited benefits for metastatic colorectal cancer: a meta-analysis. <i>Curr Pharm Des</i> 2020;17:17	no additional information
9	2020	Casadei-Gardini, A. Vaghegini, A. Gelsomino, F. et al. Is There an Optimal Choice in Refractory Colorectal Cancer? A Network Meta-Analysis <i>Clin Colorectal Cancer</i> 2020;19(2):82-90.e9	Searched only one database
10	2020	Cao, M. Zhou, M. Zhang, J. Comparison of efficacy and safety for patients with beyond second line treated metastatic colorectal cancer: a network meta-analysis of randomized controlled trials. <i>J Chemother</i> 2020:1-8	searched only 1 database
11	2019	Zheng, B. Wang, X. Wei, M. et al. First-line cetuximab versus bevacizumab for RAS and BRAF wild-type metastatic colorectal cancer: a systematic review and meta-analysis. <i>BMC Cancer</i> 2020;19(1):280	wrong comparison
12	2019	Zhang, C. Tan, Y. Xu, H. Does adjuvant chemotherapy improve the prognosis of patients after resection of pulmonary metastasis from colorectal cancer? A systematic review and meta-analysis. <i>Int J Colorectal Dis</i> 2020;34(10):1661-1671	wrong research question



	Year	Publication	Reason for exclusion
13	2019	Xu, R. Shao, H. Zhu, J. et al. Combination strategies based on epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors for cancer patients: Pooled analysis and subgroup analysis of efficacy and safety. <i>Medicine (Baltimore)</i> 2019;98(13):e14135	wrong comparison
14	2019	Xie, G. Gong, Y. Wu, S. et al. Meta-Analysis of Regorafenib-Associated Adverse Events and Their Management in Colorectal and Gastrointestinal Stromal Cancers. <i>Adv Ther</i> 2019; 36(8):1986-1998	wrong outcome
15	2019	Wang, Z. X. Wu, H. X. He, M. M. et al. Chemotherapy With or Without Anti-EGFR Agents in Left- and Right-Sided Metastatic Colorectal Cancer: An Updated Meta-Analysis <i>JNCCN</i> 2019;17(7):805-811	searched only one database
16	2019	Sun, H. Li, Y. Su, Y. et al. Efficacy and safety of anti-EGFR monoclonal antibodies combined with different chemotherapy regimens in patients with RAS wild-type metastatic colorectal cancer: A meta-analysis. <i>J Evid Based Med</i> 2019;12(4):300-312	Included
17	2019	Sonbol, M. B. Mountjoy, L. J. Firwana, B. et al. The Role of Maintenance Strategies in Metastatic Colorectal Cancer: A Systematic Review and Network Meta-analysis of Randomized Clinical Trials. <i>JAMA Oncol</i> 2019;e194489	No additional informaton
18	2019	Sonbol, M. B. Benkhadra, R. Wang, Z. et al. A Systematic Review and Network Meta-Analysis of Regorafenib and TAS-102 in Refractory Metastatic Colorectal Cancer. <i>Oncologist</i> 2019;24(9):1174-1179	Included
19	2019	Serrano, P. E. Carter, D. N. Li, C. et al. Adjuvant Chemotherapy With or Without Biologics Including Antiangiogenics and Monoclonal Antibodies Targeting EGFR and EpCAM in Colorectal Cancer: A Systematic Review and Meta-analysis. <i>J Surg Res</i> 2019;239:14-21	Indication not reimbursed in Belgium
20	2019	Raouf, S. Bertelli, G. Ograbek, A. et al. Real-world use of bevacizumab in metastatic colorectal, metastatic breast, advanced ovarian and cervical cancer: a systematic literature review. <i>Fut Oncol</i> 2019;15(5):543-561	no additional information
21	2019	Mauri, G. Pizzutilo, E. G. Amatu, A. et al. Retreatment with anti-EGFR monoclonal antibodies in metastatic colorectal cancer: Systematic review of different strategies. <i>Cancer Treat Rev</i> 2019;73:41-53	Indication not reimbursed in Belgium
22	2019	Ma, H. Wu, X. Tao, M. et al. Efficacy and safety of bevacizumab-based maintenance therapy in metastatic colorectal cancer: A meta-analysis. <i>Medicine (Baltimore)</i> 2019;98(50):e18227	No additional information
23	2019	Kaveh, S. Ebrahimi, P. Rezapour, A. et al. Bevacizumab and erlotinib versus bevacizumab for colorectal cancer treatment: systematic review and meta-analysis. <i>Int J Clin Pharm</i> 2019 ;41(1):30-41	Indication not reimbursed in Belgium
24	2019	Huang, C. Huang, J. Luo, H. et al. Comparative Efficacy of Preoperative, Postoperative, and Perioperative Treatments for Resectable Colorectal Liver Metastases: A Network Meta-Analysis. <i>Front Pharmacol</i> 2019;10:1052	wrong comparison
25	2019	Geldof, T. Rawal, S. Dyck, W. V. Huys, I. Comparative and combined effectiveness of innovative therapies in cancer: a literature review <i>J Comp Eff Res</i> 2019 Mar;8(4):205-216	wrong research question



	Year	Publication	Reason for exclusion
26	2019	Galvano, A. Incorvaia, L. Badalamenti, G. et al. How to Deal with Second Line Dilemma in Metastatic Colorectal Cancer? A Systematic Review and Meta-Analysis. <i>Cancers (Basel)</i> 2019 ;11(8) :15	not a systematic review (methods not reported)
27	2019	Duan, K. F. Wang, H. The efficacy of panitumumab in refractory metastatic colorectal cancer: A meta-analysis. <i>JBUON</i> 2019;24(4):1457-1463	wrong comparison (see table 1, cetuximab included in comparator)
28	2019	Cao, D. Zheng, Y. Xu, H. et al. Bevacizumab improves survival in metastatic colorectal cancer patients with primary tumor resection: A meta-analysis. <i>Sci</i> 2019;9(1):20326	No additional information
29	2019	Baraniskin, A. Buchberger, B. Pox, C. et al. Efficacy of bevacizumab in first-line treatment of metastatic colorectal cancer: A systematic review and meta-analysis. <i>Eur J Cancer</i> 2019;106:37-44	Included
30	2018	Wang, Y. Liu, S. Liu, S. et al. Regorafenib Treatment for Management of Colorectal Cancer: A Systematic Review and Meta-analysis of 6 Randomized Controlled Trials. <i>Am J Ther</i> 2018; 25(2):e276-e278	No additional information
31	2018	Wang, J. X. Wu, H. L. Zhu, M. Zhou, R. Role of Anti-Epidermal Growth Factor Receptor Therapy Compared with Anti-Vascular Endothelial Growth Factor Therapy for Metastatic Colorectal Cancer: an Update Meta-Analysis of Randomized Clinical Trials. <i>Pathol Oncol Res</i> 2018;30:30	wrong comparison
32	2018	Wang, J. Luo, L. Wang, D. et al. Combination adjuvant chemotherapy with targeted drugs for treatment of colorectal cancer: A network meta-analysis <i>J Cell Biochem</i> 2018;119(2):1521-1537	Indication not reimbursed in Belgium
33	2018	Xue, W. S. Men, S. Y. Liu, W. Liu, R. H. A meta-analysis of safety and efficacy of regorafenib for refractory metastatic colorectal cancer. <i>Medicine (Baltimore)</i> 2018;97(40):e12635	No additional information
34	2018	Seo, M. K. Cairns, J. Do cancer biomarkers make targeted therapies cost-effective? A systematic review in metastatic colorectal cancer. <i>PLoS ONE</i> 2018;13(9):e0204496	wrong research question
35	2018	Ruan, W. C. Che, Y. P. Ding, L. Li, H. F. Efficacy and Toxicity of Addition of Bevacizumab to Chemotherapy in Patients with Metastatic Colorectal Cancer. <i>Comb Chem High Throughput Screen</i> 2018;21(10):718-724	Full text could not be obtained
36	2018	Roed Skarderud, M. Polk, A. Kjeldgaard Vistisen, K. et al. Efficacy and safety of regorafenib in the treatment of metastatic colorectal cancer: A systematic review. <i>Cancer Treat Rev</i> 2018;62:61-73	no additional information
37	2018	Petrelli, F. Ardito, R. Ghidini, A. et al. Different Toxicity of Cetuximab and Panitumumab in Metastatic Colorectal Cancer Treatment: A Systematic Review and Meta-Analysis. <i>Oncology</i> 2018;94(4):191-199	wrong outcome
38	2018	Ottaiano, A. De Stefano, A. Capozzi, M. et al. First Biologic Drug in the Treatment of RAS Wild-Type Metastatic Colorectal Cancer: Anti-EGFR or Bevacizumab? Results From a Meta-Analysis. <i>Front Pharmacol</i> 2018;9:441	wrong comparison



	Year	Publication	Reason for exclusion
39	2018	Lin, F. Li, H. Wang, J. Wang, F. Efficacy and toxicities of combination maintenance therapy in the treatment of advanced colorectal cancer: a meta-analysis of randomized controlled trials. <i>Biosci Rep</i> 2018;24:24	wrong research question
40	2018	Li, Z. Huang, Y. Zhao, R. et al. Chemotherapy plus Panitumumab Versus Chemotherapy plus Bevacizumab in Metastatic Colorectal Cancer: A Meta-analysis. <i>Sci</i> 2018;8(1):510	wrong comparison
41	2018	Koch, C. Schwing, A. M. Herrmann, E. et al. Bevacizumab-based first-line chemotherapy in elderly patients with metastatic colorectal cancer: an individual patient data based meta-analysis. <i>Oncotarget</i> 2018;9(12):10722-10283	not a systematic review (methods not reported)
42	2018	Jiang, W. Yu, Q. Ning, R. et al. Efficacy of bevacizumab versus epidermal growth factor receptor inhibitors for wild-type RAS metastatic colorectal cancer: a meta-analysis. <i>Onco Targets Ther</i> 2018;11:4271-4281	wrong comparison
43	2018	Guglielmo, A. Staropoli, N. Giancotti, M. Mauro, M. Personalized medicine in colorectal cancer diagnosis and treatment: a systematic review of health economic evaluations. <i>Cost Eff Resour Alloc</i> 2018;16:2	wrong research question
44	2018	Gouverneur, A. Salvo, F. Berdai, D. et al. Inclusion of elderly or frail patients in randomized controlled trials of targeted therapies for the treatment of metastatic colorectal cancer: A systematic review <i>J Geriatr Oncol</i> 2018;9(1):15-23	wrong research question
45	2018	da Silva, W. C. de Araujo, V. E. Lima, Emea et al. Comparative Effectiveness and Safety of Monoclonal Antibodies (Bevacizumab, Cetuximab, and Panitumumab) in Combination with Chemotherapy for Metastatic Colorectal Cancer: A Systematic Review and Meta-Analysis. <i>BioDrugs</i> 2018;32(6):585-606	wrong comparison (+ based oncohort studies)
46	2018	Ciliberto, D. Staropoli, N. Caglioti, F. et al. The best strategy for RAS wild-type metastatic colorectal cancer patients in first-line treatment: A classic and Bayesian meta-analysis. <i>Crit Rev Oncol Hematol</i> 2018;125:69-77	wrong research question
47	2018	Chen, D. Li, L. Zhang, X. et al. FOLFOX plus anti-epidermal growth factor receptor (EGFR) monoclonal antibody (mAb) is an effective first-line treatment for patients with RAS-wild left-sided metastatic colorectal cancer: A meta-analysis. <i>Medicine (Baltimore)</i> 2018; 97(10):e0097	No additional information
48	2018	Bogach, J. Levine, O. Parpia, S. et al. Does the Addition of Biologic Agents to Chemotherapy in Patients with Unresectable Colorectal Cancer Metastases Result in a Higher Proportion of Patients Undergoing Resection? A Systematic Review and Meta-analysis <i>J Gastrointest Surg</i> 2018;(22)3:523-528	no relevant outcomes included
49	2017	Xiong, Y. X. Ren, L. Wang, Z. Q. et al. The role of angiogenesis inhibitors re-challenge in colorectal cancer previously treated with bevacizumab: a meta-analysis of randomized controlled trials. <i>Eur Rev Med Pharmacol Sci</i> 2017;21(7): 1489-1494	No additional information
50	2017	Roviello, G. Bachelot, T. Hudis, C. A. et al. The role of bevacizumab in solid tumours: A literature based meta-analysis of randomised trials. <i>Eur J Cancer</i> 2017; 75:245-258	wrong population
51	2017	Pinto, C. Antonuzzo, L. Porcu, L. et al. Efficacy and Safety of Bevacizumab Combined With Fluoropyrimidine Monotherapy for Unfit or Older Patients With Metastatic Colorectal	No additional information



Year	Publication	Reason for exclusion	
	Cancer: A Systematic Review and Meta-Analysis. Clin Colorectal Cancer 2017; 16(2):e61-e72		
52	2017	Montagnani, F. Di Leonardo, G. Pino, M. et al. Protracted Inhibition of Vascular Endothelial Growth Factor Signaling Improves Survival in Metastatic Colorectal Cancer: A Systematic Review. Journal of translational internal medicine 2017;5(1):18-26	No additional information
53	2017	Mocellin, S. Baretta, Z. Roque, I. Figuls M. et al. Second-line systemic therapy for metastatic colorectal cancer. Cochrane Database Syst Rev 2017;1	Included
54	2017	Lv, W. Zhang, G. Q. Jiao, A. et al. Chemotherapy Plus Cetuximab versus Chemotherapy Alone for Patients with KRAS Wild Type Unresectable Liver-Confined Metastases Colorectal Cancer: An Updated Meta-Analysis of RCTs. Gastroenterol Res Pract 2017: 8464905	no additional information (subgroup only)
55	2017	Cremolini, C. Antoniotti, C. Pietrantonio, F. et al. Surrogate Endpoints in Second-Line Trials of Targeted Agents in Metastatic Colorectal Cancer: A Literature-Based Systematic Review and Meta-Analysis. Cancer Res 2017; 49(3):834-845	wrong research question
56	2017	Chen, X. Chen, Y. Cai, X. et al. Efficacy and safety of bevacizumab in elderly patients with advanced colorectal cancer: A meta-analysis. J Cancer Res Ther 2017; 13(5):869-877	No additional information
57	2017	Chebib, R. Verlingue, L. Cozic, N. et al. Angiogenesis inhibition in the second-line treatment of metastatic colorectal cancer: A systematic review and pooled analysis. Semin Oncol 2017; 44(2):114-128	No additional information
58	2017	Chan, D. L. H. Segelov, E. Wong, R. S. H. et al. Epidermal growth factor receptor (EGFR) inhibitors for metastatic colorectal cancer. Cochrane Database of Systematic Reviews. Cochrane Database of Systematic Reviews 2017:6	Included
59	2016	Wang, H. Ma, B. Gao, P. et al. Efficacy and safety of anti-epidermal growth factor receptor therapy compared with anti-vascular endothelial growth factor therapy for metastatic colorectal cancer in first-line and second-line therapies: a meta-analysis. Onco Targets Ther 2016;9:5405-16	wrong comparison
60	2016	Pei, X. Liu, Y. Sun, L. et al. Outcome of Molecular Targeted Agents Plus Chemotherapy for Second-Line Therapy of Metastatic Colorectal Cancer: A Meta-Analysis of Randomized Trials. Clin Colorectal Cancer 2016;15(4):e149-e156	No additional information
61	2016	Li, X. Wang, M. Liu, G. Y. Ma, J. L. Dual VEGF/EGFR inhibition versus single targeted agent treatment in patients with metastatic colorectal cancer: a meta-analysis of randomized trials. Int J Colorectal Dis 2016;31(9):1655-6	wrong comparison
62	2016	Ilic, I. Jankovic, S. Ilic, M. Bevacizumab Combined with Chemotherapy Improves Survival for Patients with Metastatic Colorectal Cancer: Evidence from Meta Analysis. PLoS ONE 2016;11(8):e0161912	No additional information
63	2016	Hofheinz, R. D. Ronellenfitsch, U. Kubicka, S. et al. Treatment with Antiangiogenic Drugs in Multiple Lines in Patients with Metastatic Colorectal Cancer: Meta-Analysis of Randomized Trials. Gastroenterol Res Pract 2016;9189483	No additional information



	Year	Publication	Reason for exclusion
64	2016	Goldstein, D. A. Zeichner, S. B. Bartnik, C. M. et al. Metastatic Colorectal Cancer: A Systematic Review of the Value of Current Therapies. Clin Colorectal Cancer 2016;15(1):1-6	No additional information
65	2016	Chen, K. Gong, Y. Zhang, Q. et al. Efficacy and safety of addition of bevacizumab to FOLFIRI or irinotecan/bolus 5-FU/LV (IFL) in patients with metastatic colorectal cancer: A meta-analysis. Medicine (Baltimore) 2016;95(46):e5221	No additional information

Appendix 3.3.2. Critical appraisal systematic reviews

	Sonbol 2019 ⁵⁴		Sun 2019 ⁵⁵	
	Score	Rationale/comment	score	Rationale/comment
1. PICO	Y		Y	
2. A priori study design	N		N	
3. Inclusion study designs	Y		Y	
4. Comprehensive literature search	Partial Y	No search of reference lists, no search of trial registries	Y	
5. Duplicate study selection	Y		N	(unclear)
6. Duplicate data extraction	Y		Y	
7. List of excluded studies and rationale	N			
8. Characteristics of included studies provided	Y		Y	
9. Assessment of risk of bias	Y		Y	
10. Sources of funding reported	N		N	
11. Appropriate methods to combine findings	Y		Y	
12. Assessment of impact RoB in included studies on results MA	N		N	
13. RoB assessment used in interpretation of results and in conclusions	N		N	
14. Explanation for and discussion of any observed heterogeneity	N		N	



Sonbol 2019 ⁵⁴		Sun 2019 ⁵⁵			
	Score	Rationale/comment		score	Rationale/comment
15. Adequate investigation of publication bias and its impact on the results	N			N	
16. Potential sources of conflict of interest reported	Y			Y	

Baraniskin 2019 ⁵⁶			Chan 2017 ⁵⁷	
	Score	Rationale/comment	score	Rationale/comment
1. PICO	Y		Y	
2. A priori study design	N		N	
3. Inclusion study designs	Y		Y	
4. Comprehensive literature search	Partial Yes	No search of reference lists, no search of trial registries	Partial Yes	No search of reference lists
5. Duplicate study selection	Y		Y	
6. Duplicate data extraction	N	(unclear)	Y	
7. List of excluded studies and rationale	N		Y	
8. Characteristics of included studies provided	Y		Y	
9. Assessment of risk of bias	Y		Y	
10. Sources of funding reported	N		Y	
11. Appropriate methods to combine findings	Y		Y	
12. Assessment of impact RoB in included studies on results MA	Y		Y	
13. RoB assessment used in interpretation of results and in conclusions	Y		Y	
14. Explanation for and discussion of any observed heterogeneity	N		Y	
15. Adequate investigation of publication bias and its impact on the results	N	(risk of publication bias discussed in general)	Y	



Baraniskin 2019 ⁵⁶		Chan 2017 ⁵⁷	
	Score		Rationale/comment
16. Potential sources of conflict of interest reported	Y	Y	

Mocellin 2017 ⁵⁸	
	Score
1. PICO	Y
2. A priori study design	N
3. Inclusion study designs	Y
4. Comprehensive literature search	Y
5. Duplicate study selection	Y
6. Duplicate data extraction	Y
7. List of excluded studies and rationale	Y
8. Characteristics of included studies provided	Y
9. Assessment of risk of bias	Y
10. Sources of funding reported	Y
11. Appropriate methods to combine findings	Y
12. Assessment of impact RoB in included studies on results MA	Y
13. RoB assessment used in interpretation of results and in conclusions	Y
14. Explanation for and discussion of any observed heterogeneity	Y
15. Adequate investigation of publication bias and its impact on the results	Y
16. Potential sources of conflict of interest reported	Y

Appendix 3.3.3. Search strategy

Appendix 3.3.3.1. *Cochrane library of systematic reviews*

Date	24/06/2020 20:08:17	
Database	Cochrane@Wiley.com	
Search strategy		
#1	[mh "colorectal neoplasms"]	8000
#2	((rectum or rectal or colorectal) NEAR/4 (cancer* or tumor* or tumour* or carcin* or adenocarcin* or metasta* or malignan* or lymphom* or leiomyosarcom* or melanom*)):ab,ti	16270
#3	((colon or colonic) NEAR/4 (cancer* or tumor* or tumour* or carcin* or adenocarcin* or metasta* or malignan* or lymphom* or leiomyosarcom* or melanom*)):ab,ti	4076
#4	(sigmoid NEAR/4 (cancer* or tumor* or tumour* or carcin* or adenocarcin* or metasta* or malignan* or lymphom* or leiomyosarcom* or melanom*)):ab,ti	85
#5	lynch syndrome:ab,ti	128
#6	(adenomatous NEAR/3 polypos*):ab,ti	215
#7	(gardner* NEAR/3 syndrome):ab,ti	2
#8	#2 or #3 or #4 or #5 or #6 or #7	18840
#9	#1 or #8	20163
#10	aflibercept:ab,ti	743
#11	ZALTRAP:ab,ti	16
#12	EYLEA:ab,ti	108
#13	15C2VL427D:ab,ti	0
#14	"VEGF TRAP":ab,ti	85
#15	"VEGF TRAP-EYE":ab,ti	36
#16	"BAY-86-5321":ab,ti	5
#17	"BAY-865321":ab,ti	0
#18	"BAY86-5321":ab,ti	5
#19	BAY865321:ab,ti	0
#20	"AVE-0005":ab,ti	1
#21	AVE0005:ab,ti	22



Date	24/06/2020 20:08:17	
#22	"vascular endothelial growth factor trap":ab,ti	11
#23	"vasculotropin trap":ab,ti	0
#24	"845771-78-0":ab,ti	0
#25	"862111-32-8":ab,ti	29
#26	#10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25	799
#27	[mh ^"Bevacizumab"]	1857
#28	bevacizumab:ab,ti	5628
#29	avastin:ab,ti	839
#30	mvasi:ab,ti	0
#31	zirabev:ab,ti	0
#32	ainex:ab,ti	0
#33	altuzan:ab,ti	1
#34	bevax:ab,ti	0
#35	bryxta:ab,ti	0
#36	krabeva:ab,ti	0
#37	kyomarc:ab,ti	0
#38	2S9ZZM9Q9V:ab,ti	0
#39	"1438851-35-4":ab,ti	1
#40	"216974-75-3":ab,ti	185
#41	RHUMAB:ab,ti	152
#42	"rhuMAb-VEGF":ab,ti	58
#43	"12-IGG1":ab,ti	0
#44	"ABP-215":ab,ti	17
#45	ABP215:ab,ti	0
#46	AVA1:ab,ti	0
#47	"AVA-1":ab,ti	14
#48	"ask b1202":ab,ti	0



Date	24/06/2020 20:08:17	
#49	askb1202:ab,ti	1
#50	"BI 695502":ab,ti	5
#51	BI695502:ab,ti	0
#52	BS503:ab,ti	0
#53	"BS-503":ab,ti	0
#54	"BS-503A":ab,ti	1
#55	BS503A:ab,ti	0
#56	"bat 1706":ab,ti	0
#57	bat1706:ab,ti	8
#58	"bcd 021":ab,ti	5
#59	bcd021:ab,ti	0
#60	"bevz 92":ab,ti	0
#61	bevz92:ab,ti	6
#62	"CHS-5217":ab,ti	0
#63	CHS5217:ab,ti	0
#64	"CT-16":ab,ti	22
#65	CT16:ab,ti	0
#66	"CT-P16":ab,ti	7
#67	CTP16:ab,ti	7
#68	"FKB-238":ab,ti	0
#69	FKB238:ab,ti	3
#70	"hd 204":ab,ti	0
#71	hd204:ab,ti	5
#72	"HLX-04":ab,ti	0
#73	HLX04:ab,ti	5
#74	"mb 02":ab,ti	0



Date	24/06/2020 20:08:17	
#75	mb02:ab,ti	11
#76	"mil 60":ab,ti	0
#77	mil60:ab,ti	3
#78	"myl 14020":ab,ti	0
#79	myl14020:ab,ti	0
#80	"myl 1402o":ab,ti	5
#81	myl1402o:ab,ti	0
#82	"nsc 704865":ab,ti	6
#83	nsc704865:ab,ti	0
#84	"ons 1045":ab,ti	0
#85	ons1045:ab,ti	0
#86	"ons 5010":ab,ti	1
#87	ons5010:ab,ti	0
#88	PF06439535:ab,ti	0
#89	"PF-06439535":ab,ti	12
#90	PF6439535:ab,ti	0
#91	"PF-6439535":ab,ti	0
#92	"ql 1101":ab,ti	0
#93	ql1101:ab,ti	5
#94	"RG-435":ab,ti	0
#95	RG435:ab,ti	0
#96	"R-435":ab,ti	1
#97	R435:ab,ti	4
#98	"ro 4876646":ab,ti	9
#99	ro4876646:ab,ti	74
#100	"sb 8":ab,ti	5
#101	sb8:ab,ti	4



Date	24/06/2020 20:08:17	
#102	"stc 103":ab,ti	0
#103	stc103:ab,ti	0
#104	#28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 or #53 or #54 or #55 or #56 or #57 or #58 or #59 or #60 or #61 or #62 or #63 or #64 or #65 or #66 or #67 or #68 or #69 or #70 or #71 or #72 or #73 or #74 or #75 or #76 or #77 or #78 or #79 or #80 or #81 or #82 or #83 or #84 or #85 or #86 or #87 or #88 or #89 or #90 or #91 or #92 or #93 or #94 or #95 or #96 or #97 or #98 or #99 or #100 or #101 or #102 or #103	5855
#105	#27 or #104	6003
#106	[mh ^"cetuximab"]	562
#107	cetuximab:ab,ti	2046
#108	Erbitux:ab,ti	216
#109	C225:ab,ti	26
#110	"C-225":ab,ti	40
#111	PQX0D8J21J:ab,ti	0
#112	IMC225:ab,ti	0
#113	"CMAB-009":ab,ti	0
#114	CMAB009:ab,ti	7
#115	"ABP-494":ab,ti	0
#116	ABP494:ab,ti	0
#117	"205923-56-4":ab,ti	45
#118	#107 or #108 or #109 or #110 or #111 or #112 or #113 or #114 or #115 or #116 or #117	2118
#119	#106 or #118	2168
#120	[mh ^"Panitumumab"]	83
#121	panitumumab:ab,ti	647
#122	panitunumab:ab,ti	2
#123	Vectibix:ab,ti	59
#124	Vectibex:ab,ti	0
#125	abenix:ab,ti	0



Date	24/06/2020 20:08:17	
#126	"E7.6.3":ab,ti	0
#127	"ABX-EGF":ab,ti	6
#128	6A901E312A:ab,ti	0
#129	"339177-26-3":ab,ti	32
#130	#121 or #122 or #123 or #124 or #125 or #126 or #127 or #128 or #129	651
#131	#120 or #130	653
#132	regorafenib:ab,ti	458
#133	24T2A1DOYB:ab,ti	0
#134	STIVARGA:ab,ti	19
#135	"BAY-734506":ab,ti	0
#136	"BAY 73-4506":ab,ti	14
#137	BAY734506:ab,ti	0
#138	"1019206-88-2":ab,ti	1
#139	"755037-03-7":ab,ti	16
#140	#132 or #133 or #134 or #135 or #136 or #137 or #138 or #139	458
#141	#26 or #105 or #119 or #131 or #140	9202
#142	#9 and #141	2862
#143	(vegfr NEAR/5 (inhibit* or antagonist? or target* or block* or against or anti or "multi-target" or "multi-targets" or reduc*)):ab,ti	2077
#144	(egfr NEAR/5 (inhibit* or antagonist? or target* or block* or against or anti or "multi-target" or "multi-targets" or reduc*)):ab,ti	1943
#145	(vegfr* NEAR/5 (inhibit* or antagonist? or target* or block* or against or anti or "multi-target" or "multi-targets" or reduc*)):ab,ti	590
#146	((HER1 or HER-1) NEAR/5 (inhibit* or antagonist? or target* or block* or against or anti or "multi-target" or "multi-targets" or reduc*)):ab,ti	33
#147	((erbb-1 or erbb1) NEAR/5 (inhibit* or antagonist? or target* or block* or against or anti or "multi-target" or "multi-targets" or reduc*)):ab,ti	12
#148	(egf NEAR/5 (inhibit* or antagonist? or target* or block* or against or anti or "multi-target" or "multi-targets" or reduc*)):ab,ti	86



Date	24/06/2020 20:08:17	
#149	#143 or #144 or #145 or #146 or #147 or #148	4394
#150	[mh "Vascular Endothelial Growth Factors"/AI]	539
#151	[mh "Receptors, Vascular Endothelial Growth Factor"/AI]	86
#152	[mh ^"Epidermal Growth Factor"/AI]	5
#153	[mh "ErbB Receptors"/AI]	275
#154	#150 or #151 or #152 or #153	886
#155	#149 or #154	5018
#156	#9 and #155	705
#157	[mh ^"Protein Kinase Inhibitors"]	762
#158	[mh "Protein-Tyrosine Kinases"/AI]	640
#159	[mh "Antibodies, Monoclonal"]	12727
#160	#157 or #158 or #159	13669
#161	tki:ab,ti	1225
#162	(kinase? NEAR/3 (inhibit* or antagonist? or target* or block* or against or anti or "multi-target" or "multi-targets" or reduc*)):ab,ti	3959
#163	(monoclonal NEAR/3 antibod*):ab,ti	8824
#164	#161 or #162 or #163	13179
#165	#160 or #164	23942
#166	#9 and #165	1207
#167	((new class* or innovative or target*) NEAR/3 (drug? or therapy or therapies or therapeutic* or treatment? or chemotherap*)):ab,ti	34196
#168	#9 and #167	641
#169	#142 or #156 or #166 or #168	3586
#170	#169 in Cochrane Reviews	10
Comments		



Appendix 3.3.3.2. Medline + PreMedline

Date	June 23, 2020	
Database	Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946 to June 23, 2020>	
Search strategy		
1	exp Colorectal Neoplasms/	200186
2	((rectum or rectal or colorectal) adj4 (cancer* or tumor* or tumour* or carcin* or adenocarcin* or metasta* or malignan* or lymphom* or leiomyosarcom* or melanom*)).ab,ti,kf.	159915
3	((colon or colonic) adj4 (cancer* or tumor* or tumour* or carcin* or adenocarcin* or metasta* or malignan* or lymphom* or leiomyosarcom* or melanom*)).ab,ti,kf.	91577
4	(sigmoid adj4 (cancer* or tumor* or tumour* or carcin* or adenocarcin* or metasta* or malignan* or lymphom* or leiomyosarcom* or melanom*)).ab,ti,kf.	2944
5	lynch syndrome.ab,ti,kf.	3172
6	(adenomatous adj3 polypos*).ab,ti,kf.	7295
7	(gardner* adj3 syndrome).ab,ti,kf.	1172
8	2 or 3 or 4 or 5 or 6 or 7	231379
9	1 or 8	277882
10	aflibercept.ab,ti,kf,rn.	2200
11	ZALTRAP.ab,ti,kf,rn.	30
12	EYLEA.ab,ti,kf,rn.	123
13	15C2VL427D.ab,ti,kf,rn.	1298
14	VEGF TRAP.ab,ti,kf,rn.	286
15	VEGF TRAP-EYE.ab,ti,kf,rn.	45
16	BAY-86-5321.ab,ti,kf,rn.	1
17	BAY-865321.ab,ti,kf,rn.	0
18	BAY86-5321.ab,ti,kf,rn.	1
19	BAY865321.ab,ti,kf,rn.	0
20	AVE-0005.ab,ti,kf,rn.	2
21	AVE0005.ab,ti,kf,rn.	3



Date	June 23, 2020	
22	vascular endothelial growth factor trap.ab,ti,kf,rn.	55
23	vasculotropin trap.ab,ti,kf,rn.	0
24	845771-78-0.ab,ti,kf,rn.	0
25	862111-32-8.ab,ti,kf,rn.	1
26	10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25	2362
27	Bevacizumab/	11513
28	bevacizumab.ab,ti,kf,rn.	18098
29	avastin.ab,ti,kf,rn.	1534
30	mvasi.ab,ti,kf,rn.	5
31	zirabev.ab,ti,kf,rn.	2
32	ainex.ab,ti,kf,rn.	1
33	altuzan.ab,ti,kf,rn.	2
34	bevax.ab,ti,kf,rn.	0
35	bryxta.ab,ti,kf,rn.	0
36	krabeva.ab,ti,kf,rn.	0
37	kyomarc.ab,ti,kf,rn.	0
38	2S9ZZM9Q9V.ab,ti,kf,rn.	11514
39	1438851-35-4.ab,ti,kf,rn.	0
40	216974-75-3.ab,ti,kf,rn.	1
41	RHUMAB.ab,ti,kf,rn.	137
42	rhuMAb-VEGF.ab,ti,kf,rn.	18
43	12-IGG1.ab,ti,kf,rn.	3
44	ABP-215.ab,ti,kf,rn.	9
45	ABP215.ab,ti,kf,rn.	1
46	AVA1.ab,ti,kf,rn.	8
47	AVA-1.ab,ti,kf,rn.	42



Date	June 23, 2020	
48	ask b1202.ab,ti,kf,rn.	0
49	askb1202.ab,ti,kf,rn.	0
50	BI 695502.ab,ti,kf,rn.	1
51	BI695502.ab,ti,kf,rn.	0
52	BS503.ab,ti,kf,rn.	0
53	BS-503.ab,ti,kf,rn.	0
54	BS-503A.ab,ti,kf,rn.	1
55	BS503A.ab,ti,kf,rn.	0
56	bat 1706.ab,ti,kf,rn.	0
57	bat1706.ab,ti,kf,rn.	2
58	"bcd 021".ab,ti,kf,rn.	0
59	bcd021.ab,ti,kf,rn.	1
60	bevz 92.ab,ti,kf,rn.	0
61	bevz92.ab,ti,kf,rn.	1
62	CHS-5217.ab,ti,kf,rn.	0
63	CHS5217.ab,ti,kf,rn.	0
64	CT-16.ab,ti,kf,rn.	120
65	CT16.ab,ti,kf,rn.	37
66	CT-P16.ab,ti,kf,rn.	1
67	CTP16.ab,ti,kf,rn.	0
68	FKB-238.ab,ti,kf,rn.	0
69	FKB238.ab,ti,kf,rn.	0
70	hd 204.ab,ti,kf,rn.	2
71	hd204.ab,ti,kf,rn.	0
72	HLX-04.ab,ti,kf,rn.	0
73	HLX04.ab,ti,kf,rn.	0
74	"mb 02".ab,ti,kf,rn.	18



Date	June 23, 2020	
75	mb02.ab,ti,kf,rn.	4
76	mil 60.ab,ti,kf,rn.	2
77	mil60.ab,ti,kf,rn.	2
78	myl 14020.ab,ti,kf,rn.	0
79	myl14020.ab,ti,kf,rn.	0
80	myl 1402o.ab,ti,kf,rn.	0
81	myl1402o.ab,ti,kf,rn.	0
82	nsc 704865.ab,ti,kf,rn.	2
83	nsc704865.ab,ti,kf,rn.	0
84	ons 1045.ab,ti,kf,rn.	0
85	ons1045.ab,ti,kf,rn.	0
86	ons 5010.ab,ti,kf,rn.	0
87	ons5010.ab,ti,kf,rn.	0
88	PF06439535.ab,ti,kf,rn.	0
89	PF-06439535.ab,ti,kf,rn.	5
90	PF6439535.ab,ti,kf,rn.	0
91	PF-6439535.ab,ti,kf,rn.	0
92	ql 1101.ab,ti,kf,rn.	0
93	ql1101.ab,ti,kf,rn.	1
94	RG-435.ab,ti,kf,rn.	1
95	RG435.ab,ti,kf,rn.	0
96	R-435.ab,ti,kf,rn.	53
97	R435.ab,ti,kf,rn.	15
98	ro 4876646.ab,ti,kf,rn.	0
99	ro4876646.ab,ti,kf,rn.	0
100	sb 8.ab,ti,kf,rn.	30



Date	June 23, 2020	
101	sb8.ab,ti,kf,rn.	19
102	stc 103.ab,ti,kf,rn.	0
103	stc103.ab,ti,kf,rn.	0
104	28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102 or 103	18733
105	27 or 104	18733
106	cetuximab/	4449
107	cetuximab.ab,ti,kf,rn.	7321
108	Erbitux.ab,ti,kf,rn.	344
109	C225.ab,ti,kf,rn.	478
110	C-225.ab,ti,kf,rn.	76
111	PQX0D8J21J.ab,ti,kf,rn.	4450
112	IMC225.ab,ti,kf,rn.	1
113	CMAB-009.ab,ti,kf,rn.	0
114	CMAB009.ab,ti,kf,rn.	3
115	ABP-494.ab,ti,kf,rn.	0
116	ABP494.ab,ti,kf,rn.	0
117	205923-56-4.ab,ti,kf,rn.	1
118	107 or 108 or 109 or 110 or 111 or 112 or 113 or 114 or 115 or 116 or 117	7696
119	106 or 118	7696
120	Panitumumab/	972
121	panitumumab.ab,ti,kf,rn.	1794
122	panitunumab.ab,ti,kf,rn.	7
123	Vectibix.ab,ti,kf,rn.	47
124	Vectibex.ab,ti,kf,rn.	0
125	abenix.ab,ti,kf,rn.	2



Date	June 23, 2020	
126	"E7.6.3".ab,ti,kf,rn.	6
127	ABX-EGF.ab,ti,kf,rn.	40
128	6A901E312A.ab,ti,kf,rn.	973
129	339177-26-3.ab,ti,kf,rn.	1
130	121 or 122 or 123 or 124 or 125 or 126 or 127 or 128 or 129	1827
131	120 or 130	1827
132	regorafenib.ab,ti,kf,rn.	1123
133	24T2A1DOYB.ab,ti,kf,rn.	494
134	STIVARGA.ab,ti,kf,rn.	32
135	BAY-734506.ab,ti,kf,rn.	0
136	BAY 73-4506.ab,ti,kf,rn.	23
137	BAY734506.ab,ti,kf,rn.	0
138	1019206-88-2.ab,ti,kf,rn.	0
139	755037-03-7.ab,ti,kf,rn.	1
140	132 or 133 or 134 or 135 or 136 or 137 or 138 or 139	1127
141	26 or 105 or 119 or 131 or 140	27953
142	9 and 141	6991
143	(vegfr adj5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)).ab,ti,kf.	20933
144	(egfr adj5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)).ab,ti,kf.	22013
145	(vegfr* adj5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)).ab,ti,kf.	4593
146	((HER1 or HER-1) adj5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)).ab,ti,kf.	294
147	((erbb-1 or erbb1) adj5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)).ab,ti,kf.	267
148	(egf adj5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)).ab,ti,kf.	7632
149	143 or 144 or 145 or 146 or 147 or 148	51425
150	exp Vascular Endothelial Growth Factors/ai	8313
151	exp Receptors, Vascular Endothelial Growth Factor/ai	2960



Date	June 23, 2020	
152	Epidermal Growth Factor/ai	570
153	exp ErbB Receptors/ai	11721
154	150 or 151 or 152 or 153	22460
155	149 or 154	61371
156	9 and 155	4911
157	Protein Kinase Inhibitors/	45263
158	exp Protein-Tyrosine Kinases/ai	38056
159	exp Antibodies, Monoclonal/	235325
160	157 or 158 or 159	299853
161	t.ki.ab,ti,kf.	7579
162	(kinase? adj3 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)).ab,ti,kf.	118162
163	(monoclonal adj3 antibod*).ab,ti,kf.	196475
164	161 or 162 or 163	312405
165	160 or 164	468390
166	9 and 165	15716
167	((new class* or innovative or target*) adj3 (drug? or therapy or therapies or therapeutic* or treatment? or chemotherap*)).ab,ti,kf.	330433
168	9 and 167	11340
169	142 or 156 or 166 or 168	27558
170	((systematic review or systematic literature review or systematic scoping review or systematic narrative review or systematic qualitative review or systematic evidence review or systematic quantitative review or systematic meta-review or systematic critical review or systematic mixed studies review or systematic mapping review or systematic cochrane review or "systematic search and review" or systematic integrative review).ti. not comment.pt. not (protocol or protocols).ti. not medline.st.) or (Cochrane Database Syst Rev.ja. and review.pt.) or systematic review.pt.	159535
171	meta-analys*.ti.	109097
172	meta-analysis.pt.	116362
173	exp Technology Assessment, Biomedical/	11075
174	health technology assessment.ti,kf.	1925



Date	June 23, 2020	
175	HtA.ti,kf.	596
176	170 or 171 or 172 or 173 or 174 or 175	253258
177	169 and 176	414
Comments		



Appendix 3.4. Economic literature

Appendix 3.4.1. Search economic literature (HTA reports)

The search strategy in CRD's HTA database identified 254 references (Table 41). In a first round, 12 references were selected based on a review of title, keywords and abstract. The 242 remaining references were excluded for the following reasons: intervention (219), design (18) or language (5). In a second round, the full text of the 12 selected references was reviewed. Seven references were excluded (design (4), update available (2), price of the report (1)). Five references were retained. These references are indicated in Table 42 with an asterix (*).

Furthermore, in May 2020, the website of the National Institute for Health Research (NIHR) was searched for relevant reports. The following search terms were used together: bevacizumab cetuximab panitumumab aflibercept regorafenib (63 hits, 7 with a focus on colorectal cancer, 5 not previously identified).

Finally, also in May 2020, the website of the National Institute for Health and Care Excellence (NICE) was searched. The following search terms were used: bevacizumab (47 hits, 3 relevant Technology Assessments (TAs), 1 not previously identified); cetuximab (24 hits, 5 relevant TAs, 2 not previously identified); panitumumab (9 hits, 3 relevant TAs, 1 not previously identified); aflibercept (18 hits, 1 relevant TA, 1 not previously identified); regorafenib (14 hits, 1 relevant TA, 1 not previously identified).

An overview of the identified references is provided in Table 42.

Table 41 – Search strategy and results for CRD: HTA

Date			
Date covered	All		
Search Strategy	1	MeSH DESCRIPTOR Colorectal Neoplasms EXPLODE ALL TREES	1438
	2	* IN HTA	17351
	3	#1 AND #2	254 references
Note	/		

**Table 42 – Colorectal cancer – Identified HTA reports for the selected drugs**

Selected reports	
Bevacizumab, cetuximab and panitumumab	
<ul style="list-style-type: none"> NICE, TA242. January 2012. Cetuximab, bevacizumab and panitumumab for the treatment of metastatic colorectal cancer after first-line chemotherapy: Cetuximab (monotherapy or combination chemotherapy), bevacizumab (in combination with non-oxaliplatin chemotherapy) and panitumumab (monotherapy) for the treatment of metastatic colorectal cancer after first-line chemotherapy.^{59 β} <ul style="list-style-type: none"> Hoyle M, Crathorne L, Peters J, Jones-Hughes T, Cooper C. The clinical effectiveness and cost-effectiveness of cetuximab (mono- or combination chemotherapy), bevacizumab (combination with non-oxaliplatin chemotherapy) and panitumumab (monotherapy) for the treatment of metastatic colorectal cancer after first-line chemotherapy (review of technology appraisal No. 150 and part review of technology appraisal No. 118): a systematic review and economic model. Health Technol Assess 2013;17(14).^{60 α} 	
Bevacizumab and cetuximab	
<ul style="list-style-type: none"> NICE, TA118. January 2007. Bevacizumab and cetuximab for the treatment of metastatic colorectal cancer.^{61 * β} <ul style="list-style-type: none"> Tappenden P, Jones R, Paisley S, Carroll C. Systematic review and economic evaluation of bevacizumab and cetuximab for the treatment of metastatic colorectal cancer. Health Technol Assess 2007;11(12).^{62 * α} This guidance has been partially updated by NICE technology appraisal guidance 242. 	
Cetuximab and panitumumab	
<ul style="list-style-type: none"> NICE, TA439. March 2017. Cetuximab and panitumumab for previously untreated metastatic colorectal cancer.^{63 * β} <ul style="list-style-type: none"> Huxley N, Crathorne L, Varley-Campbell J, Tikhonova I, Snowsill T, Briscoe S, et al. The clinical effectiveness and cost-effectiveness of cetuximab (review of technology appraisal no. 176) and panitumumab (partial review of technology appraisal no. 240) for previously untreated metastatic colorectal cancer: a systematic review and economic evaluation. Health Technol Assess 2017;21(38).^{64 α} 	
Bevacizumab	
<ul style="list-style-type: none"> NICE, TA212. December 2010. Bevacizumab in combination with oxaliplatin and either fluorouracil plus folinic acid or capecitabine for the treatment of metastatic colorectal cancer.^{65 * β} <ul style="list-style-type: none"> Whyte S, Pandor A, Stevenson M, Rees A. Bevacizumab in combination with fluoropyrimidine-based chemotherapy for the first-line treatment of metastatic colorectal cancer. Health Technol Assess 2010;14(Suppl 2 Article 7).^{66 * α} Whyte S, Pandor A, Stevenson M, Rees A. Bevacizumab in combination with fluoropyrimidine-based chemotherapy for the first-line treatment of metastatic colorectal cancer - a single technology appraisal. September 2009.^{67 α} 	
Panitumumab	
<ul style="list-style-type: none"> NICE, TA240. December 2011. Panitumumab in combination with chemotherapy for the treatment of metastatic colorectal cancer (terminated appraisal).^{68 β} 	
Aflibercept	
<ul style="list-style-type: none"> NICE, TA307. March 2014. Aflibercept in combination with irinotecan and fluorouracil-based therapy for treating metastatic colorectal cancer that has progressed following prior oxaliplatin-based chemotherapy.^{69 β} 	
Regorafenib	



- NICE, TA334. February 2015. Regorafenib for metastatic colorectal cancer after treatment for metastatic disease (terminated appraisal).^{70 β}

Excluded reports

Cetuximab

- NICE, TA150. June 2008. Cetuximab for the treatment of metastatic colorectal cancer following failure of oxaliplatin-containing chemotherapy.^{71 β}
 - This appraisal has been updated and replaced by NICE technology appraisal guidance 242.
- NICE, TA176. August 2009. Cetuximab for the first-line treatment of metastatic colorectal cancer.^{72 β}
 - Meads C, Round J, Tubeuf S, Moore D, Pennant M. Cetuximab for the first-line treatment of metastatic colorectal cancer. Health Technol Assess 2010;14(Suppl 1 Article 1).^{73 α}
 - Meads C, Round J, Tubeuf S, Moore D, Pennant M, Bayliss S, McCabe C. Cetuximab for the first-line treatment of metastatic colorectal cancer. STA Report. WMHTAC, University of Birmingham. July 2008.^{74 α}
 - This guidance has been updated and replaced by NICE technology appraisal guidance 439.

* These references were identified in CRD's HTA database. α References identified on NIHR's website. β References identified on NICE's website.

Appendix 3.4.2. Results economic literature (HTA reports)

Appendix 3.4.2.1. NICE, TA242 (2012): bevacizumab, cetuximab and panitumumab

- QoL:
 - The generic HUI instrument is used in the CO.17 trial (cetuximab) and the EQ-5D VAS is used in a study for panitumumab.
 - "The Committee noted that the utility estimates for each of the disease states were not consistent with the expectation that quality of life worsens with progression of disease. The Committee also noted that the utility estimates in the model (for example, 0.81 for progression-free disease for cetuximab plus best supportive care) were similar to those expected for people of the same age without metastatic colorectal cancer. The Committee concluded that the utility values in the manufacturer's model were highly uncertain."⁵⁹
- Results:
 - "The Assessment Group produced a series of pairwise comparisons of cost effectiveness in people with KRAS wild-type metastatic colorectal cancer:
 - Cetuximab plus best supportive care compared with best supportive care alone produced a base-case ICER of £98,000 per QALY gained.
 - Cetuximab plus irinotecan plus best supportive care compared with best supportive care alone produced a base-case ICER of £88,000 per QALY gained.
 - Panitumumab plus best supportive care compared with best supportive care alone produced a base-case ICER of £150,000 per QALY gained."⁵⁹
 - "No data were available for bevacizumab in combination with nonoxaliplatin-based chemotherapy in previously treated patients."⁶⁰ "The Committee discussed the likely cost effectiveness of bevacizumab plus non-oxaliplatin chemotherapy compared with best supportive care and noted the



Assessment Group's view that lack of relevant evidence on clinical effectiveness meant that it was not feasible to carry out a cost-effectiveness evaluation of bevacizumab.”⁵⁹

- Uncertainty/sensitivity:
 - “The Committee concluded that the utility values in the manufacturer's model were highly uncertain.”⁵⁹
 - “The Committee noted that one of the main factors affecting the cost effectiveness of cetuximab was the assumption about the mean duration of treatment. ... For panitumumab, the estimate of overall survival was the main factor found to substantially change the ICER.”⁵⁹
 - “The uncertainties were: - the overall survival gain with bevacizumab plus non-oxaliplatin chemotherapy in people with metastatic colorectal cancer who had previously received chemotherapy; - the estimates of overall survival for cetuximab plus irinotecan based on the mixed treatment comparison; - the magnitude of the survival benefit of panitumumab relative to best supportive care.”⁵⁹
 - “The deterministic sensitivity analysis suggests that progression-free survival, overall survival, time on drug treatment, drug acquisition costs and drug administration costs strongly influence cost-effectiveness estimates.”⁶⁰
- Conclusions:
 - “Cetuximab monotherapy or combination chemotherapy, bevacizumab in combination with non-oxaliplatin (fluoropyrimidine-based) chemotherapy, and panitumumab monotherapy are not recommended for the treatment of people with metastatic colorectal cancer that has progressed after first-line chemotherapy.
This is because:
 - It was not possible to confirm by how much bevacizumab in combination with nonoxaliplatin (fluoropyrimidine-based) chemotherapy would extend life when used as second-line therapy, and evidence from previous assessments of bevacizumab with other combination regimens or for first-line treatment does not allow a justification for a positive recommendation in this appraisal.
 - The ICERs for cetuximab monotherapy or combination chemotherapy and for panitumumab monotherapy were very high (£98,000, £88,000 and £110,000–£150,000 per QALY gained respectively) and therefore these technologies did not represent a cost-effective use of NHS resources.”⁵⁹
- (Confidential) prices:
 - The interventions were not recommended for reimbursement. No results of analyses with confidential prices were reported.



Reference Costs (list prices & remarks)	Population, Intervention & comparator IC, IE and ICERs	Remarks on use of generic utility instrument (e.g. EQ- 5D) to measure impact on QoL in economic evaluations	Most uncertain variables or important variables in sensitivity analysis
Bevacizumab, cetuximab and panitumumab			
NICE, TA242 (2012) ⁵⁹ Hoyle (2013) ⁶⁰	Patients with metastatic colorectal cancer that has progressed after first-line chemotherapy. Cetuximab (mono- or combination chemotherapy), bevacizumab (combination with non-oxaliplatin chemotherapy) and panitumumab (monotherapy) versus best supportive care.		
List prices. Drug costs per month: 1 st next Month months Cetuximab: £3421 first month, £3026 subsequently Panitumumab: £4104 Irinotecan: £935	Results of the incremental analysis (with list prices): Costs (£) IC QALYs IE ICER CET vs BSC / £24,500 / 0.25 £98,000 PAN vs BSC / £29,000 / 0.19 £150,000 CET+IRI vs BSC / £53,100 / 0.60 £88,000 / Remark: it is reported that "In common with the manufacturer, we were not able to estimate the cost-effectiveness of bevacizumab in combination with non-oxaliplatin chemotherapy second or subsequent line because of the absence of RCT evidence."	HUI is used in CO.17 trial (cetuximab) and EQ-5D VAS in a study for panitumumab.	Progression-free and overall survival Utilities Treatment duration Acquisition & administration costs.

BSC: best supportive care; CET: cetuximab; PAN: panitumumab; IRI: irinotecan.



Appendix 3.4.2.2. NICE, TA118 (2007): bevacizumab and cetuximab

- QoL:
 - There is no head-to-head trial available in which QoL is measured with a generic utility instrument.
 - “Bevacizumab – manufacturer's models: ... The models assumed equivalent utility scores for both the intervention and control groups, with a utility of 0.80 given to the pre-progression health state and 0.50 to the post-progression health state. Utility decrements associated with adverse events were not included.
 - Bevacizumab – assessment group models: ... The utility value for pre-progression was the same as was used in the manufacturer's models (0.80), whereas that for post-progression was slightly higher (0.60).”⁶¹
 - “Cetuximab – manufacturer's model: ... Outcomes were presented as life years gained, with sensitivity analyses to examine the impact of quality of life using alternative utilities for metastatic colorectal cancer of 0.95 and 0.71, both constant over the lifetime and based on published data. Additional data were presented using a utility of 0.73, constant over the lifetime, based on data collected as part of a single-arm study that investigated the effectiveness of cetuximab as a second and subsequent-line treatment for patients with metastatic colorectal cancer (MABEL).
 - Cetuximab assessment group models: ... Health-related quality of life was estimated in the same way as in the bevacizumab model, applying a utility of 0.80 to pre-progression disease states and 0.60 to post-progression states.”⁶¹
- Results:
 - “Bevacizumab – assessment group models: ... The base-case costs per QALY gained for the assessment group models were £62,857 for bevacizumab combined with IFL and £88,436 for bevacizumab combined with 5-FU/LV, compared with IFL or 5-FU/LV alone, respectively.”⁶¹
 - “Cetuximab assessment group models: ... Indirect comparisons are associated with a high level of uncertainty, but they yielded estimates of the cost per QALY gained that ranged from £77,210 to £370,044.”⁶¹
- Uncertainty/sensitivity:
 - “None of the studies reported the impact of bevacizumab treatment on HRQoL. Given that improving quality of life is a key objective of treatment, this represents a crucial gap in the current evidence base.”⁶²
 - “The Committee noted that there were currently no clinical studies available comparing cetuximab with FOLFOX, and therefore the relative clinical effectiveness of cetuximab as a second-line treatment could not as yet be determined.”⁶¹
 - “This review highlights a number of areas for further research, including clarifying the true impact of first-line bevacizumab in combination with irinotecan and/or infusional 5-FU/FA, without subsequent bevacizumab treatment following disease progression, on OS in patients with metastatic CRC who are representative of the typical population of CRC patients in England and Wales. Further research concerning the impact of therapies on health-related quality of life is essential.”⁶²



- Conclusions:
 - “It [the Committee] concluded that bevacizumab in combination with 5-FU/FA, with or without irinotecan as a first-line treatment for metastatic colorectal cancer would not be a cost-effective use of NHS resources. ...

Considering all the available evidence on clinical and cost effectiveness, the Committee therefore concluded that cetuximab, either as a second-line or a subsequent-line treatment for metastatic colorectal cancer would not be a cost-effective use of NHS resources.”⁶¹

- (Confidential) prices:
 - The interventions were not recommended for reimbursement. No results of analyses with confidential prices were reported.

Reference	Population, Intervention & comparator	Costs (list prices & remarks)	IC, IE and ICERs	Remarks on use of generic utility instrument (e.g. EQ-5D) to measure impact on QoL in economic evaluations	Most uncertain variables or important variables in sensitivity analysis
Bevacizumab and cetuximab					
NICE, TA118 (2007) ⁶¹	Patients with metastatic colorectal cancer.				
Tappenden (2007) ⁶²	First-line treatment of metastatic colorectal cancer: bevacizumab + IFL vs. IFL or bevacizumab + 5-FU/FA vs. 5-FU/FA.				
	Patients with EGFR-expressing metastatic colorectal cancer who have previously failed on irinotecan-including therapy: cetuximab plus irinotecan vs. active/best supportive care.				
List prices.	Results of the incremental analysis (with list prices):				
Bevacizumab is available in 100-mg and 400-mg vials at net prices of £242.66 and £924.40 respectively (excluding VAT; 'British national formulary')	A) Bevacizumab:				
		Costs (£)	IC	QALYs	IE
	Bev.+ IFL	43 007		1.44	
	IFL	23 646	19 361	1.13	0.31
Cetuximab is provided in 50-ml vials containing 2 mg cetuximab per ml. The net price for a 50-ml vial is £136.50 (excluding VAT; 'British national formulary').		Costs (£)	IC	QALYs	IE
	Bev.+ 5-FU/FA	37 113		1.19	
	5-FU/FA	21 459	15 654	1.01	0.18
					87 980*
	*The reported result in the underlying report is somewhat different from the results in the TA report (£88 436 per QALY gained).				
	B) Cetuximab				

Bevacizumab: None of the studies reported the impact of bevacizumab treatment on HRQoL.

Cetuximab: MABEL single-arm study: At baseline, EQ-5D assessed utility was 0.73; this level of utility is seen to remain fairly constant when patients receive cetuximab plus irinotecan over the evaluable period. This suggests that treatment with cetuximab plus irinotecan does not detract from a patient's level of

Relative clinical effectiveness. QoL.



The base-case threshold analysis suggests it is not possible for cetuximab combined with irinotecan to have a cost per QALY gained of less than £20,000, irrespective of the application of the continuation rule. ... A sensitivity analysis using utility values from the MABEL study suggested that with the continuation rule applied cetuximab plus irinotecan must provide 0.60 additional life years (7.2 months) compared with ASC/BSC in order to achieve a cost per QALY gained of £30,000. Indirect comparisons are associated with a high level of uncertainty, but they yielded estimates of the cost per QALY gained that ranged from £77,210 to £370,044.

HRQoL as measured by the EQ-5D.

5-FU/FA = 5-fluorouracil plus folinic acid; Bev.: bevacizumab; IFL = irinotecan, fluorouracil and leucovorin.

Appendix 3.4.2.3. NICE, TA439 (2017): cetuximab and panitumumab

- QoL:

- “None of the included publications reported HRQoL estimates for the RAS WT population.”⁶⁴
- “In the absence of RAS WT data, EuroQol 5-Dimensions data from two trials with Kirsten rat sarcoma (KRAS) WT populations was used to inform first- and second-line utility values (0.767 and 0.762, respectively). Third-line utility (0.641) was taken from published literature.”⁶⁴
- “Bennett et al.115 is the only full paper that reports utility data collected for the KRAS WT population from the PRIME trial and it also includes utility results for a second-line panitumumab trial. It includes the results of EQ-5D questionnaires valued on the UK value set calculated by Dolan.119 Bennett et al.115 also report that the utility change from baseline until disease progression for both arms is not clinically significant and that the difference between arms is not statistically or clinically significant.”⁶⁴

- Results:

- Without discounts: “For the independent economic evaluation, the base-case incremental cost-effectiveness ratio (ICER) for RAS WT patients for cetuximab plus oxaliplatin-based chemotherapy (folinic acid + 5-fluorouracil + oxaliplatin) (FOLFOX) compared with FOLFOX was £104,205 per quality-adjusted life-year (QALY) gained; for panitumumab plus FOLFOX compared with FOLFOX was £204,103 per QALY gained; and for cetuximab plus FOLFIRI compared with FOLFIRI was £122,554 per QALY gained.”⁶⁴
- “In the independent economic assessment the ICERs for anti-EGFR therapy compared with chemotherapy alone were all > £100,000 per QALY gained.”⁶⁴
- With discounts: “The committee noted that the assessment group's ICERs for cetuximab plus FOLFIRI compared with FOLFIRI alone and panitumumab plus FOLFOX compared with FOLFOX alone were all below £50,000 per quality-adjusted life year (QALY) gained. The exact ICERs are not reported to prevent calculation of the discount associated with the patient access scheme and commercial access agreement.”⁶³

“Cetuximab plus FOLFOX compared with FOLFOX alone: It [the committee] noted that ICERs adjusted for subsequent treatments were not presented because of limited data. It recalled hearing that the clinical experts considered FOLFOX and FOLFIRI to be broadly equivalent The committee



concluded that the ICER for cetuximab plus FOLFOX compared with FOLFOX alone was likely to be similar to that for cetuximab plus FOLFIRI compared with FOLFIRI alone”⁶³

“Panitumumab plus FOLFIRI compared with FOLFIRI alone: It [the committee] noted that ICERs were not presented because of a lack of relevant clinical evidence ... It recalled its earlier conclusion that the effectiveness of panitumumab plus FOLFIRI was likely to be similar to that of panitumumab plus FOLFOX. The committee concluded that the ICER for panitumumab plus FOLFIRI compared with FOLFIRI alone was likely to be similar to that for panitumumab plus FOLFOX compared with FOLFOX alone.”⁶³

- Uncertainty/sensitivity:
 - “The adjustment for further treatments was a source of uncertainty. The committee concluded that, although the effect of these adjustments on survival were small, they were more plausible than the unadjusted estimates.
 - The difference in resection rates between treatment arms was a source of uncertainty. Although it was appropriate to source these from the clinical trials, the discrepancies between them were considered clinically implausible.”⁶³
 - “There are some important sources of uncertainty that may impact on the conclusions, including the use of subgroup analyses of intention-to-treat trial populations; the lack of evidence to estimate the effectiveness of panitumumab plus FOLFIRI; the lack of direct evidence to compare cetuximab + FOLFOX with panitumumab plus FOLFOX or FOLFOX-containing regimens with FOLFIRI-containing regimens; unclear time points at which ORR was measured in the trials; and the lack of reported HRQoL estimates for the RAS WT population.”⁶⁴
 - “The ICERs were sensitive to treatment duration, progression-free survival, overall survival (resected patients only) and resection rates.”⁶⁴
 - “First-line drug acquisition costs were the largest cost items.”⁶⁴
- Conclusions:
 - Without discounts: “Although cetuximab and panitumumab in combination with chemotherapy appear to be clinically beneficial for RAS WT patients compared with chemotherapy alone, they are likely to represent poor value for money when judged by cost-effectiveness criteria currently used in the UK.”⁶⁴
 - With discounts: “The committee concluded that panitumumab and cetuximab plus either FOLFOX or FOLFIRI could be considered a cost-effective use of NHS resources for previously untreated RAS wild-type metastatic colorectal cancer in adults.”⁶³
- (Confidential) prices:
 - Cetuximab: “The pricing arrangement considered during guidance development was that Merck had agreed a patient access scheme with the Department of Health. This scheme provided a simple discount to the list price of cetuximab with the discount applied at the point of purchase or invoice. After guidance publication in March 2017, the company agreed a commercial access agreement with NHS England that replaces the patient access scheme on equivalent terms. The financial terms of the agreement are commercial in confidence.”⁶³
 - Panitumumab: “The company has agreed a patient access scheme with the Department of Health, providing a simple discount to the list price of panitumumab with the discount applied at the point of purchase or invoice. The level of the discount is commercial in confidence.”⁶³



Reference	Costs (list prices & remarks)	Population, Intervention & comparator IC, IE and ICERs	Remarks on use of generic utility instrument (e.g. EQ-5D) to measure impact on QoL in economic evaluations	Most uncertain variables or important variables in sensitivity analysis																																										
Cetuximab and panitumumab																																														
NICE, TA439 (2017) ⁶³ Huxley (2017) ⁶⁴		Patients with rat sarcoma (RAS) wild-type (WT) metastatic colorectal cancer. Cetuximab plus FOLFOX compared with FOLFOX alone (OPUS trial), cetuximab plus FOLFIRI compared with FOLFIRI alone (CRYSTAL trial), and panitumumab plus FOLFOX compared with FOLFOX alone (PRIME trial).																																												
	List prices, negotiated discounts are hidden. Drug costs per month: The monthly costs of drug acquisition were calculated using list prices for cetuximab (£3859) and panitumumab (£4109). Cetuximab costs £178.10 per 20-ml vial and £890.50 per 100-ml vial (excluding VAT, 'British national formulary' [BNF]). ... Panitumumab costs £379.29 per 5-ml vial and £1,517.16 per 20-ml vial (excluding VAT, BNF).	Results of the incremental analysis (with list prices): A) Results in comparison with FOLFOX: <table><thead><tr><th></th><th>Costs (£)</th><th>IC</th><th>QALYs</th><th>IE</th><th>ICER</th></tr></thead><tbody><tr><td>FOLFOX</td><td>30 585</td><td></td><td>1.26</td><td></td><td></td></tr><tr><td>CET+FOLFOX</td><td>67 057</td><td>36 471</td><td>1.61</td><td>0.35</td><td>104 205</td></tr><tr><td>PAN+FOLFOX</td><td>61 225</td><td>30 640</td><td>1.41</td><td>0.15</td><td>204 103</td></tr></tbody></table> <p>Remark: on the efficiency frontier, PAN+FOLFOX is extendedly dominated.</p> B) Results in comparison with FOLFIRI: <table><thead><tr><th></th><th>Costs (£)</th><th>IC</th><th>QALYs</th><th>IE</th><th>ICER</th></tr></thead><tbody><tr><td>FOLFIRI</td><td>28 250</td><td></td><td>1.23</td><td></td><td></td></tr><tr><td>CET+FOLFIRI</td><td>65 380</td><td>37 130</td><td>1.53</td><td>0.30</td><td>122 554</td></tr></tbody></table> <p>Remark: with discounts: The committee noted that the assessment group's ICERs for cetuximab plus FOLFIRI compared with FOLFIRI alone and panitumumab plus FOLFOX compared with FOLFOX alone were all below £50,000 per quality-adjusted life year (QALY) gained. The exact ICERs are not reported to prevent calculation of the discount associated with the patient access scheme and commercial access agreement.</p>		Costs (£)	IC	QALYs	IE	ICER	FOLFOX	30 585		1.26			CET+FOLFOX	67 057	36 471	1.61	0.35	104 205	PAN+FOLFOX	61 225	30 640	1.41	0.15	204 103		Costs (£)	IC	QALYs	IE	ICER	FOLFIRI	28 250		1.23			CET+FOLFIRI	65 380	37 130	1.53	0.30	122 554	None of the included publications reported HRQoL estimates for the RAS WT population. Utility data (using the EQ-5D) were collected for the KRAS WT population in the PRIME trial.	Progression-free survival, overall survival, resection rates, QoL, impact following treatments.
	Costs (£)	IC	QALYs	IE	ICER																																									
FOLFOX	30 585		1.26																																											
CET+FOLFOX	67 057	36 471	1.61	0.35	104 205																																									
PAN+FOLFOX	61 225	30 640	1.41	0.15	204 103																																									
	Costs (£)	IC	QALYs	IE	ICER																																									
FOLFIRI	28 250		1.23																																											
CET+FOLFIRI	65 380	37 130	1.53	0.30	122 554																																									
CET, cetuximab; FOLFIRI: folinic acid + 5-fluorouracil + irinotecan; FOLFOX folinic acid + 5-fluorouracil + oxaliplatin; KRAS: Kirsten rat sarcoma; PAN, panitumumab; RAS: rat sarcoma; WT: wild-type.																																														



Appendix 3.4.2.4. NICE, TA212 (2010): bevacizumab

- QoL:
 - “The Committee noted that no health-related quality-of-life data were collected in the study and that the utility values were taken from ‘Cetuximab for the first-line treatment of metastatic colorectal cancer’ (NICE technology appraisal guidance 176). The ERG stated that the reporting of utility values in metastatic colorectal cancer was inconsistent and there is a paucity of data.”⁶⁵
 - “... the utility values in the economic model were not regimen-specific. It further noted that decreasing the utility values by 20% increased the ICERs substantially. The Committee concluded that these issues also increased the uncertainty associated with the base-case ICERs.”⁶⁵
 - “The Committee noted that disutility due to adverse events was not included in the economic model. The manufacturer stated that because the utility values were obtained using the EQ-5D, then disutility due to adverse events would be included implicitly within this measure. The Committee noted that a higher incidence of grade 3 and 4 adverse events associated with bevacizumab had been reported in the trial. ... The Committee further noted that the utility values used by the manufacturer could not have accounted for the adverse effects of bevacizumab because they were obtained from a study that examined cetuximab. The Committee therefore concluded that the ICERs would increase if the disutility due to adverse events related to bevacizumab treatment was included.”⁶⁵
- Results:
 - Details on incremental costs and incremental effects were presented as being confidential.
 - 1st line treatment – without versus with discount for intervention: “The Committee discussed the details of the patient access scheme and the impact of the patient access scheme on the ICERs. It noted that when the amended patient access scheme was applied the ICERs decreased from £105,000 to £30,000 per QALY gained for B-XELOX compared with XELOX, and from £108,000 to £24,600 per QALY gained for B-FOLFOX-6 compared with FOLFOX-6.”⁶⁵
 - 1st line treatment – also including discount for comparator: “The Committee also noted information provided by the Commercial Medicines Unit of the Department of Health which stated that oxaliplatin is widely available in the NHS through procurement contracts at a discount of more than 90% off the list price. The Committee noted the ERG’s exploratory analyses, which showed that when the oxaliplatin list price was discounted by 90% the ICERs with the patient access scheme were greatly increased to £68,100 per QALY gained for B-XELOX compared with XELOX, and to £70,500 per QALY gained for B-FOLFOX compared with FOLFOX-6. The Committee considered that it was more appropriate to use the discounted cost of oxaliplatin when assessing the impact of the patient access scheme on cost effectiveness and therefore did not accept the manufacturer’s estimates that ICERs of £105,000 and £108,000 per QALY gained were reduced to £30,000 and £24,600 respectively with the amended patient access scheme.”⁶⁵
 - 2nd line treatment – without discount: “As a second-line treatment, B-FOLFOX-4 compared with FOLFOX-4 resulted in an ICER of £102,644 per QALY gained.”⁶⁵



- Uncertainty/sensitivity:
 - “The main areas of uncertainty within the cost-effectiveness analysis relate to the choice of efficacy and health related quality of life (HRQoL) data, and the differences in treatment duration and continuity between the trial and clinical practice.”⁶⁷
- Conclusions:
 - Bevacizumab as a first-line treatment for metastatic colorectal cancer: “...giving ICERs of £105,000 per QALY gained for B-XELOX and £108,000 per QALY gained for B-FOLFOX-6 (without the patient access scheme) and £68,100 per QALY gained for B-XELOX and £70,500 per QALY gained for B-FOLFOX-6 (with the patient access scheme applied and the discounted price of oxaliplatin used). ... The Committee concluded that bevacizumab in combination with oxaliplatin and either fluorouracil plus folinic acid or capecitabine could not be recommended as a cost-effective use of NHS resources for the first-line treatment of metastatic colorectal cancer.”⁶⁵
 - Bevacizumab in combination with oxaliplatin-containing regimens as a second-line treatment for metastatic colorectal cancer: “The Committee noted that the base-case ICER presented by the manufacturer was £103,000 per QALY gained. The Committee noted that this ICER was substantially higher than those normally considered an acceptable use of NHS resources. ... The Committee further noted that no evidence of bevacizumab given after second-line treatment was submitted by the manufacturer. Therefore, the Committee concluded that bevacizumab in combination with oxaliplatin-containing regimens could not be recommended as a cost-effective use of NHS resources for second-line or later treatment of metastatic colorectal cancer.”⁶⁵
 - “Bevacizumab in combination with oxaliplatin and either fluorouracil plus folinic acid or capecitabine is not recommended for the treatment of metastatic colorectal cancer.”⁶⁵
- (Confidential) prices:
 - “The manufacturer of bevacizumab (Roche Products) proposed a patient access scheme to the Department of Health for the use of bevacizumab in metastatic colorectal cancer. The Department of Health was content for NICE to consider the patient access scheme proposed by Roche. However, it had concerns about the scheme's complexity and believed that the administrative burden of the scheme was greater than that originally set out by the manufacturer.”⁶⁵



Reference Costs (list prices & remarks)	Population, Intervention & comparator IC, IE and ICERs	Remarks on use of generic utility instrument (e.g. EQ- 5D) to measure impact on QoL in economic evaluations	Most uncertain variables or important variables in sensitivity analysis
Bevacizumab			
NICE, TA212 (2010) ⁶⁵ Whyte (2009) ⁶⁷	Patients with metastatic colorectal cancer. 1 st line: bevacizumab plus FOLFOX and XELOX compared with FOLFOX and XELOX alone. 2 nd line: bevacizumab in FOLFOX-4 compared with FOLFOX-4.		
List prices, negotiated discounts are hidden. Bevacizumab is available in 100-mg and 400-mg vials at net prices of £242.66 and £924.40 respectively (excluding VAT; 'British national formulary' [BNF])	Results of the incremental analysis: A) 1 st line treatment - without discount: B-XELOX versus XELOX: £105,000 per QALY gained B-FOLFOX-6 versus FOLFOX-6: £108,000 per QALY gained - with discount for bevacizumab: B-XELOX versus XELOX: £30,000 per QALY gained B-FOLFOX-6 versus FOLFOX-6: £24,600 per QALY gained - with discount for bevacizumab and discounted cost of oxaliplatin: B-XELOX versus XELOX: £68,100 per QALY gained B-FOLFOX-6 versus FOLFOX-6: £70,500 per QALY gained B) 2 nd line treatment (without discount): B-FOLFOX-4 compared with FOLFOX-4 resulted in an ICER of £102,644 per QALY gained.	No health-related quality-of-life data were collected in the NO16966 study.	Treatment efficacy, health-related quality of life (HRQoL) data, treatment duration.
<i>B-FOLFOX: bevacizumab plus FOLFOX; B-FOLFOX-4: bevacizumab in FOLFOX-4; B-XELOX: bevacizumab plus XELOX; FOLFOX: intravenous 5- fluorouracil plus folinic acid plus oxaliplatin; FOLFOX-4: the FOLFOX regimen given every 2 weeks, with two long infusions in the first 48 hours; FOLFOX-6: the FOLFOX regimen delivered over 2 weeks but with only one long infusion in the first 48 hours; XELOX: oral capecitabine plus intravenous oxaliplatin.</i>			



Appendix 3.4.2.5. NICE, TA240 (2011): panitumumab

- “NICE is unable to recommend panitumumab with 5 fluorouracil, folinic acid and irinotecan (FOLFIRI) for previously treated metastatic colorectal cancer in adults because no evidence submission was received from the manufacturer or sponsor of the technology.”⁶⁸
- “In July 2011, Amgen informed NICE that it would not be making an evidence submission. Amgen stated that, taking into account approaches previously used by NICE to appraising drugs for the treatment of colorectal cancer, there was not sufficient evidence to robustly estimate the cost effectiveness of panitumumab for this indication. NICE has therefore terminated this single technology appraisal.”⁶⁸
- “This guidance is partially replaced by TA439.”⁶⁸

Appendix 3.4.2.6. NICE, TA307 (2014): aflibercept

- QoL:
 - “The Committee noted that the evidence on the clinical effectiveness of aflibercept was derived from the VELOUR trial. ... the Committee would have liked the manufacturer to have collected and presented trial data relating to health-related quality of life,”⁶⁹
 - “Data on health-related quality of life were not collected in the VELOUR trial. The manufacturer conducted the 'mCRC utilities study', an observational, crosssectional study to estimate utility values in patients with metastatic colorectal cancer who would be eligible for treatment with aflibercept plus FOLFIRI as per the licensed indication, or who had progressed to subsequent phases of the disease. The study took place in the Netherlands and the UK, and collected EQ-5D data. The manufacturer used these data as its main source to estimate health-related quality of life for the cost-effectiveness analysis.”⁶⁹
 - “Regarding the utility estimates in the model, the ERG had concerns about the generalisability of the manufacturer's 'mCRC utilities study' because the study population appeared to be younger than UK patients, and the proportion of patients who had an ECOG PS of 2 was lower than that seen in UK clinical practice. Moreover, the ERG noted that the study was small, and produced counter-intuitive estimates in a subgroup analysis including UK patients only because the mean utility value for patients whose disease progressed was higher than for those who had stable disease and received second-line treatment.”⁶⁹
- Results:
 - “The Committee noted that the manufacturer's ICER closest to its preferred assumptions was £44,000 per QALY gained (for age 60), but would increase for the higher age bracket, if the mean value was used from the manufacturer's survey of clinical oncologists after removing the outlier and if an extrapolation function with a less heavy tail had been used. Because the manufacturer's ICERs incorporated a utility value for progressed disease deemed by the Committee to be high, the Committee considered the ICER produced by the ERG using the Committee's preferred assumptions, but which used a utility value for progressed disease of 0.6. The Committee noted that this was approximately £51,000 per QALY gained and would be higher if an extrapolation function with a less heavy tail had been used. The Committee therefore concluded that the most plausible ICER was higher than the normally acceptable maximum ICER range of £20,000–30,000 per QALY gained.”⁶⁹



- Uncertainty/sensitivity:
 - “The ERG explained that extrapolating overall survival data from the VELOUR trial, in which the median follow-up time was just under 2 years, over a 15-year time horizon meant that the assumptions underpinning the extrapolation are key to explaining the large differences between the observed median and the extrapolated mean estimates of overall survival. The ERG stressed that extrapolating the overall survival curves beyond the trial period is highly uncertain given that no data were available for more than 3 years’ follow-up, and particularly that the progression-free survival curves separated and then converged at around 1 year.”⁶⁹
 - “Having considered the estimates obtained using different parametric functions and extrapolation periods, the Committee was concerned that the loglogistic function had a very ‘heavy tail’, and that this is likely to have overestimated the survival benefit of aflibercept. ... The Committee concluded that extrapolating overall survival with the log-logistic function over 15 years did not provide a plausible mean overall survival benefit.”⁶⁹
 - “The Committee was aware that the longer the time horizon, the greater the influence of the ‘tails’ of the extrapolation curves, which define the difference in mean overall survival between the treatment arms, and to which the model is highly sensitive.”⁶⁹
 - “The Committee noted that, because approximately three-quarters of the QALY gain in the model was accrued after disease progression, the model is highly sensitive to utility value for the progressed-disease state in the model.”⁶⁹
 - “The manufacturer presented deterministic sensitivity analyses in which it varied the 20 parameters with the largest impact on the ICER, one at a time. The results showed that the ICER is most sensitive to the parametric function chosen for overall survival, the utility value chosen for the progressed-disease health state, and the number of administrations assumed for second-line treatment drugs.”⁶⁹
- Conclusions:
 - “The Committee therefore concluded that the most plausible ICER was higher than the normally acceptable maximum ICER range of £20,000–30,000 per QALY gained, and that aflibercept in combination with irinotecan and fluorouracil-based therapy could not be considered a cost-effective use of NHS resources for patients with metastatic colorectal cancer.”⁶⁹
 - “Aflibercept in combination with irinotecan and fluorouracil-based therapy is not recommended within its marketing authorisation for treating metastatic colorectal cancer that is resistant to or has progressed after an oxaliplatin-containing regimen.”⁶⁹
- (Confidential) prices:
 - “The manufacturer of aflibercept (Sanofi) has agreed a patient access scheme with the Department of Health that makes aflibercept available with a discount. The size of the discount is commercial in confidence.”⁶⁹



Reference Costs (list prices & remarks)	Population, Intervention & comparator IC, IE and ICERs	Remarks on use of generic utility instrument (e.g. EQ- 5D) to measure impact on QoL in economic evaluations	Most uncertain variables or important variables in sensitivity analysis
Aflibercept			
NICE, TA307 (2014) ⁶⁹	Patients with metastatic colorectal cancer that has progressed following prior oxaliplatin-based chemotherapy. Aflibercept plus FOLFIRI compared with FOLFIRI alone.		
List prices, negotiated discounts are hidden. The net price of a vial of 100 mg aflibercept is £295.65, and the net price of a vial of 200 mg aflibercept is £591.30.	The manufacturer's deterministic base-case results estimated that the addition of aflibercept to FOLFIRI provides an additional 0.243 quality-adjusted life years (QALYs). This benefit is achieved with an additional cost of £8816, resulting in an incremental cost-effectiveness ratio (ICER) of £36,294 per QALY gained for aflibercept plus FOLFIRI compared with FOLFIRI alone. The Committee noted that the manufacturer's ICER closest to its preferred assumptions was £44,000 per QALY gained (for age 60), but would increase for the higher age bracket, if the mean value was used from the manufacturer's survey of clinical oncologists after removing the outlier and if an extrapolation function with a less heavy tail had been used.	Data on health-related quality of life were not collected in the underlying VELOUR trial.	Overall survival extrapolation, utilities for progressed disease, administrations for 2 nd line treatment drugs.

Appendix 3.4.2.7. NICE, TA334. (2015): regorafenib

- “NICE is unable to make a recommendation about the use in the NHS of regorafenib for metastatic colorectal cancer after treatment for metastatic disease because no evidence submission was received from Bayer for the technology.”⁷⁰
- “The company has now reviewed the baseline characteristics of the people recruited to that trial. It considered that the number of people in the trial who have had care equivalent to standard care in the UK is too small to form the basis of a submission for this appraisal.
- NICE has therefore terminated this single technology appraisal.”⁷⁰



APPENDIX 4. HEAD & NECK CANCER

Appendix 4.1. BCR data

Appendix 4.1.1. Descriptive statistics

Appendix 4.1.1.1. Head and Neck cancers, exploration

Table 43 – Head and neck cancers (2004-2017): Frequency table of patient and tumour characteristics

Characteristic	Total	Incidence period		
		2004-2008	2009-2013	2014-2017
Overall	29,328	9,950	10,591	8,787
Gender				
Male	22,692 (77.4)	7,928 (79.7)	8,128 (76.7)	6,636 (75.5)
Female	6,636 (22.6)	2,022 (20.3)	2,463 (23.3)	2,151 (24.5)
Age at diagnosis (year)				
<50 years	2,797 (9.5)	1,267 (12.7)	947 (8.9)	583 (6.6)
50-59 years	9,305 (31.7)	3,478 (35.0)	3,416 (32.3)	2,411 (27.4)
60-69 years	9,724 (33.2)	2,804 (28.2)	3,556 (33.6)	3,364 (38.3)
70-79 years	5,217 (17.8)	1,732 (17.4)	1,854 (17.5)	1,631 (18.6)
80+ years	2,285 (7.8)	669 (6.7)	818 (7.7)	798 (9.1)
WHO - Performance Status				
0 – Asymptomatic	4,353 (14.8)	1,360 (13.7)	1,684 (15.9)	1,309 (14.9)
1 – Symptomatic but completely ambulatory	16,490 (56.2)	4,413 (44.4)	6,347 (59.9)	5,730 (65.2)
2 – Symptomatic, <50% in bed during the day	886 (3.0)	378 (3.8)	267 (2.5)	241 (2.7)
3 – Symptomatic, >50% in bed, but not bedbound	268 (0.9)	84 (0.8)	102 (1.0)	82 (0.9)
4 – Bedbound	96 (0.3)	25 (0.3)	33 (0.3)	38 (0.4)
Not reported	7,235 (24.7)	3,690 (37.1)	2,158 (20.4)	1,387 (15.8)
Combined stage				
0	10 (0.0)	1 (0.0)	5 (0.0)	4 (0.0)
is	7 (0.0)	0 (0.0)	3 (0.0)	4 (0.0)
I	5,469 (18.6)	1,503 (15.1)	2,101 (19.8)	1,865 (21.2)



II	3,556 (12.1)	1,122 (11.3)	1,307 (12.3)	1,127 (12.8)
III	4,049 (13.8)	1,333 (13.4)	1,479 (14.0)	1,237 (14.1)
IV	11,823 (40.3)	3,610 (36.3)	4,381 (41.4)	3,832 (43.6)
X/NA	4,414 (15.1)	2,381 (23.9)	1,315 (12.4)	718 (8.2)

Note: the values between parentheses are column percentages.

Table 44 – Head and neck cancers (2004-2017): Frequency table of patient and tumour characteristics (cut-off point: 2007)

Characteristic	Total	2004-2007	2009-2013
Overall	27 240	5 772	21 468
Gender			
Male	21 009 (77.1)	4 589 (79.5)	16 420 (76.5)
Female	6 231 (22.9)	1 183 (20.5)	5 048 (23.5)
Age at diagnosis (year)			
<50 years	2 559 (9.4)	792 (13.7)	1 767 (8.2)
50-59 years	8 559 (31.4)	2 020 (35.0)	6 539 (30.5)
60-69 years	9 096 (33.4)	1 558 (27.0)	7 538 (35.1)
70-79 years	4 879 (17.9)	1 019 (17.7)	3 860 (18.0)
80+ years	2 147 (7.9)	383 (6.6)	1 764 (8.2)
WHO - Performance Status			
0 – Asymptomatic	4 054 (14.9)	755 (13.1)	3 299 (15.4)
1 – Symptomatic but completely ambulatory	15 574 (57.2)	2 462 (42.7)	13 112 (61.1)
2 – Symptomatic, <50% in bed during the day	812 (3.0)	245 (4.2)	567 (2.6)
3 – Symptomatic, >50% in bed, but not bedbound	255 (0.9)	56 (1.0)	199 (0.9)
4 – Bedbound	93 (0.3)	17 (0.3)	76 (0.4)
Not reported	6 452 (23.7)	2 237 (38.8)	4 215 (19.6)
Combined stage			
0	9 (0.0)	0 (0.0)	9 (0.0)
is	7 (0.0)	0 (0.0)	7 (0.0)
I	5 157 (18.9)	862 (14.9)	4 295 (20.0)
II	3 323 (12.2)	649 (11.2)	2 674 (12.5)



III	3 784 (13.9)	777 (13.5)	3 007 (14.0)
IV	11 052 (40.6)	2 073 (35.9)	8 979 (41.8)
X/NA	3 908 (14.3)	1 411 (24.4)	2 497 (11.6)

Note: the values between parentheses are column percentages.

Table 45 – Head and neck cancers (2004-2017), Combined stage I, Frequency table of patient and tumour characteristics

Characteristic	Total	Incidence period		
		2004-2008	2009-2013	2014-2017
Overall	5,469	1,503	2,101	1,865
Gender				
Male	4,144 (75.8)	1,173 (78.0)	1,580 (75.2)	1,391 (74.6)
Female	1,325 (24.2)	330 (22.0)	521 (24.8)	474 (25.4)
Age at diagnosis (year)				
<50 years	521 (9.5)	190 (12.6)	196 (9.3)	135 (7.2)
50-59 years	1,549 (28.3)	453 (30.1)	603 (28.7)	493 (26.4)
60-69 years	1,833 (33.5)	456 (30.3)	712 (33.9)	665 (35.7)
70-79 years	1,077 (19.7)	293 (19.5)	409 (19.5)	375 (20.1)
80+ years	489 (8.9)	111 (7.4)	181 (8.6)	197 (10.6)
WHO - Performance Status				
0 – Asymptomatic	1,127 (20.6)	342 (22.8)	414 (19.7)	371 (19.9)
1 – Symptomatic but completely ambulatory	3,249 (59.4)	751 (50.0)	1,295 (61.6)	1,203 (64.5)
2 – Symptomatic, <50% in bed during the day	81 (1.5)	47 (3.1)	15 (0.7)	19 (1.0)
3 – Symptomatic, >50% in bed, but not bedbound	7 (0.1)	2 (0.1)	4 (0.2)	1 (0.1)
4 – Bedbound	8 (0.1)	3 (0.2)	2 (0.1)	3 (0.2)
Not reported	997 (18.2)	358 (23.8)	371 (17.7)	268 (14.4)

Note: the values between parentheses are column percentages.


Table 46 – Head and neck cancers (2004-2017), Combined stage I, Frequency table of patient and tumour characteristics (cut-off point: 2007)

Characteristic	Total	Incidence period	
		2004-2006	2008-2017
Overall	5 157	862	4 295
Gender			
Male	3 901 (75.6)	683 (79.2)	3 218 (74.9)
Female	1 256 (24.4)	179 (20.8)	1 077 (25.1)
Age at diagnosis (year)			
<50 years	488 (9.5)	111 (12.9)	377 (8.8)
50-59 years	1 458 (28.3)	271 (31.4)	1 187 (27.6)
60-69 years	1 732 (33.6)	252 (29.2)	1 480 (34.5)
70-79 years	1 014 (19.7)	169 (19.6)	845 (19.7)
80+ years	465 (9.0)	59 (6.8)	406 (9.5)
WHO - Performance Status			
0 – Asymptomatic	1 061 (20.6)	195 (22.6)	866 (20.2)
1 – Symptomatic but completely ambulatory	3 080 (59.7)	405 (47.0)	2 675 (62.3)
2 – Symptomatic, <50% in bed during the day	72 (1.4)	33 (3.8)	39 (0.9)
3 – Symptomatic, >50% in bed, but not bedbound	7 (0.1)	0 (0.0)	7 (0.2)
4 – Bedbound	8 (0.2)	2 (0.2)	6 (0.1)
Not reported	929 (18.0)	227 (26.3)	702 (16.3)

Note: the values between parentheses are column percentages.



Table 47 – Head and neck cancers (2004-2017), Combined stage II, Frequency table of patient and tumour characteristics

Characteristic	Total	Incidence period		
		2004-2008	2009-2013	2014-2017
Overall	3,556	1,122	1,307	1,127
Gender				
Male	2,673 (75.2)	866 (77.2)	978 (74.8)	829 (73.6)
Female	883 (24.8)	256 (22.8)	329 (25.2)	298 (26.4)
Age at diagnosis (year)				
<50 years	316 (8.9)	126 (11.2)	115 (8.8)	75 (6.7)
50-59 years	1,044 (29.4)	369 (32.9)	398 (30.5)	277 (24.6)
60-69 years	1,146 (32.2)	332 (29.6)	413 (31.6)	401 (35.6)
70-79 years	733 (20.6)	220 (19.6)	259 (19.8)	254 (22.5)
80+ years	317 (8.9)	75 (6.7)	122 (9.3)	120 (10.6)
WHO - Performance Status				
0 – Asymptomatic	623 (17.5)	210 (18.7)	247 (18.9)	166 (14.7)
1 – Symptomatic but completely ambulatory	2,272 (63.9)	636 (56.7)	860 (65.8)	776 (68.9)
2 – Symptomatic, <50% in bed during the day	85 (2.4)	41 (3.7)	24 (1.8)	20 (1.8)
3 – Symptomatic, >50% in bed, but not bedbound	17 (0.5)	3 (0.3)	9 (0.7)	5 (0.4)
4 – Bedbound	9 (0.3)	0 (0.0)	4 (0.3)	5 (0.4)
Not reported	550 (15.5)	232 (20.7)	163 (12.5)	155 (13.8)

Note: the values between parentheses are column percentages.


Table 48 – Head and neck cancers (2004-2017), Combined stage II, Frequency table of patient and tumour characteristics (cut-off point: 2007)

Characteristic	Total	Incidence period	
		2004-2006	2008-2017
Overall	3 323	649	2 674
Gender			
Male	2 486 (74.8)	497 (76.6)	1 989 (74.4)
Female	837 (25.2)	152 (23.4)	685 (25.6)
Age at diagnosis (year)			
<50 years	297 (8.9)	79 (12.2)	218 (8.2)
50-59 years	962 (28.9)	213 (32.8)	749 (28.0)
60-69 years	1 062 (32.0)	177 (27.3)	885 (33.1)
70-79 years	700 (21.1)	133 (20.5)	567 (21.2)
80+ years	302 (9.1)	47 (7.2)	255 (9.5)
WHO - Performance Status			
0 – Asymptomatic	580 (17.5)	121 (18.6)	459 (17.2)
1 – Symptomatic but completely ambulatory	2 141 (64.4)	358 (55.2)	1 783 (66.7)
2 – Symptomatic, <50% in bed during the day	73 (2.2)	23 (3.5)	50 (1.9)
3 – Symptomatic, >50% in bed, but not bedbound	17 (0.5)	3 (0.3)	9 (0.7)
4 – Bedbound	9 (0.3)	0 (0.0)	9 (0.3)
Not reported	503 (15.1)	146 (22.5)	357 (13.4)

Note: the values between parentheses are column percentages.



Table 49 – Head and neck cancers (2004-2017), Combined stage III, Frequency table of patient and tumour characteristics

Characteristic	Total	Incidence period		
		2004-2008	2009-2013	2014-2017
Overall	4,049	1,333	1,479	1,237
Gender				
Male	3,159 (78.0)	1,068 (80.1)	1,146 (77.5)	945 (76.4)
Female	890 (22.0)	265 (19.9)	333 (22.5)	292 (23.6)
Age at diagnosis (year)				
<50 years	375 (9.3)	166 (12.5)	117 (7.9)	92 (7.4)
50-59 years	1,263 (31.2)	456 (34.2)	468 (31.6)	339 (27.4)
60-69 years	1,402 (34.6)	397 (29.8)	531 (35.9)	474 (38.3)
70-79 years	695 (17.2)	228 (17.1)	246 (16.6)	221 (17.9)
80+ years	314 (7.8)	86 (6.5)	117 (7.9)	111 (9.0)
WHO - Performance Status				
0 – Asymptomatic	698 (17.2)	240 (18.0)	247 (16.7)	211 (17.1)
1 – Symptomatic but completely ambulatory	2,627 (64.9)	774 (58.1)	996 (67.3)	857 (69.3)
2 – Symptomatic, <50% in bed during the day	148 (3.7)	61 (4.6)	55 (3.7)	32 (2.6)
3 – Symptomatic, >50% in bed, but not bedbound	39 (1.0)	15 (1.1)	13 (0.9)	11 (0.9)
4 – Bedbound	5 (0.1)	2 (0.2)	2 (0.1)	1 (0.1)
Not reported	532 (13.1)	241 (18.1)	166 (11.2)	125 (10.1)

Note: the values between parentheses are column percentages.


Table 50 – Head and neck cancers (2004-2017), Combined stage III, Frequency table of patient and tumour characteristics (cut-off point: 2007)

Characteristic	Total	Incidence period	
		2004-2006	2008-2017
Overall	3 784	777	3 007
Gender			
Male	2 949 (77.9)	624 (80.3)	2 325 (77.3)
Female	835 (22.1)	153 (19.7)	682 (22.7)
Age at diagnosis (year)			
<50 years	345 (9.1)	114 (14.7)	231 (7.7)
50-59 years	1 171 (30.9)	256 (32.9)	915 (30.4)
60-69 years	1 312 (34.7)	216 (27.8)	1 096 (36.4)
70-79 years	654 (17.3)	139 (17.9)	515 (17.1)
80+ years	302 (8.0)	52 (6.7)	250 (8.3)
WHO - Performance Status			
0 – Asymptomatic	655 (17.3)	146 (18.8)	509 (16.9)
1 – Symptomatic but completely ambulatory	2 469 (65.2)	428 (55.1)	2 041 (67.9)
2 – Symptomatic, <50% in bed during the day	135 (3.6)	41 (5.3)	94 (3.1)
3 – Symptomatic, >50% in bed, but not bedbound	36 (1.0)	10 (1.3)	26 (0.9)
4 – Bedbound	5 (0.1)	1 (0.1)	4 (0.1)
Not reported	484 (12.8)	151 (19.4)	333 (11.1)

Note: the values between parentheses are column percentages.



Table 51 – Head and neck cancers (2004-2017), Combined stage IV, Frequency table of patient and tumour characteristics

Characteristic	Total	Incidence period		
		2004-2008	2009-2013	2014-2017
Overall	11,823	3,610	4,381	3,832
Gender				
Male	9,310 (78.7)	2,958 (81.9)	3,426 (78.2)	2,926 (76.4)
Female	2,513 (21.3)	652 (18.1)	955 (21.8)	906 (23.6)
Age at diagnosis (year)				
<50 years	1,150 (9.7)	506 (14.0)	396 (9.0)	248 (6.5)
50-59 years	4,071 (34.4)	1,380 (38.2)	1,549 (35.4)	1,142 (29.8)
60-69 years	4,038 (34.2)	1,017 (28.2)	1,486 (33.9)	1,535 (40.1)
70-79 years	1,858 (15.7)	524 (14.5)	693 (15.8)	641 (16.7)
80+ years	706 (6.0)	183 (5.1)	257 (5.9)	266 (6.9)
WHO - Performance Status				
0 – Asymptomatic	1,756 (14.9)	513 (14.2)	718 (16.4)	525 (13.7)
1 – Symptomatic but completely ambulatory	7,737 (65.4)	2,129 (59.0)	2,928 (66.8)	2,680 (69.9)
2 – Symptomatic, <50% in bed during the day	535 (4.5)	214 (5.9)	162 (3.7)	159 (4.1)
3 – Symptomatic, >50% in bed, but not bedbound	192 (1.6)	61 (1.7)	71 (1.6)	60 (1.6)
4 – Bedbound	63 (0.5)	19 (0.5)	17 (0.4)	27 (0.7)
Not reported	1,540 (13.0)	674 (18.7)	485 (11.1)	381 (9.9)

Note: the values between parentheses are column percentages.


Table 52 – Head and neck cancers (2004-2017), Combined stage IV, Frequency table of patient and tumour characteristics (cut-off point: 2007)

Characteristic	Total	Incidence period	
		2004-2006	2008-2017
Overall	11 052	2 073	8 979
Gender			
Male	8 670 (78.4)	1 688 (81.4)	6 982 (77.8)
Female	2 382 (21.6)	385 (18.6)	1 997 (22.2)
Age at diagnosis (year)			
<50 years	1 050 (9.5)	311 (15.0)	739 (8.2)
50-59 years	3 773 (34.1)	814 (39.3)	2 959 (33.0)
60-69 years	3 812 (34.5)	548 (26.4)	3 264 (36.4)
70-79 years	1 748 (15.8)	303 (14.6)	1 445 (16.1)
80+ years	669 (6.1)	97 (4.7)	572 (6.4)
WHO - Performance Status			
0 – Asymptomatic	1 624 (14.7)	274 (13.2)	1 350 (15.0)
1 – Symptomatic but completely ambulatory	7 299 (66.0)	1 198 (57.8)	6 101 (67.9)
2 – Symptomatic, <50% in bed during the day	498 (4.5)	137 (6.6)	361 (4.0)
3 – Symptomatic, >50% in bed, but not bedbound	182 (1.6)	43 (2.1)	139 (1.5)
4 – Bedbound	60 (0.5)	13 (0.5)	47 (0.5)
Not reported	1 389 (12.6)	408 (19.7)	981 (10.9)

Note: the values between parentheses are column percentages.



Appendix 4.1.1.2. Head and neck cancers (2004-2017), Observed and Relative Survival graphs

Head and Neck cancers (2004-2017)

Figure 66 – Head and neck cancers (2004-2017), Kaplan-Meier graphs observed survival by incidence period

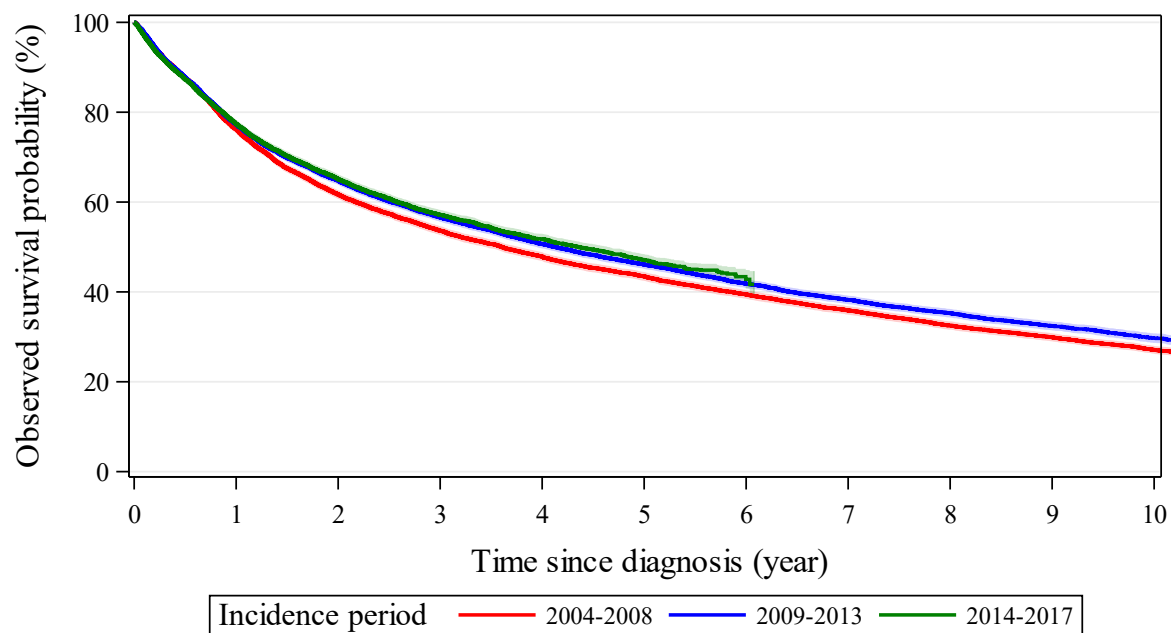


Figure 67 – Head and neck cancers (2004-2017), Kaplan-Meier graphs observed survival by incidence period (cut-off point: 2007)

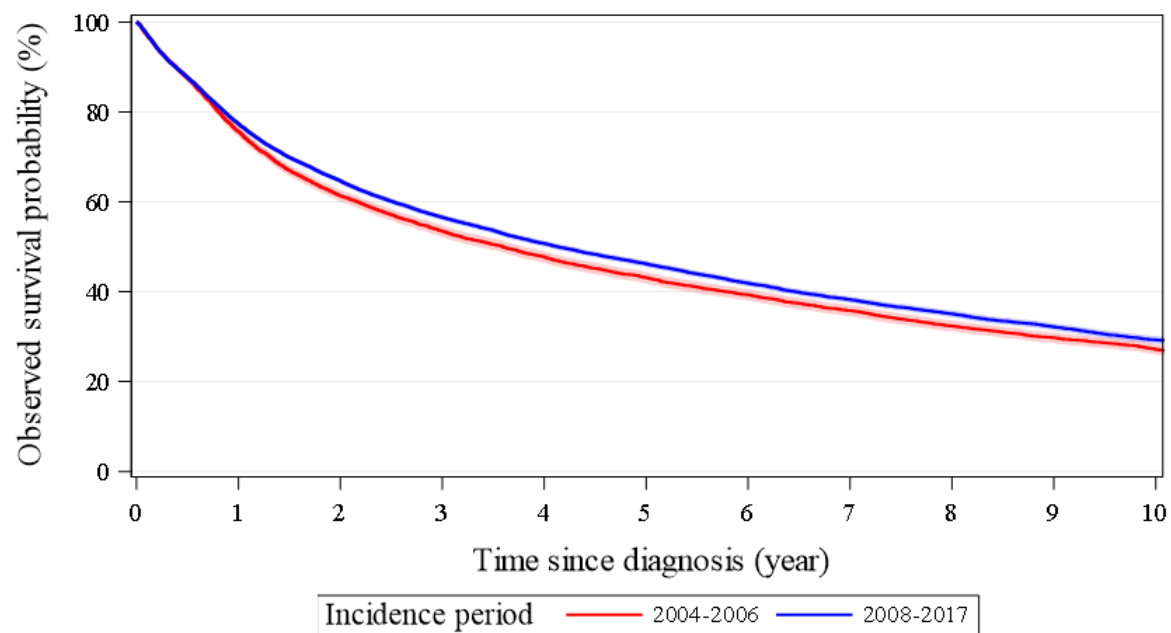




Figure 68 – Head and neck cancers (2004-2017), relative survival graphs by incidence period

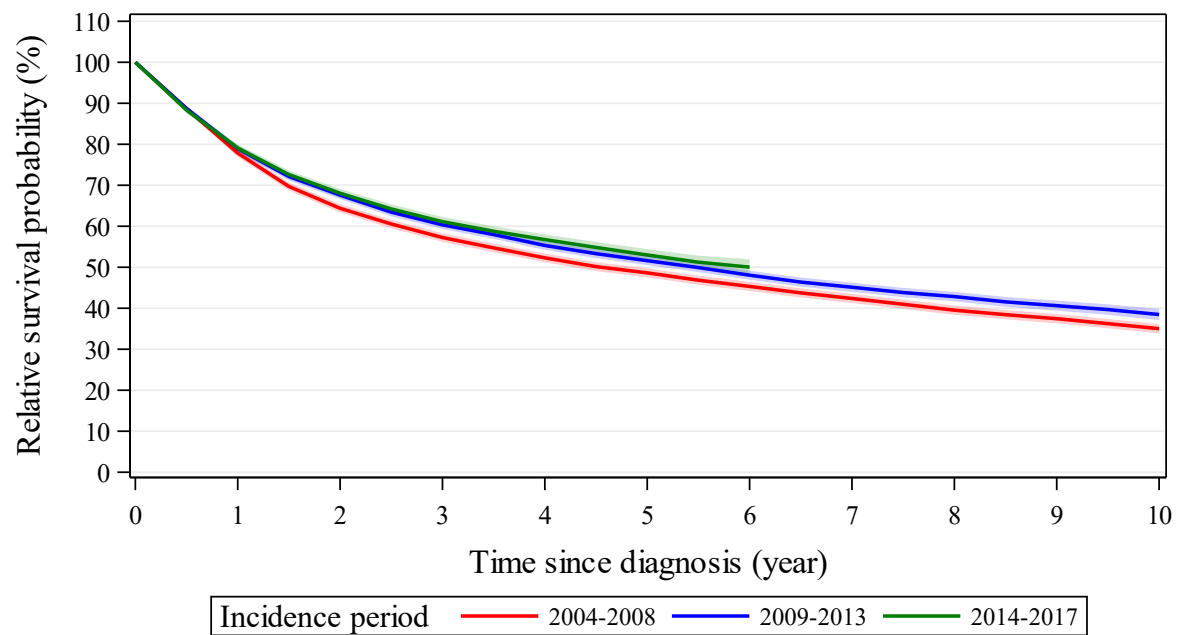
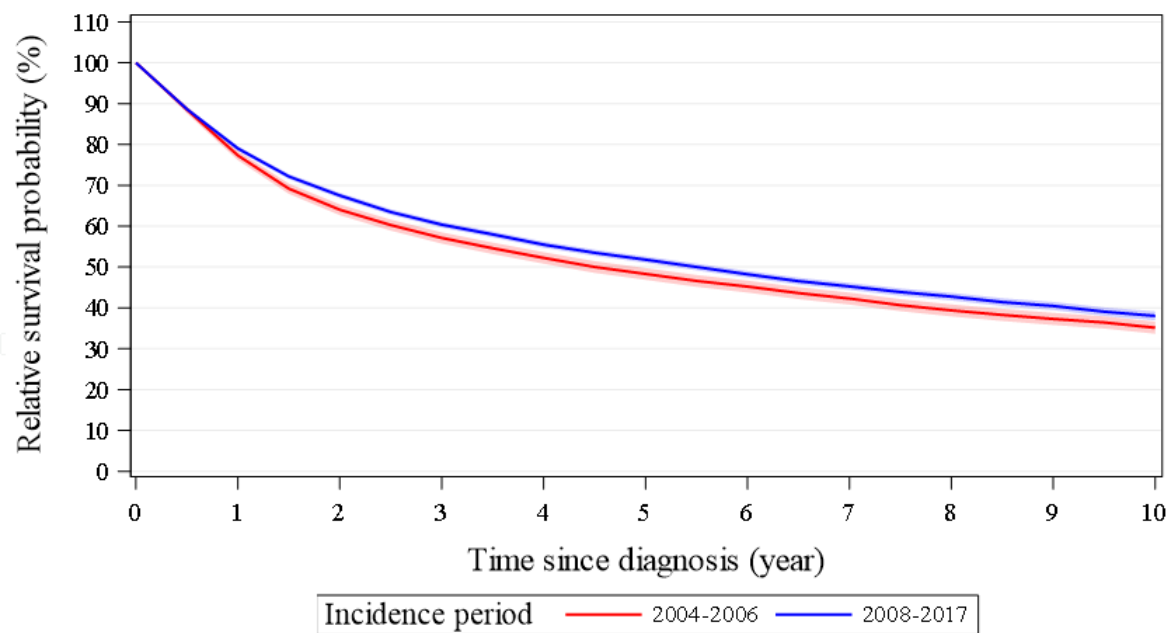




Figure 69 – Head and neck cancers (2004-2017), relative survival graphs by incidence period (cut-off point: 2007)



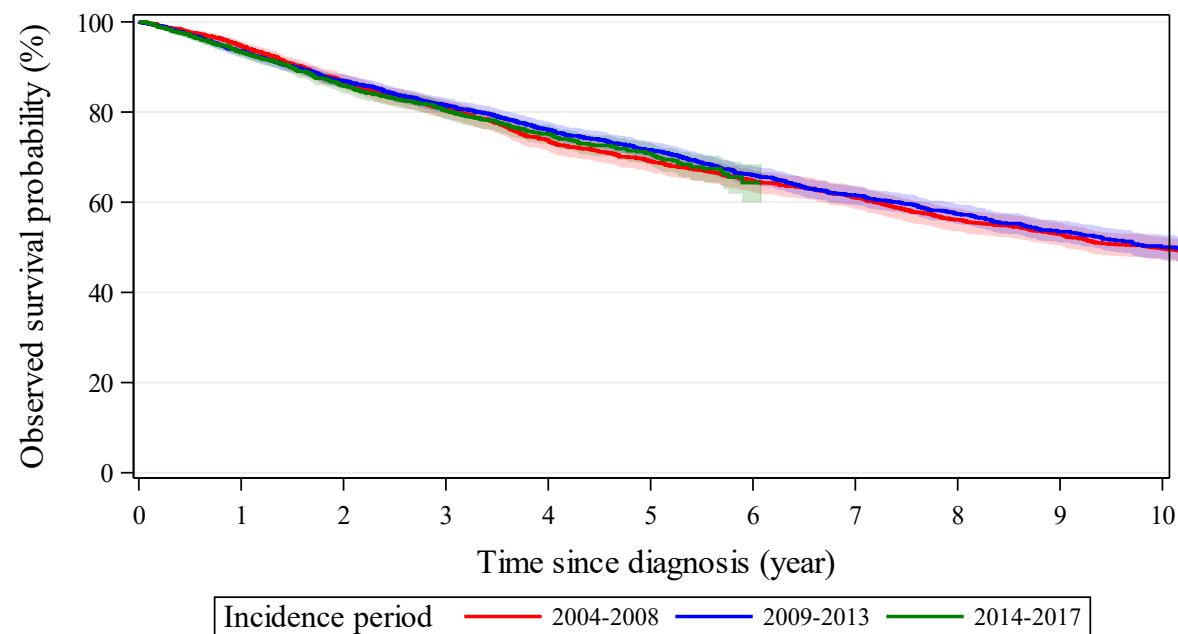
**Head and Neck cancers, combined stage I (2004-2017)****Figure 70 – Head and neck cancers (2004-2017), combined stage I, Kaplan-Meier graphs observed survival by incidence period**



Figure 71 – Head and neck cancers (2004-2017), combined stage I, Kaplan-Meier graphs observed survival by incidence period (cut-off point: 2007)

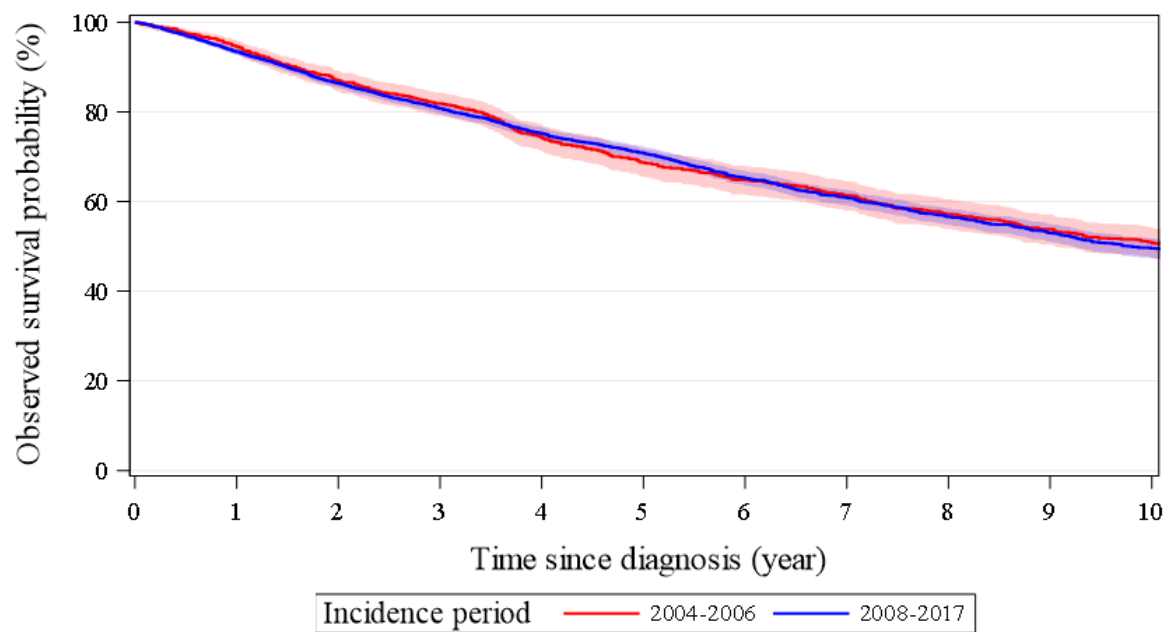




Figure 72 – Head and neck cancers (2004-2017), combined stage I, relative survival graphs by incidence period

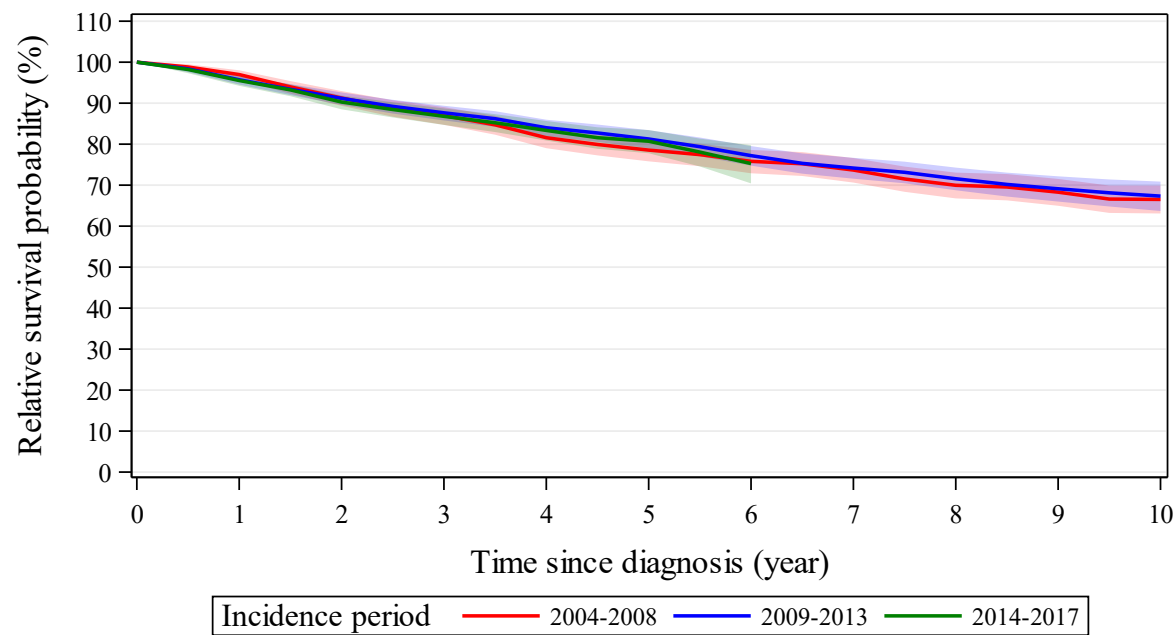
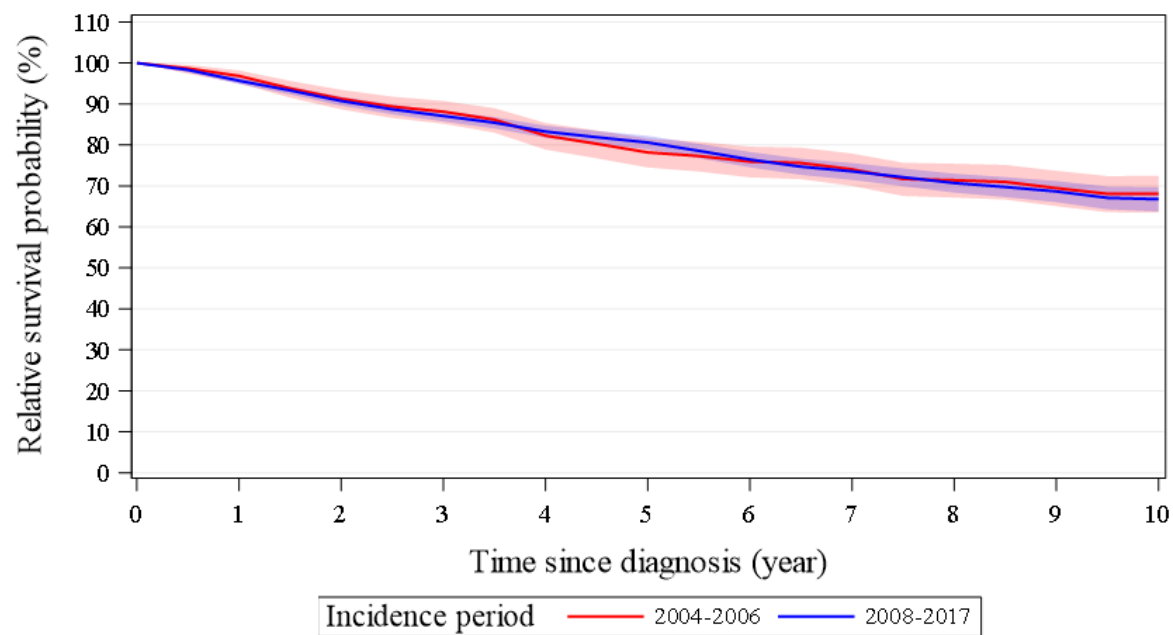




Figure 73 – Head and neck cancers (2004-2017), combined stage I, relative survival graphs by incidence period (cut-off point: 2007)



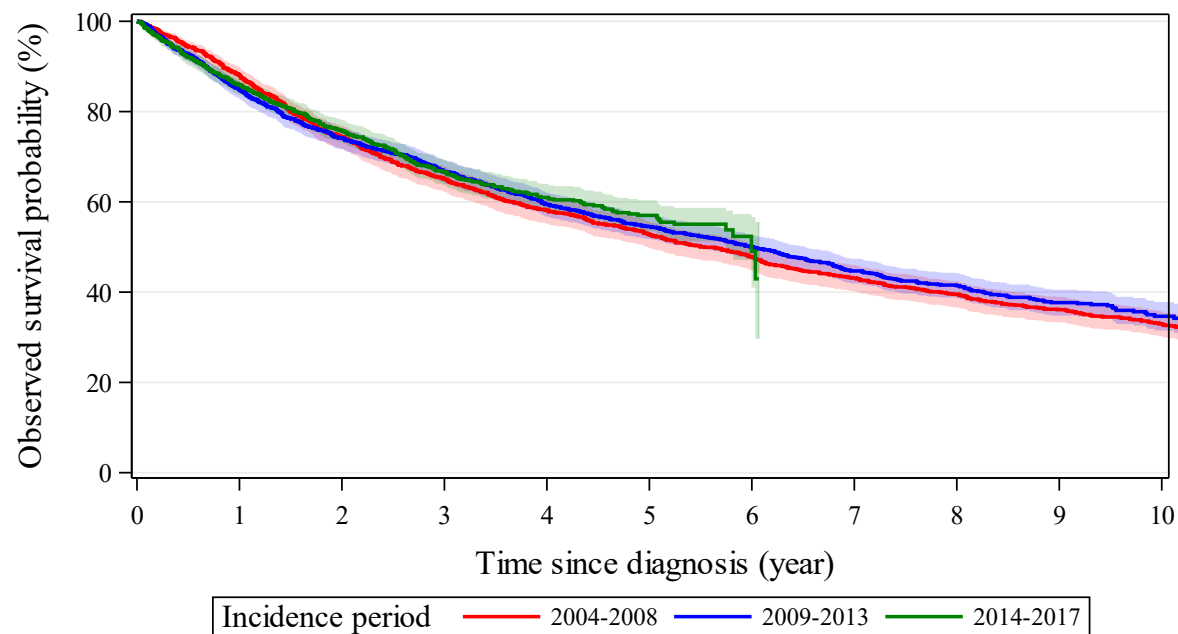
**Head and Neck cancers, combined stage II (2004-2017)****Figure 74 – Head and neck cancers (2004-2017), combined stage II, Kaplan-Meier graphs observed survival by incidence period**



Figure 75 – Head and neck cancers (2004-2017), combined stage II, Kaplan-Meier graphs observed survival by incidence period (cut-off point: 2007)

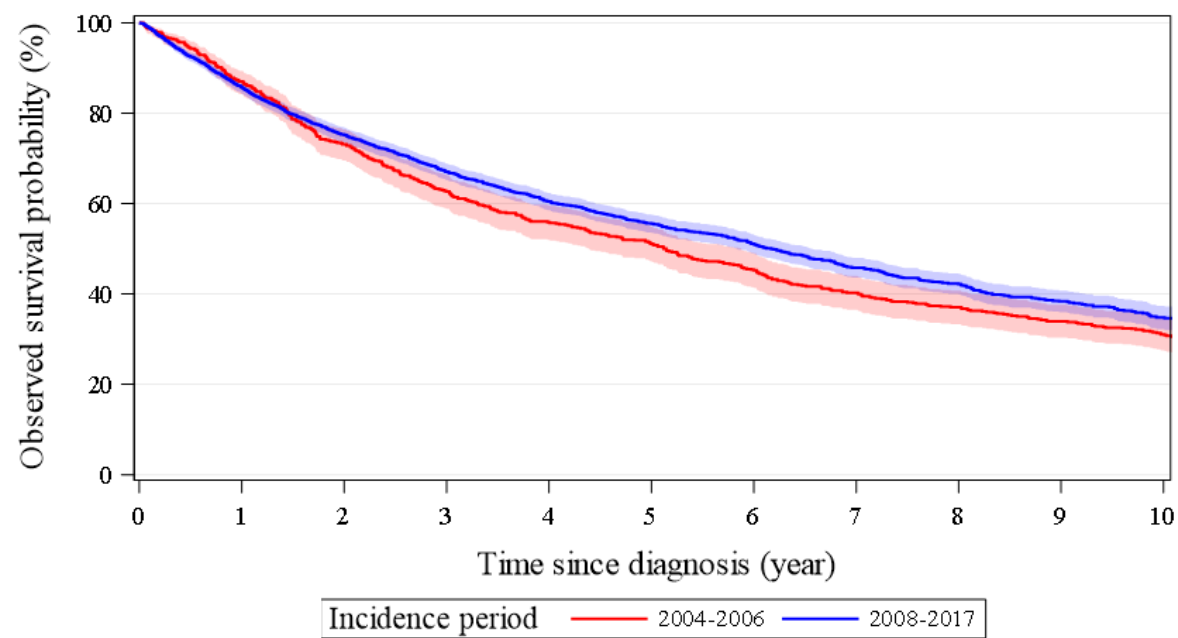




Figure 76 – Head and neck cancers (2004-2017), combined stage II, relative survival graphs by incidence period

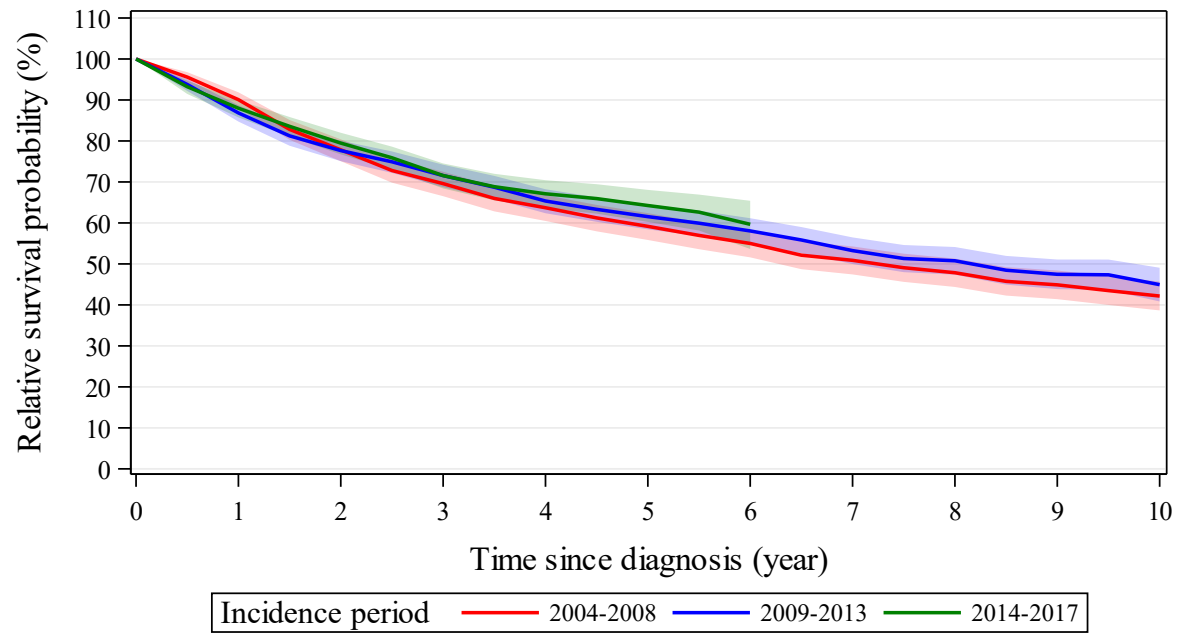
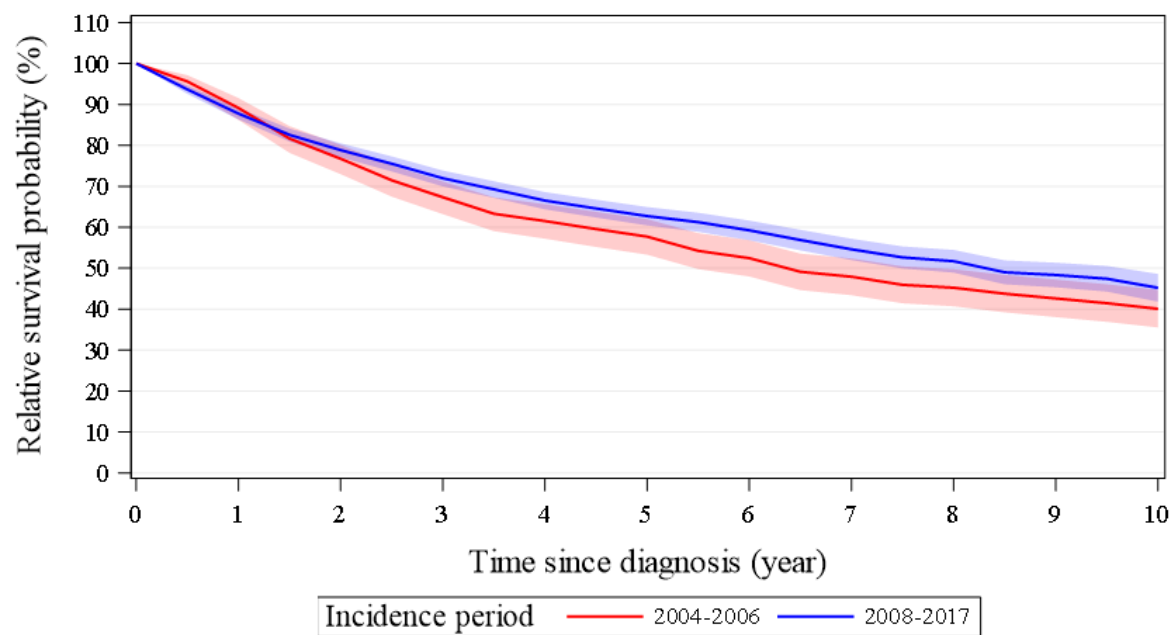


Figure 77 – Head and neck cancers (2004-2017), combined stage II, relative survival graphs by incidence period (cut-off point: 2007)



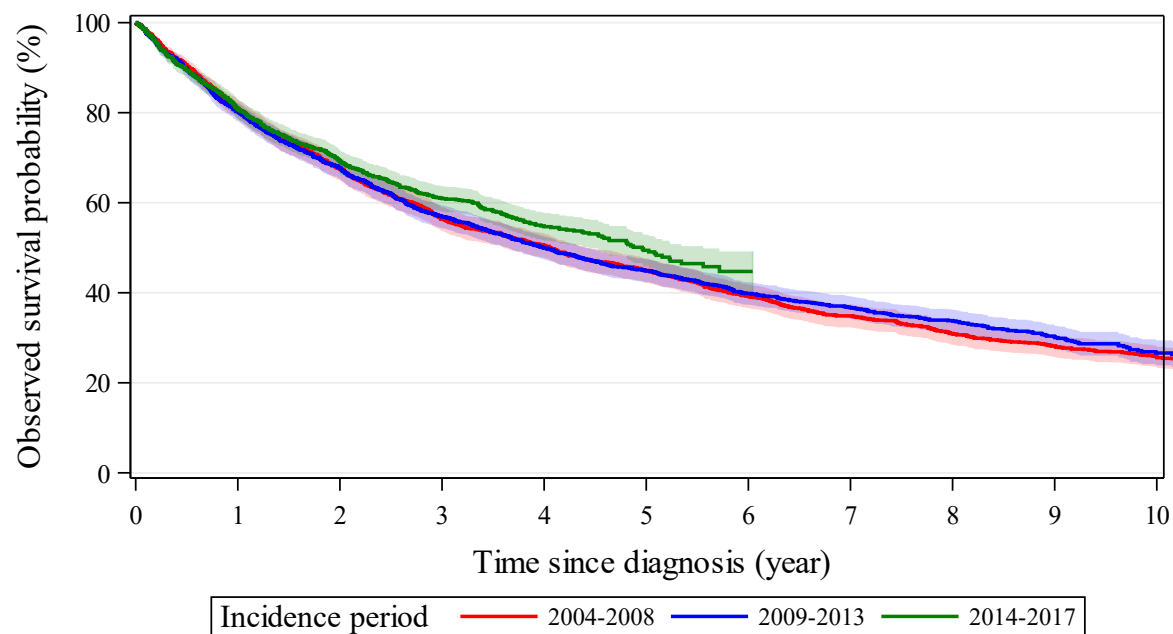
**Head and Neck cancers, combined stage III (2004-2017)****Figure 78 – Head and neck cancers (2004-2017), combined stage III, Kaplan-Meier graphs observed survival by incidence period**



Figure 79 – Head and neck cancers (2004-2017), combined stage III, Kaplan-Meier graphs observed survival by incidence period (cut-off point: 2007)

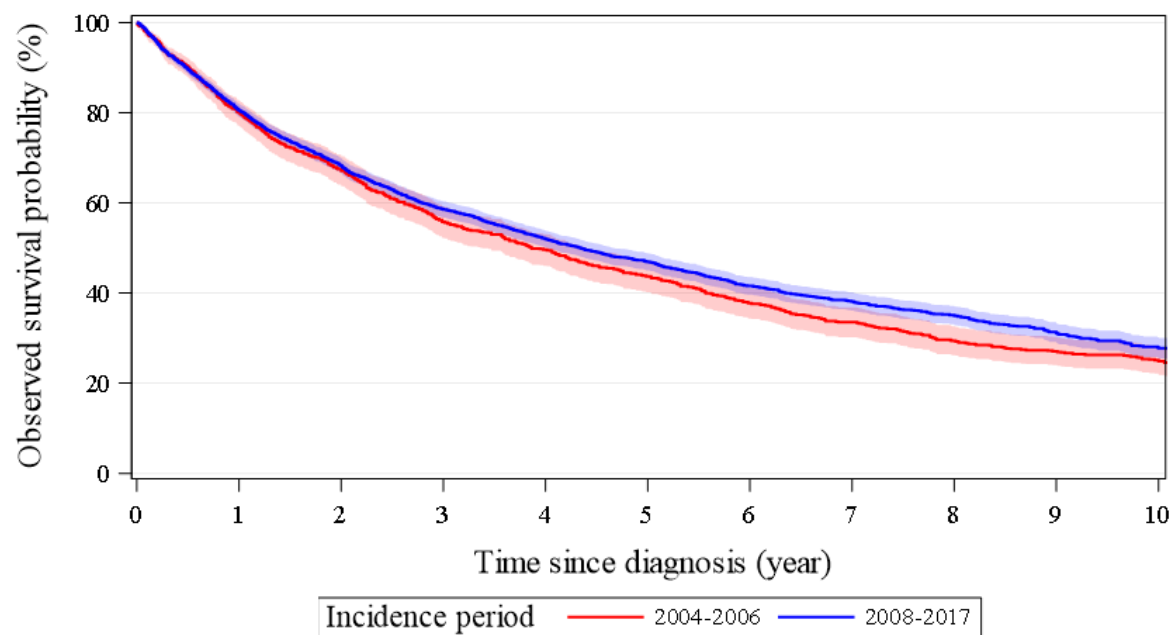




Figure 80 – Head and neck cancers (2004-2017), combined stage III, relative survival graphs by incidence period

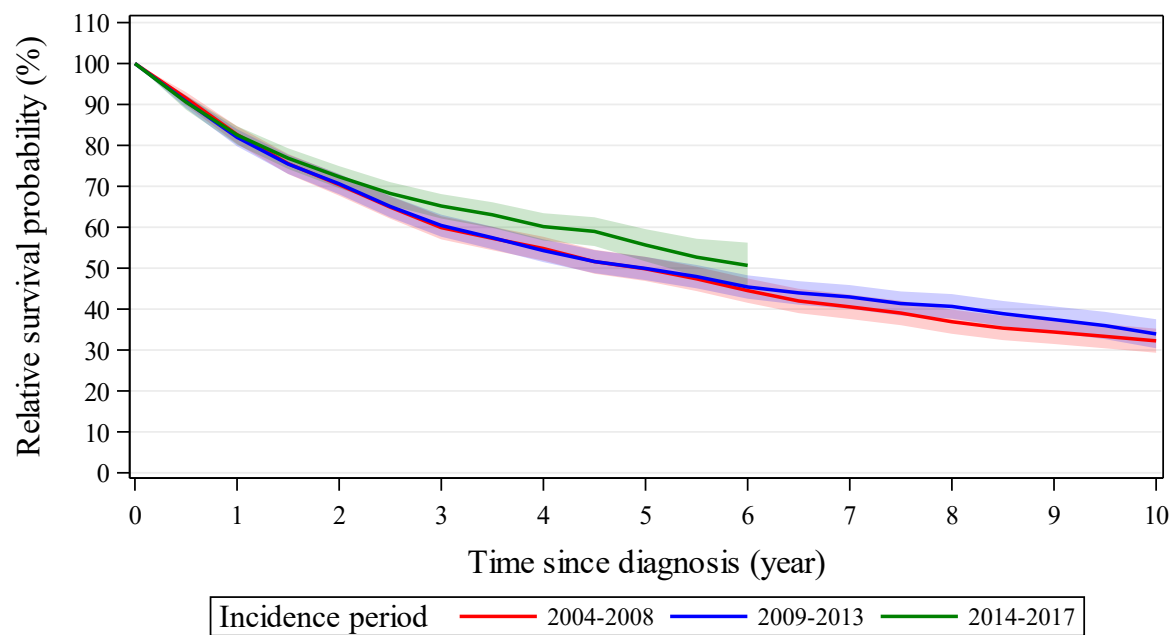
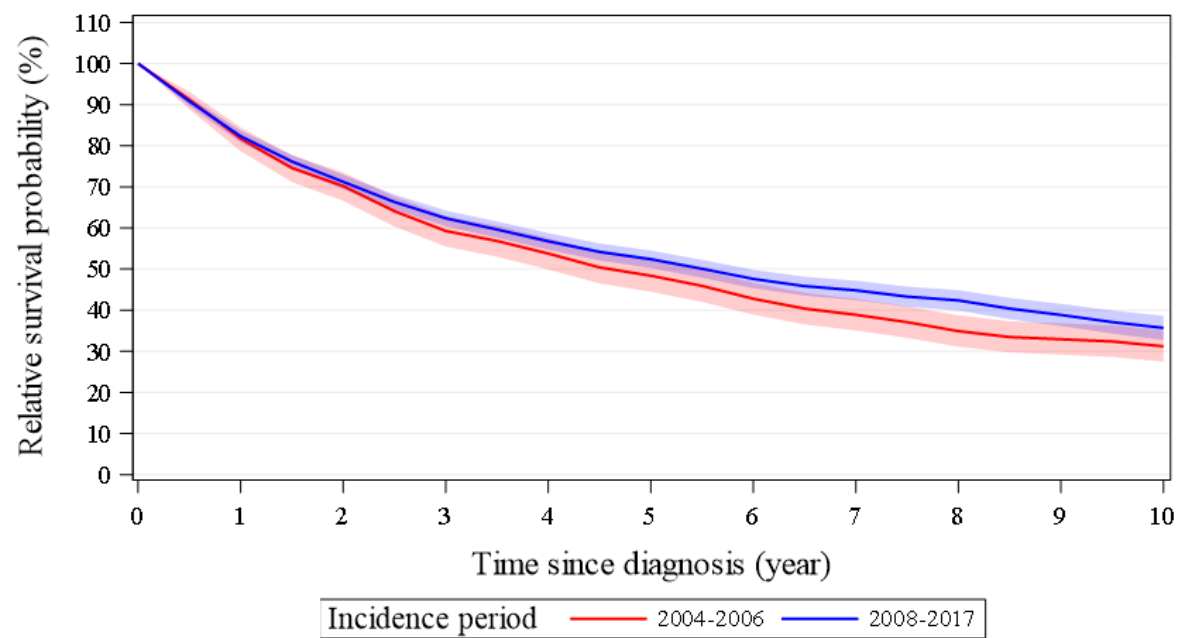




Figure 81 – Head and neck cancers (2004-2017), combined stage III, relative survival graphs by incidence period (cut-off point: 2007)



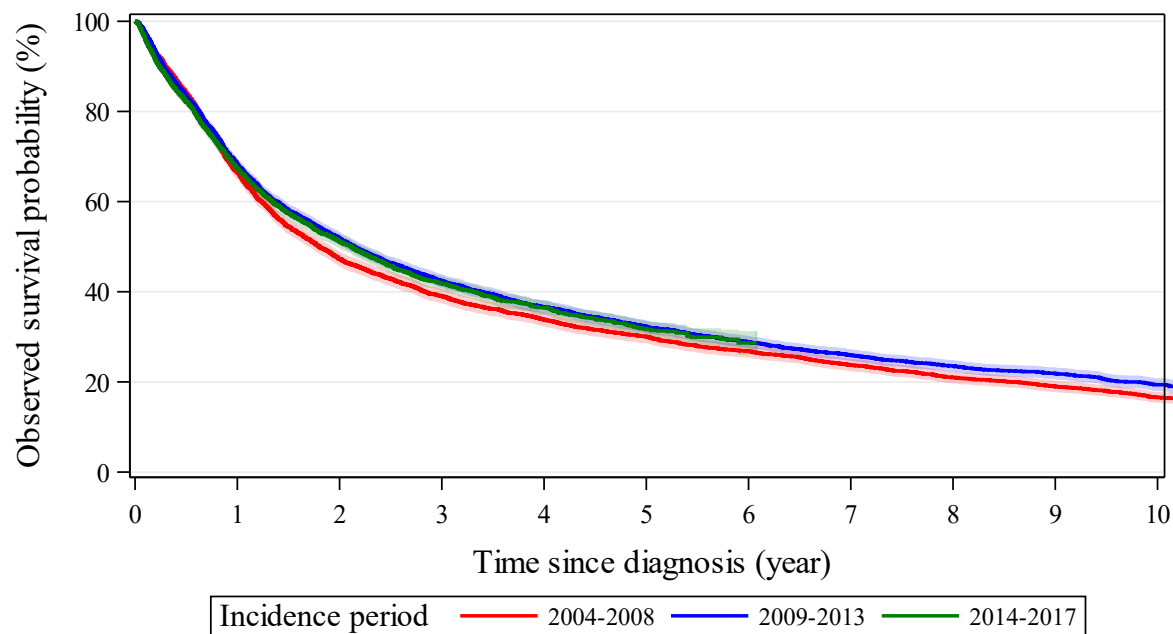
**Head and Neck cancers, combined stage IV (2004-2017)****Figure 82 – Head and neck cancers (2004-2017), combined stage IV, Kaplan-Meier graphs observed survival by incidence period**

Figure 83 – Head and neck cancers (2004-2017), combined stage IV, Kaplan-Meier graphs observed survival by incidence period (cut-off point: 2007)

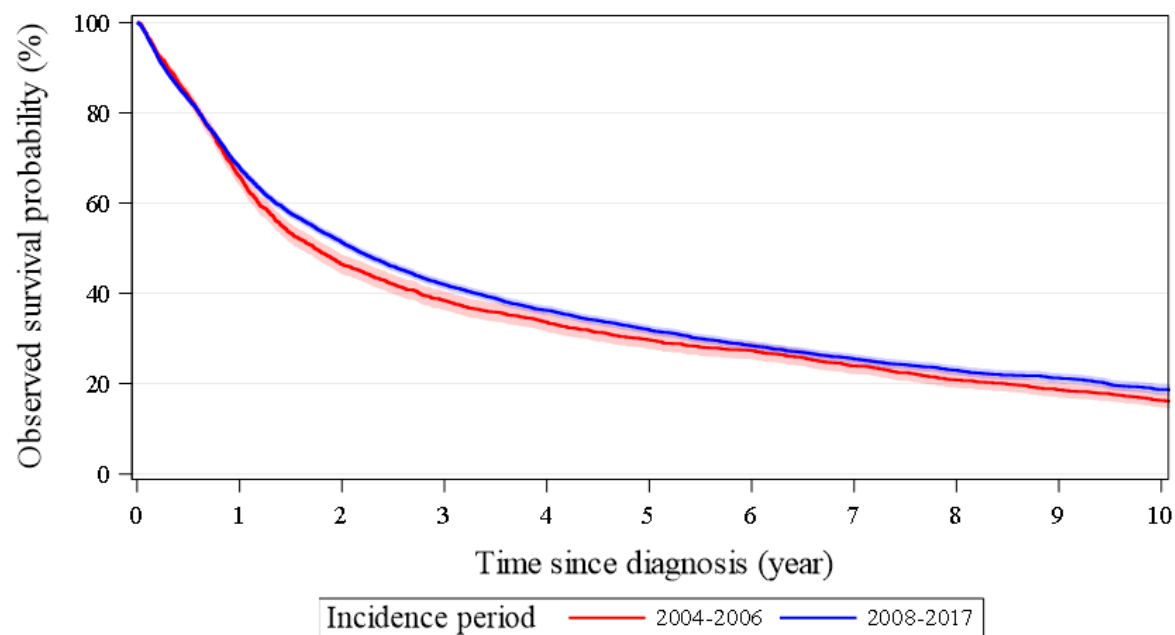




Figure 84 – Head and neck cancers (2004-2017), combined stage IV, relative survival graphs by incidence period

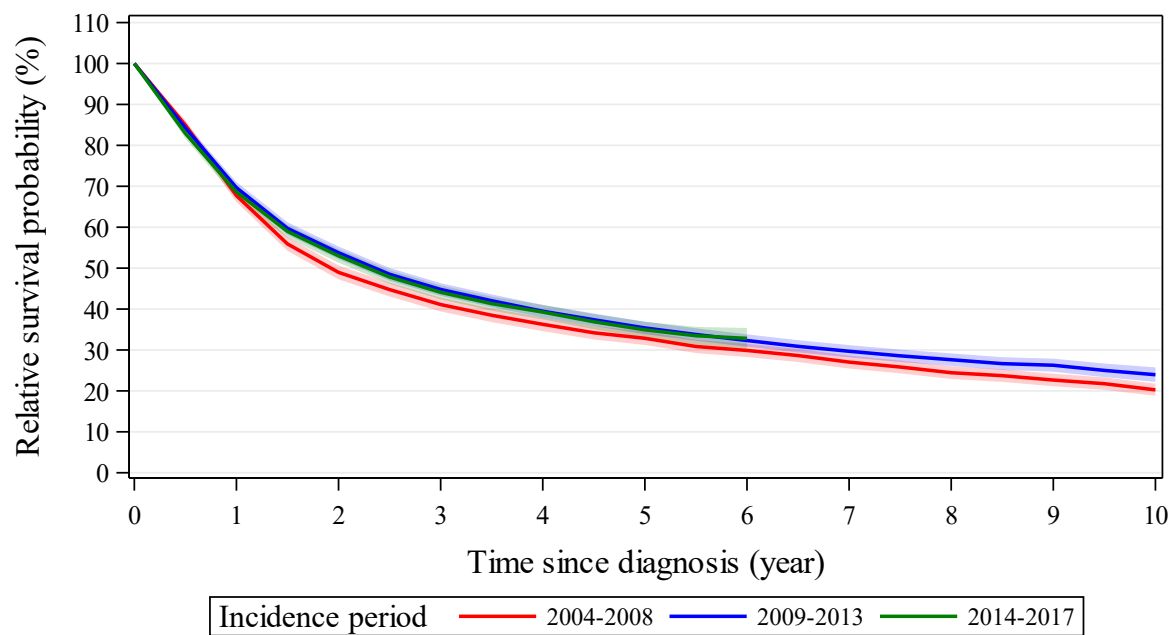
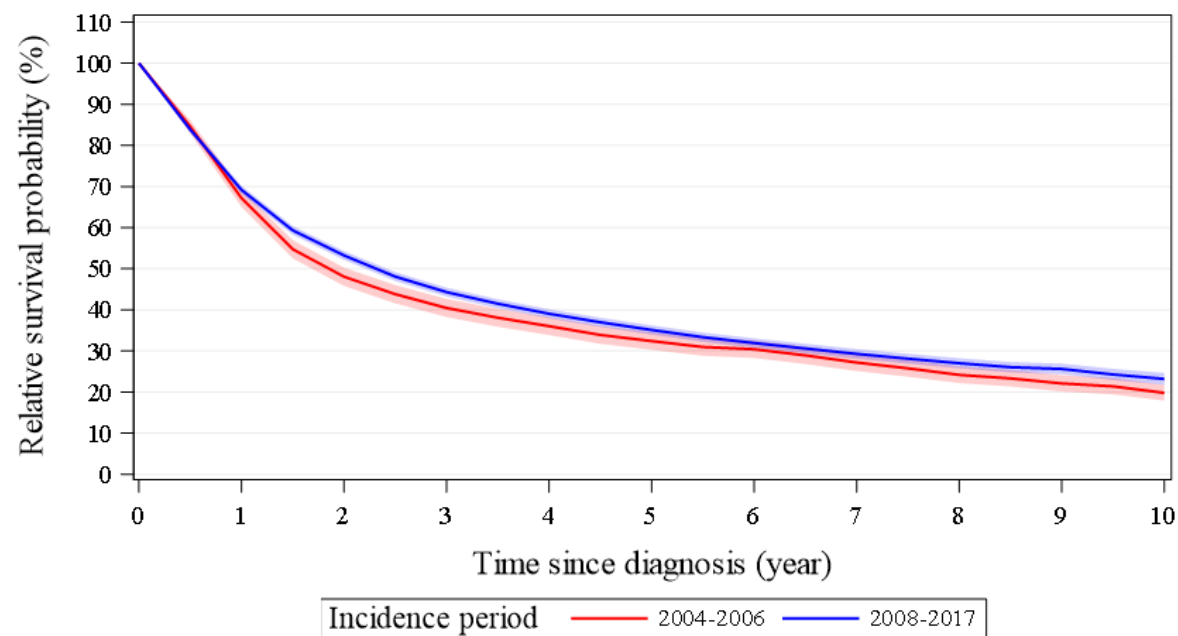


Figure 85 – Head and neck cancers (2004-2017), combined stage IV, relative survival graphs by incidence period (cut-off point: 2007)

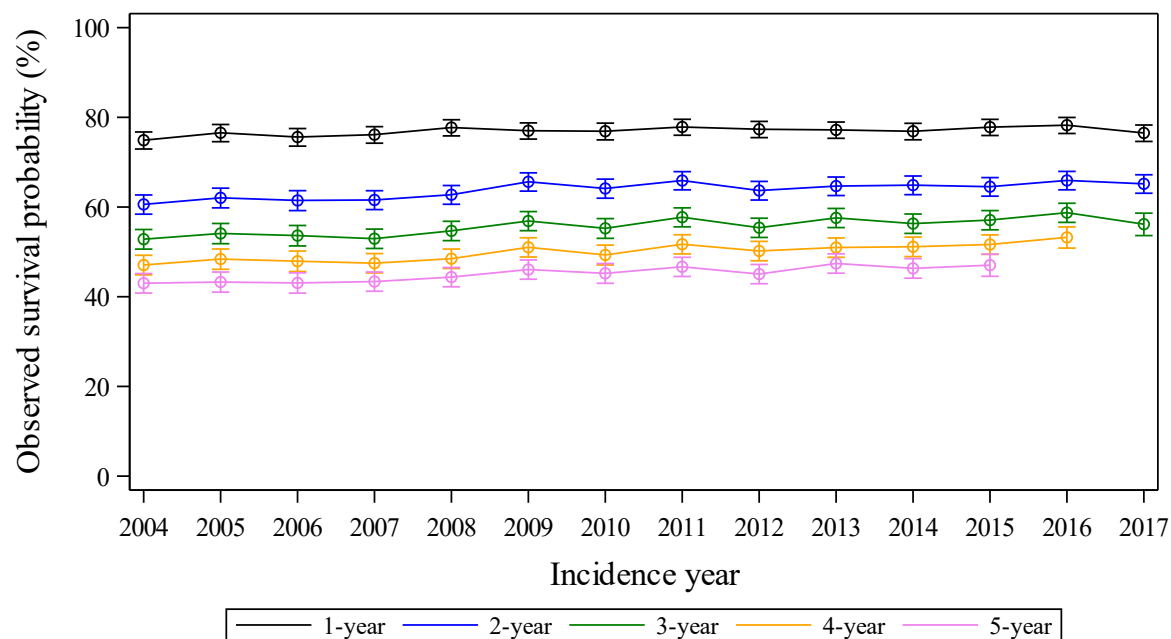




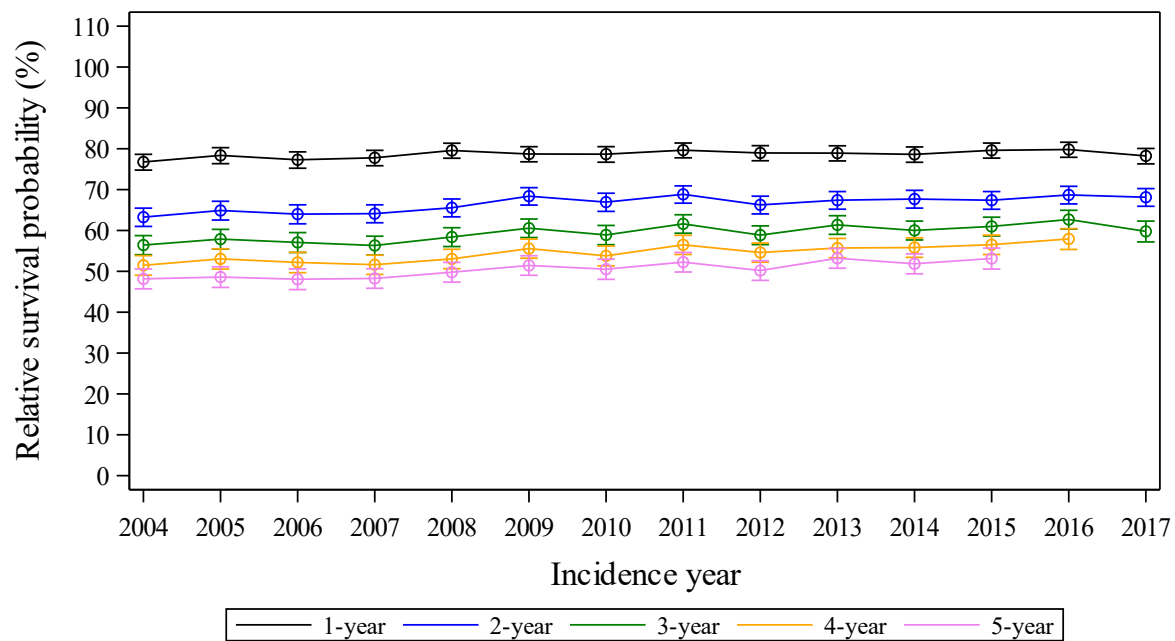
Appendix 4.1.1.3. Head and Neck cancers, time trend Observed and Relative Survival

Head and Neck cancers (2004-2017)

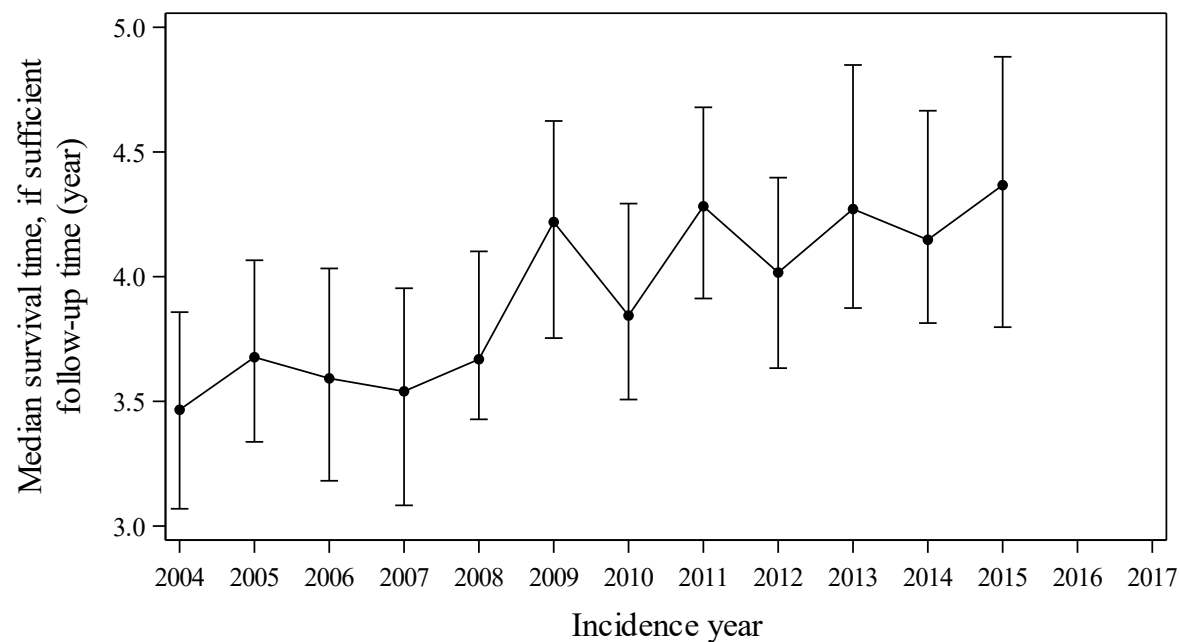
Figure 86 – Head and neck cancers (2004-2017), time trend observed survival with incidence year



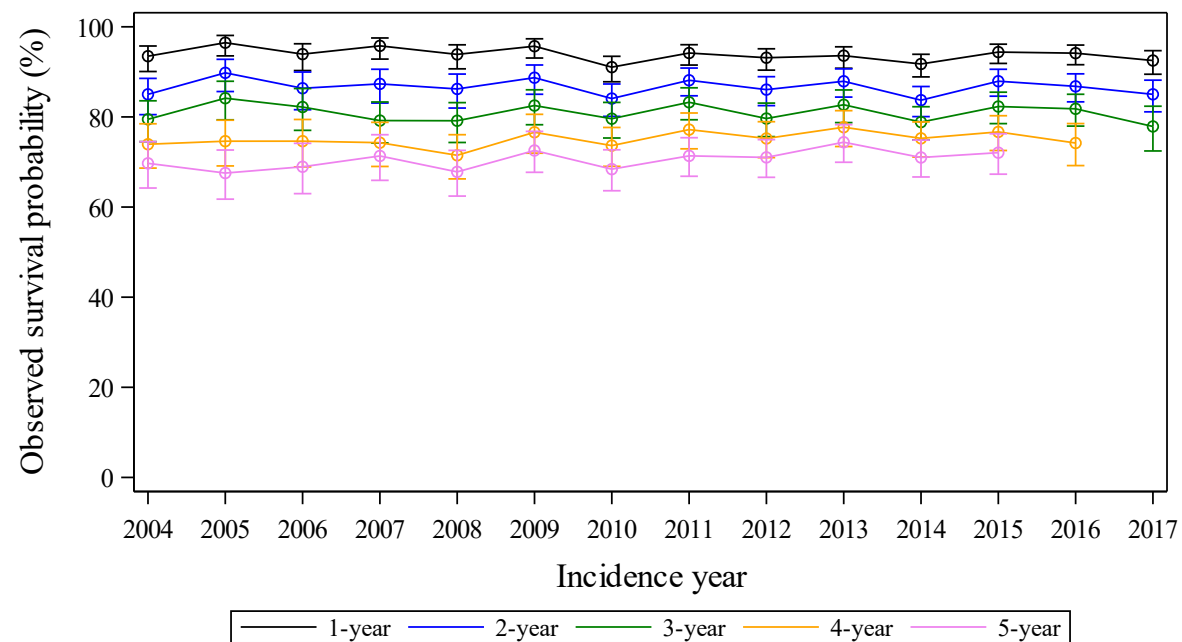
Note: the error bars represent the 95% CI.

**Figure 87 – Head and neck cancers (2004-2017), time trend relative survival with incidence year**

Note: the error bars represent the 95% CI.

**Figure 88 – Head and neck cancers (2004-2017), Median time observed survival**

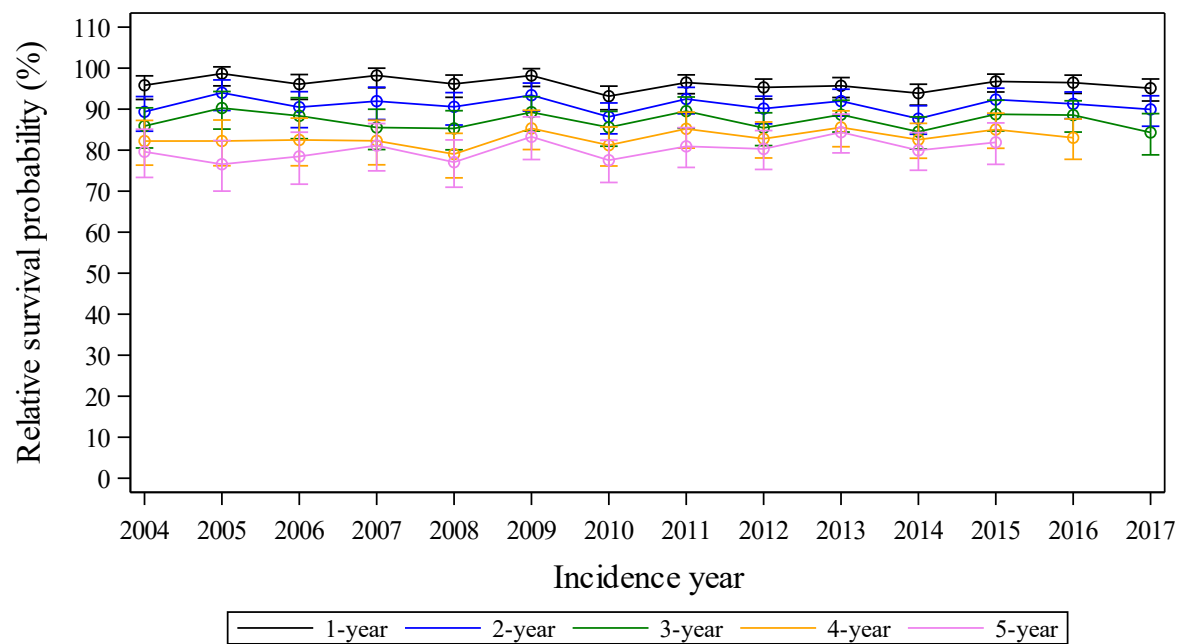
Note: the error bars represent the 95% CI. When the upper error is not plotted, the upper limit could not be determined with the follow-up available.

**Head and Neck cancers, combined stage I (2004-2017)****Figure 89 – Head and neck cancers (2004-2017), combined stage I, time trend observed survival with incidence year**

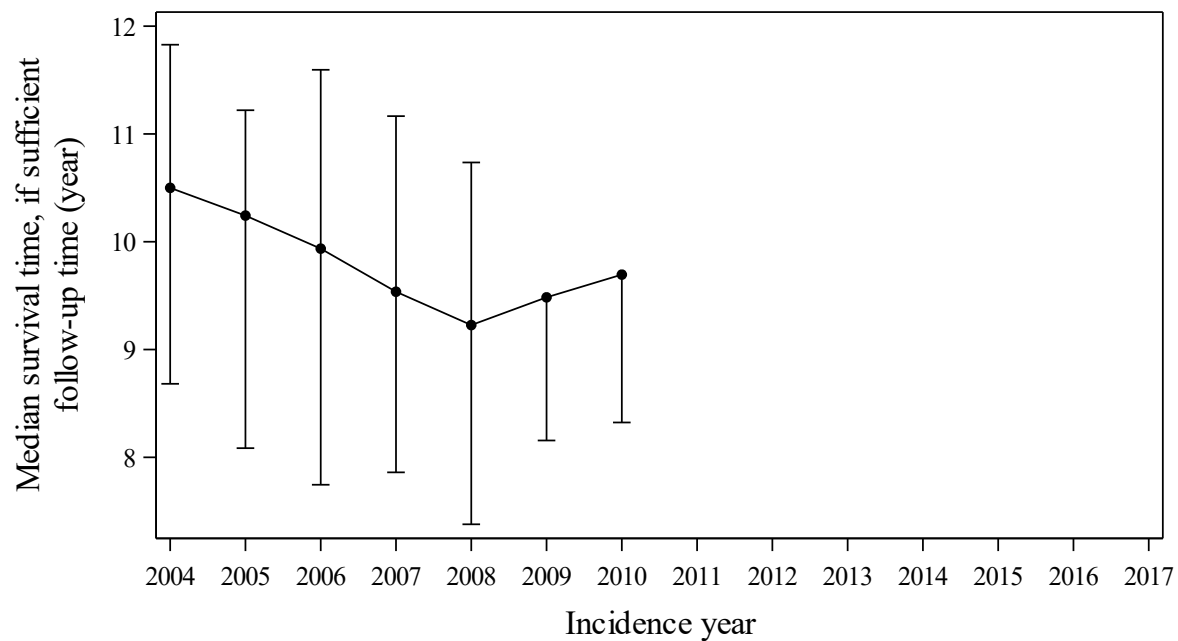
Note: the error bars represent the 95% CI.



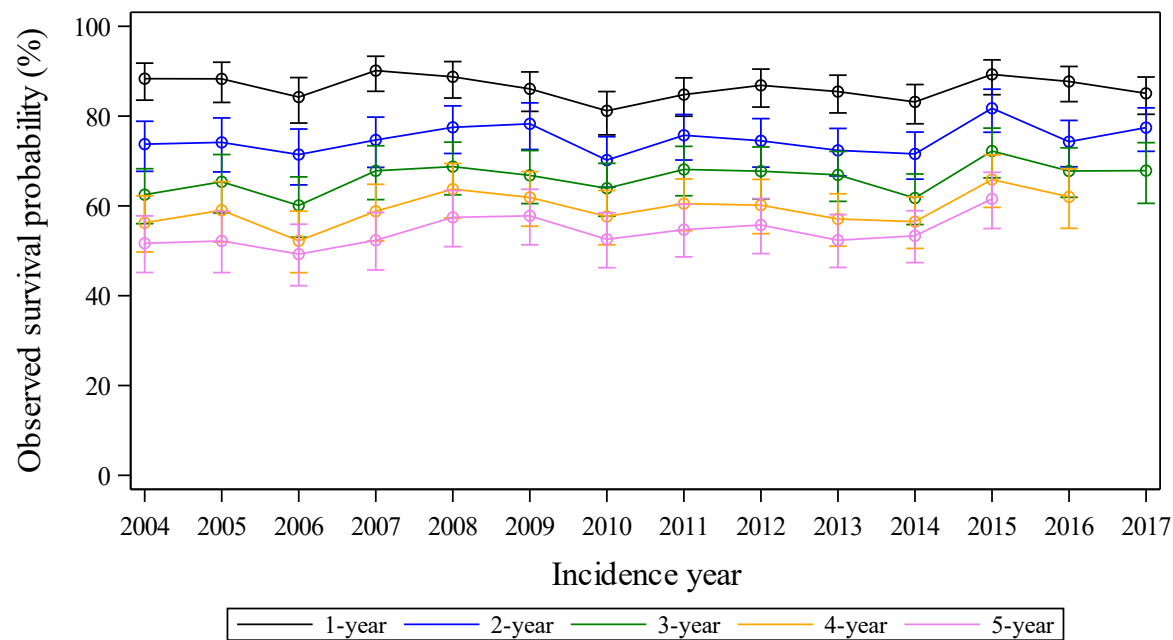
Figure 90 – Head and neck cancers (2004-2017), combined stage I, time trend relative survival with incidence year



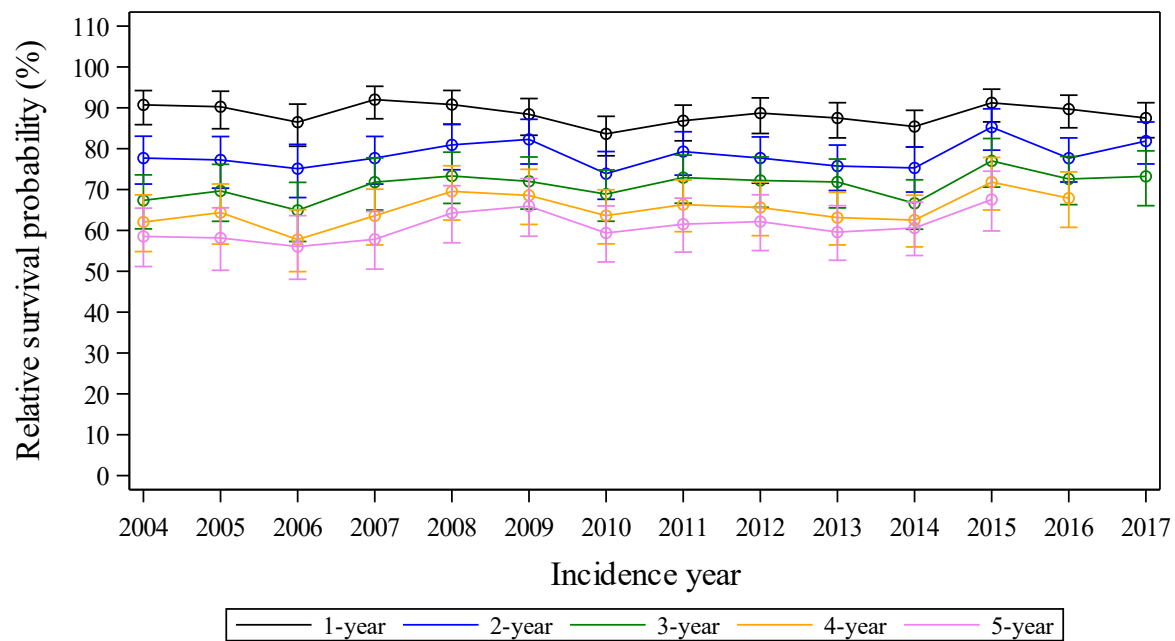
Note: the error bars represent the 95% CI.

**Figure 91 – Head and neck cancers (2004-2017), combined stage I, median time observed survival**

Note: the error bars represent the 95% CI. When the upper error is not plotted, the upper limit could not be determined with the follow-up available.

**Head and Neck cancers, combined stage II (2004-2017)****Figure 92 – Head and neck cancers (2004-2017), combined stage II, time trend observed survival with incidence year**

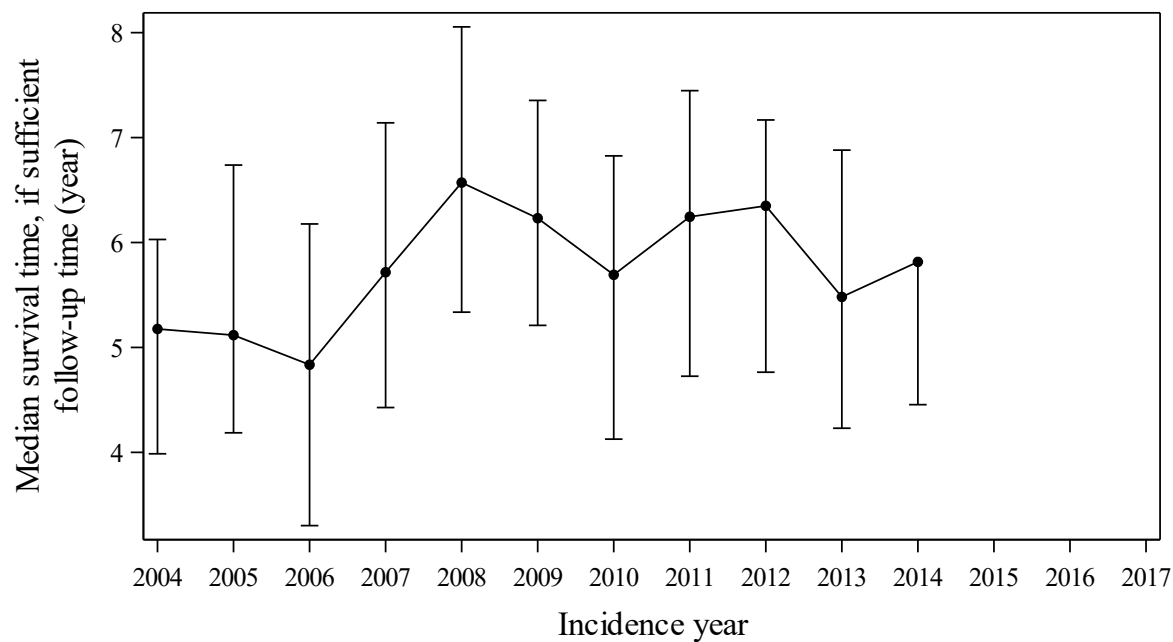
Note: the error bars represent the 95% CI.

**Figure 93 – Head and neck cancers (2004-2017), combined stage II, time trend relative survival with incidence year**

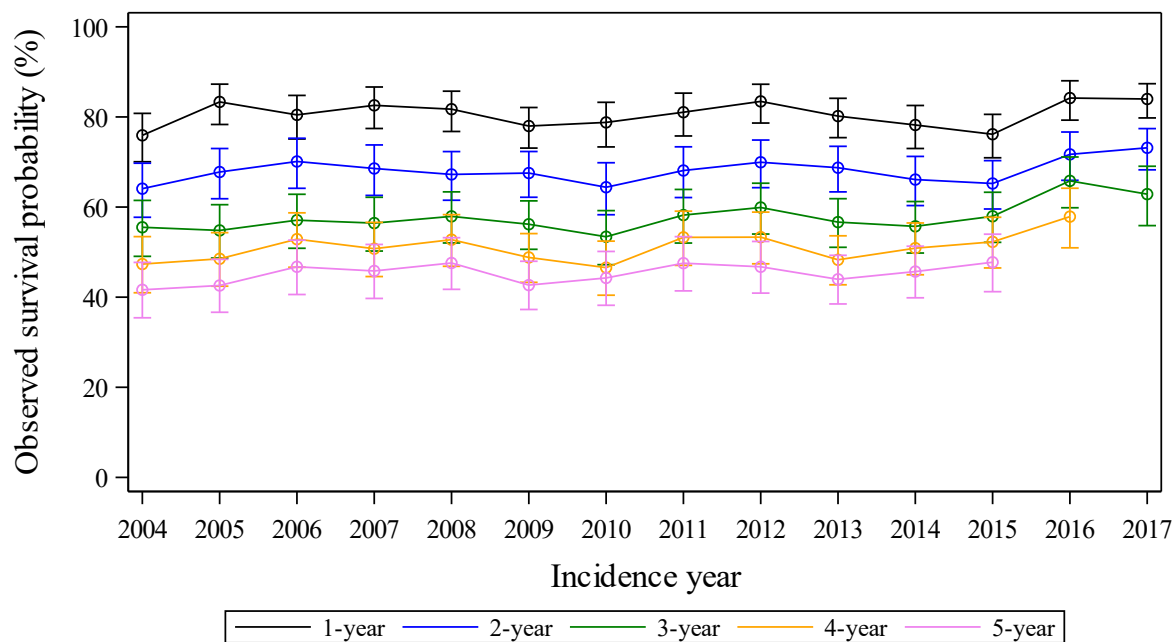
Note: the error bars represent the 95% CI.



Figure 94 – Head and neck cancers (2004-2017), combined stage II, median time observed survival



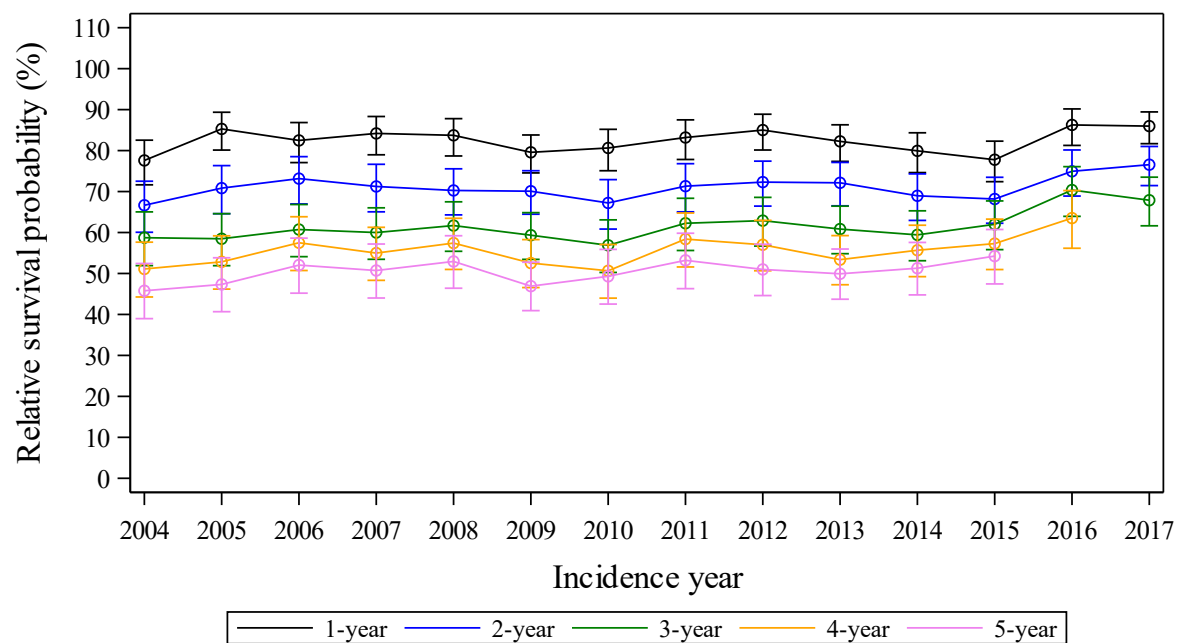
Note: the error bars represent the 95% CI. When the upper error is not plotted, the upper limit could not be determined with the follow-up available.

**Head and Neck cancers, combined stage III (2004-2017)****Figure 95 – Head and neck cancers (2004-2017), combined stage III, time trend observed survival with incidence year**

Note: the error bars represent the 95% CI.

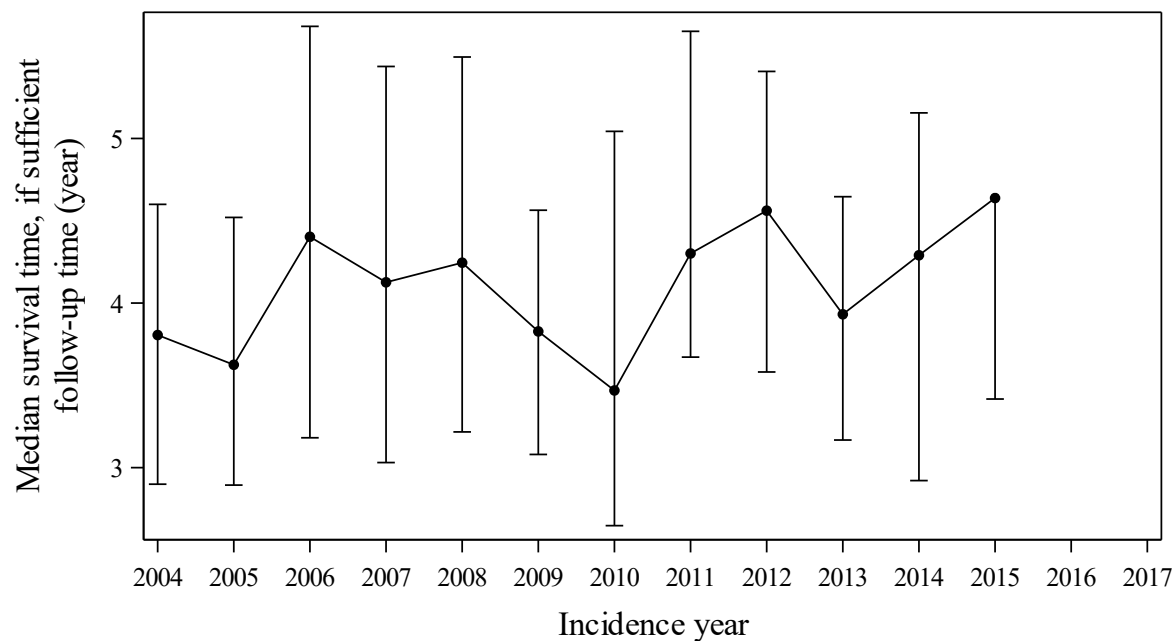


Figure 96 – Head and neck cancers (2004-2017), combined stage III, time trend relative survival with incidence year

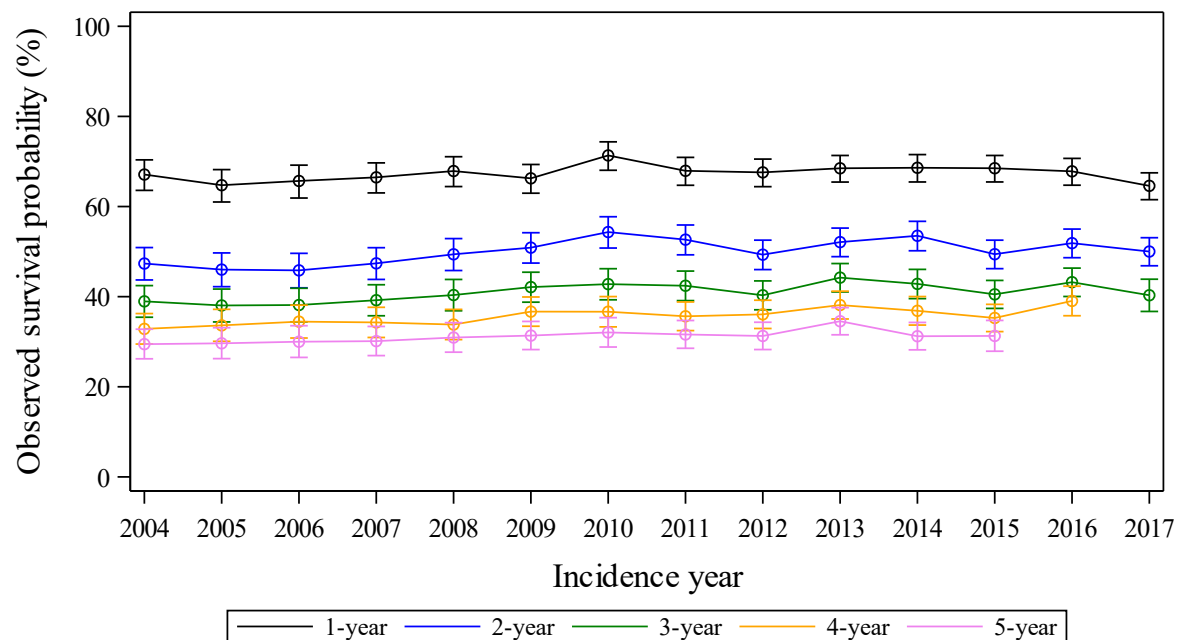


Note: the error bars represent the 95% CI.

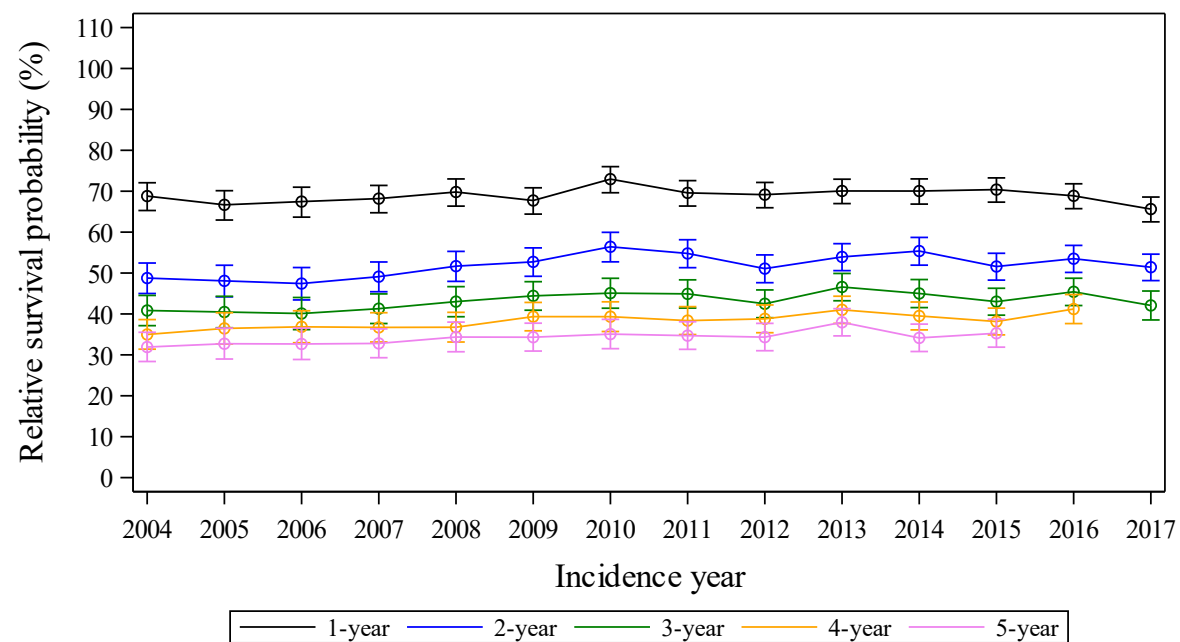
Figure 97 – Head and neck cancers (2004-2017), combined stage III, median time observed survival



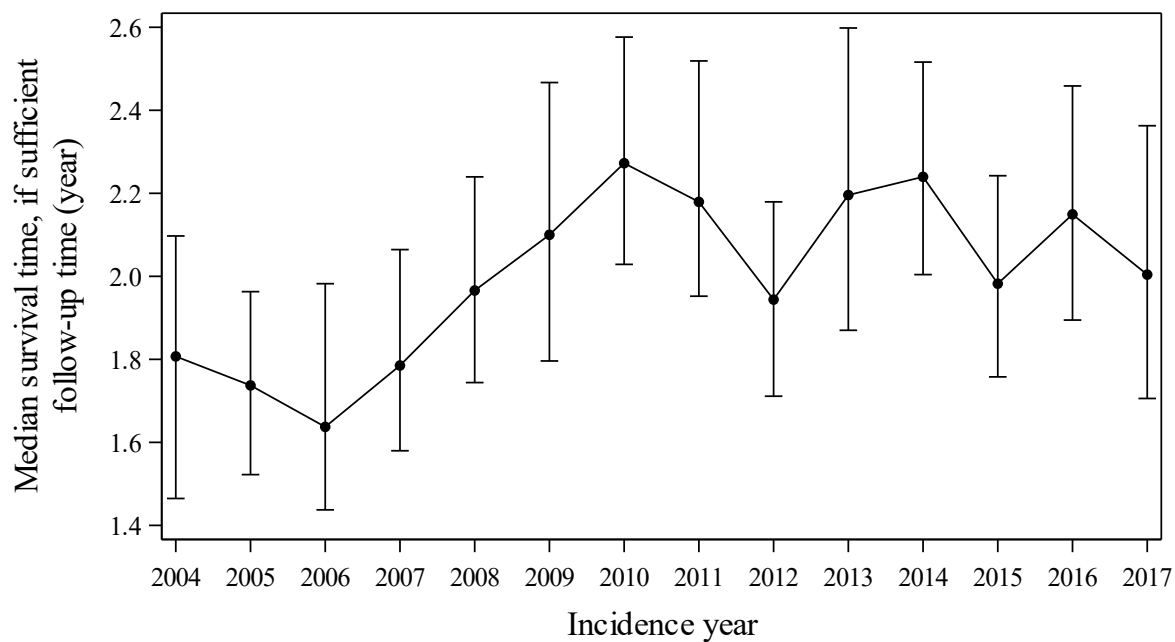
Note: the error bars represent the 95% CI. When the upper error is not plotted, the upper limit could not be determined with the follow-up available.

**Head and Neck cancers, combined stage IV (2004-2017)****Figure 98 – Head and neck cancers (2004-2017), combined stage IV, time trend observed survival with incidence year**

Note: the error bars represent the 95% CI.

**Figure 99 – Head and neck cancers (2004-2017), combined stage IV, time trend relative survival with incidence year**

Note: the error bars represent the 95% CI.

**Figure 100 – Head and neck cancers (2004-2017), combined stage IV, median time observed survival**

Note: the error bars represent the 95% CI. When the upper error is not plotted, the upper limit could not be determined with the follow-up available.



Appendix 4.1.1.4. Head and Neck cancers, time trend tables Observed and Relative Survival

Table 53 – Head and neck cancers (2004-2017), time trend observed survival with incidence year

Unadjusted observed survival, %													
Characteristic	N at risk	1 year		2 year		3 year		4 year		5 year		Median survival time (year)	
		%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI	T	95% CI
All													
2004	2,000	74.9	[72.9, 76.7]	60.6	[58.4, 62.7]	52.8	[50.6, 55.0]	47.1	[44.9, 49.2]	43.0	[40.8, 45.2]	3.5	[3.1, 3.9]
2005	1,876	76.5	[74.6, 78.4]	62.0	[59.8, 64.2]	54.1	[51.8, 56.3]	48.4	[46.1, 50.6]	43.3	[41.0, 45.5]	3.7	[3.3, 4.1]
2006	1,841	75.6	[73.6, 77.5]	61.5	[59.2, 63.6]	53.6	[51.3, 55.9]	47.9	[45.6, 50.2]	43.1	[40.8, 45.3]	3.6	[3.2, 4.0]
2007	2,053	76.1	[74.2, 77.9]	61.6	[59.4, 63.6]	52.9	[50.8, 55.1]	47.5	[45.3, 49.6]	43.4	[41.2, 45.5]	3.5	[3.1, 4.0]
2008	2,052	77.7	[75.9, 79.5]	62.7	[60.6, 64.8]	54.7	[52.5, 56.8]	48.5	[46.3, 50.6]	44.4	[42.2, 46.5]	3.7	[3.4, 4.1]
2009	2,085	77.0	[75.1, 78.8]	65.6	[63.5, 67.6]	56.9	[54.7, 59.0]	51.0	[48.8, 53.1]	46.1	[43.9, 48.2]	4.2	[3.8, 4.6]
2010	1,963	76.9	[75.0, 78.7]	64.1	[62.0, 66.2]	55.2	[53.0, 57.4]	49.3	[47.1, 51.5]	45.2	[43.0, 47.4]	3.8	[3.5, 4.3]
2011	2,100	77.8	[76.0, 79.6]	65.9	[63.8, 67.9]	57.7	[55.6, 59.8]	51.7	[49.5, 53.8]	46.7	[44.5, 48.8]	4.3	[3.9, 4.7]
2012	2,066	77.3	[75.5, 79.1]	63.7	[61.6, 65.7]	55.4	[53.2, 57.5]	50.2	[48.0, 52.3]	45.1	[42.9, 47.2]	4.0	[3.6, 4.4]
2013	2,061	77.2	[75.3, 78.9]	64.7	[62.6, 66.7]	57.6	[55.4, 59.7]	51.0	[48.8, 53.1]	47.4	[45.2, 49.6]	4.3	[3.9, 4.8]
2014	2,028	76.9	[75.0, 78.7]	64.9	[62.8, 66.9]	56.3	[54.1, 58.4]	51.1	[48.9, 53.3]	46.3	[44.1, 48.5]	4.1	[3.8, 4.7]
2015	2,051	77.8	[75.9, 79.5]	64.5	[62.4, 66.6]	57.1	[54.9, 59.2]	51.6	[49.5, 53.8]	47.0	[44.6, 49.5]	4.4	[3.8, 4.9]
2016	2,052	78.2	[76.4, 80.0]	65.9	[63.8, 67.9]	58.7	[56.6, 60.8]	53.2	[50.8, 55.6]	no FU	—	>4	
2017	2,064	76.5	[74.6, 78.3]	65.2	[63.1, 67.2]	56.2	[53.6, 58.6]	no FU	—	no FU	—	>3	
Combined Stage I													
2004	307	93.5	[90.1, 95.7]	85.0	[80.5, 88.6]	79.5	[74.5, 83.6]	73.9	[68.6, 78.5]	69.7	[64.2, 74.5]	10.5	[8.7, 11.8]
2005	284	96.5	[93.6, 98.1]	89.8	[85.6, 92.8]	84.2	[79.4, 87.9]	74.6	[69.1, 79.3]	67.5	[61.8, 72.7]	10.2	[8.1, 11.2]
2006	264	93.9	[90.3, 96.2]	86.4	[81.6, 90.0]	82.2	[77.0, 86.3]	74.6	[68.9, 79.4]	68.9	[63.0, 74.1]	9.9	[7.7, 11.6]
2007	308	95.8	[92.8, 97.5]	87.3	[83.1, 90.6]	79.2	[74.2, 83.3]	74.3	[69.0, 78.8]	71.3	[65.9, 76.1]	9.5	[7.9, 11.2]
2008	328	93.9	[90.7, 96.0]	86.2	[82.0, 89.5]	79.2	[74.3, 83.2]	71.5	[66.3, 76.1]	67.8	[62.4, 72.6]	9.2	[7.4, 10.7]



2009	373	95.7	[93.1, 97.3]	88.7	[85.0, 91.5]	82.5	[78.3, 86.0]	76.6	[72.0, 80.6]	72.6	[67.7, 76.8]	9.5	[8.2, .]
2010	403	91.0	[87.8, 93.5]	84.1	[80.1, 87.3]	79.6	[75.3, 83.2]	73.6	[69.0, 77.7]	68.4	[63.6, 72.7]	9.7	[8.3, .]
2011	430	94.2	[91.5, 96.0]	88.1	[84.7, 90.9]	83.3	[79.4, 86.5]	77.2	[72.9, 80.9]	71.4	[66.8, 75.4]	>9	
2012	452	93.1	[90.4, 95.1]	86.1	[82.5, 88.9]	79.6	[75.6, 83.1]	75.2	[71.0, 78.9]	71.0	[66.6, 75.0]	>8	
2013	422	93.6	[90.8, 95.6]	87.9	[84.4, 90.7]	82.7	[78.7, 86.0]	77.7	[73.4, 81.4]	74.4	[69.9, 78.3]	>7	
2014	474	91.8	[88.9, 93.9]	83.7	[80.1, 86.8]	78.9	[74.9, 82.3]	75.2	[71.1, 78.9]	71.0	[66.7, 74.9]	>6	
2015	464	94.4	[91.9, 96.1]	87.9	[84.6, 90.6]	82.3	[78.5, 85.5]	76.7	[72.6, 80.3]	72.1	[67.3, 76.3]	>5	
2016	463	94.2	[91.6, 96.0]	86.8	[83.4, 89.6]	81.8	[78.0, 85.0]	74.2	[69.2, 78.5]	no FU	—	>4	
2017	402	92.5	[89.5, 94.7]	85.0	[81.1, 88.2]	77.9	[72.5, 82.4]	no FU	—	no FU	—	>3	
Combined Stage II													
2004	241	88.3	[83.6, 91.8]	73.8	[67.7, 78.8]	62.5	[56.0, 68.3]	56.3	[49.7, 62.3]	51.7	[45.2, 57.8]	5.2	[4.0, 6.0]
2005	205	88.3	[83.0, 92.0]	74.1	[67.6, 79.6]	65.4	[58.4, 71.4]	59.0	[52.0, 65.4]	52.2	[45.1, 58.8]	5.1	[4.2, 6.7]
2006	203	84.2	[78.5, 88.6]	71.4	[64.7, 77.1]	60.1	[53.0, 66.5]	52.2	[45.1, 58.8]	49.3	[42.2, 55.9]	4.8	[3.3, 6.2]
2007	233	90.1	[85.5, 93.3]	74.7	[68.6, 79.8]	67.8	[61.4, 73.4]	58.8	[52.2, 64.8]	52.3	[45.7, 58.5]	5.7	[4.4, 7.1]
2008	240	88.8	[84.0, 92.1]	77.5	[71.7, 82.3]	68.8	[62.5, 74.2]	63.7	[57.3, 69.5]	57.4	[50.9, 63.4]	6.6	[5.3, 8.1]
2009	244	86.1	[81.1, 89.8]	78.3	[72.6, 82.9]	66.8	[60.5, 72.3]	61.9	[55.5, 67.6]	57.8	[51.3, 63.7]	6.2	[5.2, 7.4]
2010	255	81.2	[75.8, 85.5]	70.2	[64.2, 75.4]	63.9	[57.7, 69.5]	57.6	[51.3, 63.4]	52.5	[46.2, 58.5]	5.7	[4.1, 6.8]
2011	276	84.8	[80.0, 88.5]	75.7	[70.2, 80.4]	68.1	[62.3, 73.3]	60.5	[54.5, 66.0]	54.7	[48.6, 60.4]	6.2	[4.7, 7.4]
2012	251	86.9	[82.0, 90.5]	74.5	[68.6, 79.4]	67.7	[61.6, 73.1]	60.2	[53.8, 65.9]	55.7	[49.4, 61.6]	6.3	[4.8, 7.2]
2013	275	85.5	[80.7, 89.1]	72.4	[66.7, 77.3]	66.9	[61.0, 72.1]	57.1	[51.0, 62.7]	52.4	[46.3, 58.1]	5.5	[4.2, 6.9]
2014	285	83.2	[78.3, 87.0]	71.6	[66.0, 76.4]	61.8	[55.8, 67.1]	56.5	[50.5, 62.0]	53.3	[47.4, 58.9]	5.8	[4.5, .]
2015	252	89.3	[84.8, 92.5]	81.7	[76.4, 86.0]	72.2	[66.2, 77.3]	65.9	[59.7, 71.4]	61.6	[55.0, 67.5]	>5	
2016	277	87.7	[83.2, 91.1]	74.3	[68.7, 79.0]	67.8	[61.9, 72.9]	62.0	[55.0, 68.3]	no FU	—	>4	
2017	288	85.1	[80.4, 88.7]	77.4	[72.2, 81.8]	67.9	[60.6, 74.1]	no FU	—	no FU	—	>3	
Combined Stage III													
2004	245	75.9	[70.1, 80.8]	64.1	[57.7, 69.7]	55.5	[49.1, 61.5]	47.3	[41.0, 53.4]	41.6	[35.4, 47.7]	3.8	[2.9, 4.6]
2005	270	83.3	[78.3, 87.3]	67.8	[61.8, 73.0]	54.8	[48.7, 60.5]	48.5	[42.4, 54.3]	42.6	[36.6, 48.4]	3.6	[2.9, 4.5]
2006	261	80.5	[75.1, 84.8]	70.1	[64.2, 75.3]	57.1	[50.9, 62.8]	52.9	[46.6, 58.7]	46.7	[40.6, 52.7]	4.4	[3.2, 5.7]



2007	264	82.6	[77.4, 86.6]	68.6	[62.6, 73.8]	56.4	[50.2, 62.2]	50.8	[44.6, 56.6]	45.8	[39.7, 51.7]	4.1	[3.0, 5.4]
2008	290	81.7	[76.8, 85.7]	67.2	[61.5, 72.3]	57.9	[52.0, 63.4]	52.8	[46.9, 58.3]	47.6	[41.7, 53.2]	4.2	[3.2, 5.5]
2009	327	78.0	[73.1, 82.1]	67.5	[62.2, 72.3]	56.2	[50.6, 61.4]	48.8	[43.3, 54.1]	42.7	[37.3, 48.0]	3.8	[3.1, 4.6]
2010	264	78.8	[73.3, 83.2]	64.4	[58.3, 69.8]	53.4	[47.2, 59.2]	46.6	[40.4, 52.4]	44.3	[38.2, 50.1]	3.5	[2.6, 5.0]
2011	264	81.0	[75.8, 85.3]	68.1	[62.1, 73.4]	58.2	[52.0, 63.9]	53.3	[47.1, 59.1]	47.5	[41.4, 53.4]	4.3	[3.7, 5.7]
2012	290	83.4	[78.6, 87.3]	69.9	[64.3, 74.9]	59.9	[54.0, 65.3]	53.3	[47.4, 58.9]	46.7	[40.9, 52.4]	4.6	[3.6, 5.4]
2013	323	80.2	[75.4, 84.1]	68.7	[63.4, 73.5]	56.7	[51.1, 61.9]	48.3	[42.7, 53.6]	44.0	[38.5, 49.3]	3.9	[3.2, 4.6]
2014	291	78.2	[73.0, 82.5]	66.1	[60.3, 71.2]	55.7	[49.8, 61.2]	50.9	[45.0, 56.5]	45.7	[39.9, 51.3]	4.3	[2.9, 5.2]
2015	302	76.2	[70.9, 80.6]	65.2	[59.6, 70.3]	57.9	[52.2, 63.3]	52.3	[46.5, 57.7]	47.7	[41.2, 54.0]	4.6	[3.4, .]
2016	273	84.2	[79.3, 88.0]	71.7	[65.9, 76.7]	65.8	[59.8, 71.1]	57.9	[51.0, 64.2]	no FU	—	>4	
2017	364	84.0	[79.8, 87.4]	73.2	[68.3, 77.4]	62.9	[55.9, 69.1]	no FU	—	no FU	—	>3	
Combined Stage IV													
2004	739	67.1	[63.6, 70.4]	47.4	[43.7, 50.9]	39.0	[35.4, 42.5]	32.9	[29.5, 36.3]	29.5	[26.2, 32.8]	1.8	[1.5, 2.1]
2005	678	64.7	[61.0, 68.2]	46.0	[42.2, 49.7]	38.1	[34.4, 41.7]	33.6	[30.1, 37.2]	29.6	[26.2, 33.1]	1.7	[1.5, 2.0]
2006	650	65.7	[61.9, 69.2]	45.8	[42.0, 49.6]	38.2	[34.4, 41.9]	34.5	[30.8, 38.1]	30.0	[26.5, 33.6]	1.6	[1.4, 2.0]
2007	770	66.5	[63.0, 69.7]	47.4	[43.8, 50.9]	39.2	[35.8, 42.7]	34.3	[30.9, 37.6]	30.1	[26.9, 33.4]	1.8	[1.6, 2.1]
2008	763	67.9	[64.4, 71.1]	49.4	[45.8, 52.9]	40.4	[36.9, 43.8]	33.8	[30.5, 37.2]	30.9	[27.7, 34.2]	2.0	[1.7, 2.2]
2009	845	66.3	[63.0, 69.3]	50.9	[47.5, 54.2]	42.1	[38.8, 45.4]	36.7	[33.4, 39.9]	31.4	[28.3, 34.5]	2.1	[1.8, 2.5]
2010	789	71.4	[68.1, 74.4]	54.3	[50.8, 57.8]	42.8	[39.3, 46.2]	36.7	[33.3, 40.0]	32.1	[28.8, 35.3]	2.3	[2.0, 2.6]
2011	875	67.9	[64.7, 70.9]	52.7	[49.3, 55.9]	42.4	[39.1, 45.7]	35.6	[32.5, 38.8]	31.6	[28.5, 34.7]	2.2	[2.0, 2.5]
2012	899	67.6	[64.4, 70.5]	49.3	[46.0, 52.6]	40.3	[37.1, 43.5]	36.1	[32.9, 39.2]	31.3	[28.3, 34.3]	1.9	[1.7, 2.2]
2013	953	68.5	[65.4, 71.3]	52.1	[48.9, 55.2]	44.2	[41.1, 47.4]	38.1	[35.1, 41.2]	34.5	[31.5, 37.6]	2.2	[1.9, 2.6]
2014	897	68.6	[65.5, 71.5]	53.5	[50.2, 56.7]	42.8	[39.6, 46.1]	36.9	[33.7, 40.0]	31.2	[28.2, 34.3]	2.2	[2.0, 2.5]
2015	960	68.5	[65.5, 71.3]	49.4	[46.2, 52.5]	40.5	[37.4, 43.6]	35.3	[32.3, 38.3]	31.3	[27.9, 34.7]	2.0	[1.8, 2.2]
2016	948	67.8	[64.8, 70.7]	51.9	[48.7, 55.0]	43.2	[40.0, 46.3]	39.1	[35.8, 42.3]	no FU	—	2.1	[1.9, 2.5]
2017	990	64.6	[61.5, 67.5]	50.0	[46.9, 53.1]	40.3	[36.7, 43.9]	no FU	—	no FU	—	2.0	[1.7, 2.4]



Table 54 – Head and neck cancers (2004-2017), time trend relative survival with incidence year

Unadjusted relative survival, %												
Characteristic	N at risk	%	1 year		2 year		3 year		4 year		5 year	
			95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI	
All												
2004	2,000	76.7	[74.8, 78.6]	63.3	[61.0, 65.5]	56.4	[54.1, 58.7]	51.5	[49.1, 53.8]	48.2	[45.7, 50.6]	
2005	1,876	78.4	[76.3, 80.3]	64.9	[62.5, 67.1]	57.9	[55.4, 60.3]	53.0	[50.5, 55.5]	48.6	[46.1, 51.1]	
2006	1,841	77.3	[75.2, 79.2]	64.0	[61.6, 66.3]	57.1	[54.6, 59.5]	52.2	[49.7, 54.6]	48.1	[45.5, 50.6]	
2007	2,053	77.8	[75.8, 79.6]	64.1	[61.9, 66.3]	56.3	[54.0, 58.6]	51.6	[49.3, 54.0]	48.3	[45.9, 50.6]	
2008	2,052	79.6	[77.7, 81.3]	65.6	[63.3, 67.7]	58.4	[56.1, 60.7]	53.0	[50.6, 55.4]	49.8	[47.4, 52.2]	
2009	2,085	78.7	[76.8, 80.5]	68.4	[66.2, 70.5]	60.6	[58.3, 62.8]	55.6	[53.2, 57.9]	51.4	[49.0, 53.8]	
2010	1,963	78.7	[76.7, 80.5]	66.9	[64.7, 69.1]	58.9	[56.5, 61.2]	53.8	[51.3, 56.2]	50.5	[48.0, 53.0]	
2011	2,100	79.6	[77.8, 81.4]	68.8	[66.7, 70.9]	61.6	[59.3, 63.8]	56.5	[54.1, 58.8]	52.2	[49.8, 54.6]	
2012	2,066	79.0	[77.0, 80.7]	66.2	[64.0, 68.4]	58.9	[56.5, 61.1]	54.6	[52.2, 56.9]	50.2	[47.8, 52.6]	
2013	2,061	78.9	[77.0, 80.7]	67.4	[65.2, 69.5]	61.4	[59.0, 63.6]	55.7	[53.3, 58.0]	53.2	[50.8, 55.6]	
2014	2,028	78.6	[76.7, 80.4]	67.7	[65.5, 69.8]	60.0	[57.7, 62.3]	55.8	[53.4, 58.2]	51.8	[49.4, 54.3]	
2015	2,051	79.6	[77.7, 81.4]	67.4	[65.2, 69.5]	61.0	[58.7, 63.2]	56.5	[54.1, 58.9]	53.1	[50.6, 55.7]	
2016	2,052	79.8	[77.9, 81.6]	68.7	[66.5, 70.8]	62.7	[60.4, 64.9]	57.9	[55.4, 60.4]	no FU	—	
2017	2,064	78.2	[76.3, 80.1]	68.1	[65.9, 70.2]	59.8	[57.2, 62.3]	no FU	—	no FU	—	
Combined Stage I												
2004	307	95.8	[92.4, 98.1]	89.4	[84.6, 93.1]	85.9	[80.5, 90.3]	82.2	[76.3, 87.3]	79.6	[73.4, 85.1]	
2005	284	98.7	[95.7, 100.3]	94.0	[89.7, 97.1]	90.3	[85.1, 94.3]	82.2	[76.2, 87.3]	76.6	[70.0, 82.3]	
2006	264	96.1	[92.4, 98.4]	90.5	[85.5, 94.3]	88.4	[82.8, 92.8]	82.5	[76.2, 87.8]	78.5	[71.7, 84.4]	
2007	308	98.2	[95.2, 100.0]	91.9	[87.5, 95.4]	85.5	[80.2, 90.0]	82.3	[76.4, 87.3]	81.1	[75.0, 86.5]	
2008	328	96.1	[92.9, 98.3]	90.6	[86.1, 94.0]	85.3	[80.1, 89.6]	79.0	[73.2, 84.1]	77.1	[71.0, 82.5]	
2009	373	98.2	[95.5, 99.9]	93.4	[89.5, 96.4]	89.2	[84.7, 93.0]	85.3	[80.1, 89.7]	83.3	[77.7, 88.1]	
2010	403	93.2	[89.9, 95.6]	88.1	[84.0, 91.5]	85.6	[81.0, 89.5]	81.2	[76.1, 85.6]	77.5	[72.1, 82.4]	
2011	430	96.5	[93.8, 98.4]	92.5	[88.9, 95.3]	89.5	[85.3, 93.0]	85.2	[80.5, 89.3]	80.9	[75.8, 85.5]	



2012	452	95.3	[92.5, 97.3]	90.1	[86.4, 93.1]	85.4	[81.1, 89.1]	82.8	[78.1, 86.9]	80.3	[75.3, 84.8]
2013	422	95.7	[92.8, 97.7]	92.0	[88.3, 94.9]	88.7	[84.4, 92.2]	85.5	[80.8, 89.6]	84.4	[79.3, 88.8]
2014	474	93.9	[91.0, 96.1]	87.7	[83.9, 90.8]	84.5	[80.3, 88.1]	82.6	[78.0, 86.5]	80.0	[75.1, 84.3]
2015	464	96.8	[94.2, 98.5]	92.3	[88.8, 95.1]	88.8	[84.7, 92.2]	85.0	[80.5, 89.0]	81.9	[76.5, 86.6]
2016	463	96.5	[93.8, 98.3]	91.3	[87.7, 94.2]	88.5	[84.4, 92.0]	83.0	[77.8, 87.6]	no FU	—
2017	402	95.1	[92.0, 97.4]	89.9	[85.8, 93.3]	84.3	[78.9, 88.9]	no FU	—	no FU	—
Combined Stage II											
2004	241	90.7	[85.9, 94.2]	77.7	[71.3, 83.0]	67.3	[60.4, 73.6]	62.0	[54.8, 68.7]	58.5	[51.2, 65.5]
2005	205	90.3	[84.9, 94.1]	77.2	[70.3, 83.0]	69.7	[62.2, 76.2]	64.4	[56.6, 71.4]	58.2	[50.2, 65.5]
2006	203	86.5	[80.6, 90.9]	75.1	[68.0, 81.1]	64.9	[57.3, 71.8]	57.8	[49.9, 65.1]	56.0	[48.0, 63.6]
2007	233	92.0	[87.3, 95.3]	77.7	[71.3, 83.0]	71.8	[65.0, 77.7]	63.6	[56.4, 70.1]	57.8	[50.5, 64.7]
2008	240	90.8	[86.0, 94.2]	80.9	[74.8, 85.9]	73.3	[66.6, 79.1]	69.6	[62.5, 75.8]	64.3	[57.0, 70.9]
2009	244	88.4	[83.3, 92.3]	82.3	[76.2, 87.2]	72.0	[65.2, 78.0]	68.6	[61.5, 75.0]	65.9	[58.6, 72.7]
2010	255	83.6	[78.3, 87.9]	73.9	[67.6, 79.3]	68.9	[62.2, 74.8]	63.6	[56.7, 69.9]	59.4	[52.3, 66.0]
2011	276	86.8	[81.9, 90.7]	79.3	[73.5, 84.1]	72.9	[66.7, 78.4]	66.3	[59.7, 72.3]	61.5	[54.7, 67.9]
2012	251	88.7	[83.7, 92.4]	77.7	[71.6, 82.9]	72.2	[65.6, 78.0]	65.6	[58.7, 71.9]	62.2	[55.1, 68.7]
2013	275	87.5	[82.6, 91.3]	75.7	[69.8, 80.9]	71.9	[65.5, 77.5]	63.1	[56.5, 69.3]	59.6	[52.7, 66.1]
2014	285	85.4	[80.4, 89.4]	75.3	[69.4, 80.4]	66.6	[60.3, 72.4]	62.5	[56.0, 68.6]	60.6	[53.9, 66.9]
2015	252	91.2	[86.6, 94.6]	85.3	[79.6, 89.8]	77.0	[70.6, 82.5]	71.8	[65.0, 77.9]	67.6	[59.9, 74.5]
2016	277	89.7	[85.1, 93.1]	77.7	[71.8, 82.6]	72.6	[66.3, 78.1]	67.9	[60.7, 74.3]	no FU	—
2017	288	87.5	[82.7, 91.3]	81.9	[76.3, 86.5]	73.2	[66.1, 79.5]	no FU	—	no FU	—
Combined Stage III											
2004	245	77.6	[71.6, 82.5]	66.7	[60.1, 72.5]	58.7	[51.9, 65.0]	51.1	[44.3, 57.6]	45.8	[39.0, 52.4]
2005	270	85.3	[80.1, 89.4]	70.8	[64.6, 76.3]	58.5	[51.9, 64.6]	52.8	[46.2, 59.2]	47.3	[40.7, 53.8]
2006	261	82.5	[77.1, 86.8]	73.2	[67.0, 78.5]	60.7	[54.1, 66.8]	57.5	[50.7, 63.8]	52.0	[45.2, 58.6]
2007	264	84.2	[79.0, 88.3]	71.2	[65.0, 76.7]	60.0	[53.5, 66.0]	55.0	[48.3, 61.3]	50.7	[44.0, 57.2]
2008	290	83.7	[78.7, 87.8]	70.3	[64.3, 75.5]	61.7	[55.4, 67.5]	57.4	[51.0, 63.5]	52.9	[46.4, 59.2]
2009	327	79.6	[74.5, 83.8]	70.1	[64.5, 75.1]	59.3	[53.4, 64.8]	52.5	[46.6, 58.3]	46.9	[40.9, 52.8]



2010	264	80.6	[75.1, 85.2]	67.2	[60.8, 72.9]	56.9	[50.2, 63.1]	50.7	[44.0, 57.1]	49.3	[42.5, 55.9]
2011	264	83.2	[77.8, 87.5]	71.3	[65.0, 76.8]	62.3	[55.6, 68.4]	58.4	[51.6, 64.8]	53.2	[46.3, 59.8]
2012	290	85.0	[80.1, 88.9]	72.3	[66.4, 77.4]	62.9	[56.7, 68.6]	57.0	[50.7, 63.0]	51.0	[44.6, 57.1]
2013	323	82.3	[77.4, 86.3]	72.1	[66.5, 77.1]	60.8	[54.8, 66.4]	53.4	[47.3, 59.2]	49.9	[43.7, 56.0]
2014	291	79.9	[74.6, 84.3]	69.0	[63.0, 74.3]	59.4	[53.1, 65.3]	55.7	[49.2, 61.8]	51.3	[44.8, 57.6]
2015	302	77.8	[72.4, 82.3]	68.2	[62.3, 73.5]	62.0	[55.8, 67.7]	57.3	[51.0, 63.3]	54.2	[47.4, 60.7]
2016	273	86.3	[81.3, 90.2]	74.9	[68.9, 80.1]	70.4	[63.9, 76.1]	63.5	[56.2, 70.2]	no FU	—
2017	364	86.0	[81.7, 89.4]	76.6	[71.5, 81.0]	67.9	[61.6, 73.5]	no FU	—	no FU	—
Combined Stage IV											
2004	739	68.8	[65.3, 72.1]	48.8	[45.0, 52.4]	40.8	[37.1, 44.5]	35.0	[31.4, 38.6]	31.9	[28.4, 35.5]
2005	678	66.7	[62.9, 70.1]	48.1	[44.2, 51.9]	40.5	[36.6, 44.3]	36.5	[32.7, 40.3]	32.7	[29.0, 36.5]
2006	650	67.5	[63.7, 71.0]	47.4	[43.4, 51.3]	40.1	[36.2, 44.0]	36.9	[33.0, 40.8]	32.7	[28.9, 36.5]
2007	770	68.2	[64.7, 71.4]	49.1	[45.4, 52.7]	41.3	[37.7, 44.9]	36.7	[33.1, 40.3]	32.8	[29.3, 36.3]
2008	763	69.8	[66.3, 73.0]	51.7	[48.0, 55.3]	43.0	[39.3, 46.7]	36.8	[33.1, 40.4]	34.4	[30.8, 38.0]
2009	845	67.7	[64.4, 70.8]	52.7	[49.2, 56.1]	44.4	[40.9, 47.9]	39.3	[35.9, 42.8]	34.3	[30.9, 37.7]
2010	789	72.9	[69.6, 76.0]	56.4	[52.7, 59.9]	45.1	[41.4, 48.7]	39.3	[35.7, 43.0]	35.1	[31.5, 38.7]
2011	875	69.6	[66.4, 72.6]	54.8	[51.3, 58.1]	44.9	[41.4, 48.3]	38.4	[35.0, 41.8]	34.7	[31.3, 38.1]
2012	899	69.2	[66.0, 72.1]	51.1	[47.6, 54.4]	42.5	[39.1, 45.9]	38.8	[35.4, 42.2]	34.3	[31.0, 37.7]
2013	953	70.1	[67.0, 72.9]	53.9	[50.6, 57.2]	46.6	[43.2, 49.9]	41.0	[37.7, 44.3]	38.0	[34.6, 41.3]
2014	897	70.0	[66.8, 73.0]	55.4	[51.9, 58.7]	45.0	[41.5, 48.4]	39.5	[36.1, 42.9]	34.1	[30.8, 37.5]
2015	960	70.4	[67.3, 73.2]	51.6	[48.3, 54.8]	43.0	[39.7, 46.3]	38.1	[34.9, 41.4]	35.3	[31.9, 38.7]
2016	948	68.9	[65.7, 71.8]	53.5	[50.1, 56.7]	45.4	[42.1, 48.7]	41.2	[37.6, 44.7]	no FU	—
2017	990	65.6	[62.5, 68.6]	51.4	[48.1, 54.6]	42.1	[38.5, 45.6]	no FU	—	no FU	—



Appendix 4.1.2. Uptake of selected drug

Table 55 – Proportion of patients who received at least one dose during 5-year period after diagnosis (stage III H&N cancer)

Drug/incidence year (n)	2004 (245)	2005 (271)	2006 (261)	2007 (265)	2008 (291)	2009 (331)	2010 (265)	2011 (265)	2012 (292)	2013 (329)	2014 (292)	2015 (303)	2016 (274)	2017 (368)
Cetuximab	0.4%	0.7%	3.1%	15.1%	13.1%	19.3%	16.2%	20.4%	20.9%	17.6%	13.0%	13.09%	11.7%	10.6%

Number in yellow indicates the first calendar year of reimbursement. Cetuximab was first reimbursed in 2006. The columns in this table indicate the incidence year. For example, for incidence year 2013, 17.6% of patients received reimbursed bevacizumab during the five years after diagnosis. Source: BCR-IMA.

Remark: IMA data were only available up to the second trimester of 2019. Five-year follow-up data are thus not complete for the last years in this table.

Table 56 – Proportion of patients who received at least one dose during 5-year period after diagnosis (stage IV H&N cancer)

Drug/incidence year (n)	2004 (741)	2005 (680)	2006 (653)	2007 (771)	2008 (767)	2009 (847)	2010 (792)	2011 (880)	2012 (903)	2013 (961)	2014 (905)	2015 (967)	2016 (958)	2017 (1003)
Cetuximab	0.5%	0.9%	2.0%	14.4%	16.2%	22.7%	24.4%	29.0%	28.6%	23.5%	23.4%	23.0%	22.0%	17.0%

Number in yellow indicates the first calendar year of reimbursement. Cetuximab was first reimbursed in 2006. The columns in this table indicate the incidence year. For example, for incidence year 2013, 23.5% of patients received reimbursed bevacizumab during the five years after diagnosis. Source: BCR-IMA.

Remark: IMA data were only available up to the second trimester of 2019. Five-year follow-up data are thus not complete for the last years in this table.



Appendix 4.2. reimbursement criteria for selected drugs

Table 57 – Cetuximab in Head and Neck cancer: reimbursement criteria in Belgium

Drug	Trade name	Date start reimbursement	Indication NI	Indication Fr
Cetuximab	Erbixux	2006	<ul style="list-style-type: none"> De specialiteit komt in aanmerking voor vergoeding indien zij wordt toegediend voor de behandeling van een stadium III of IV lokaal gevorderd niet gemetastaseerd plaveiselcelcarcinoom van de oropharynx, hypopharynx of larynx. Na multidisciplinair oncologisch consult waarbij een radiotherapeut, medisch oncoloog en neus- keeloorarts aanwezig waren werd besloten dat een radiotherapeutische behandeling in combinatie met ERBITUX is aangewezen en dat patiënt niet in aanmerking komt voor een cisplatine gebaseerde radiochemotherapie. 	<ul style="list-style-type: none"> La spécialité fait l'objet d'un remboursement si elle est administrée pour le traitement d'un carcinome épidermoïde localement avancé de l'oropharynx, hypopharynx ou larynx stade III ou IV non-métastasé. Après concertation oncologique multidisciplinaire à laquelle ont participé un radiothérapeute, un oncologue médical et un oto-rhino-laryngologiste, il a été décidé qu'un traitement par radiothérapie en combinaison avec ERBITUX est indiqué et que le patient n'est pas candidat pour une radiochimiothérapie sur base de cisplatine.
		2006	<ul style="list-style-type: none"> De specialiteit komt in aanmerking voor vergoeding indien zij tijdens de eerste behandelingscyclus samen met cisplatine als eerste lijn behandeling wordt toegediend voor de behandeling van een patiënt met een recurrent en/of gemetastaseerd plaveiselcelcarcinoom van het hoofd- halsgebied die een Karnovsky performance heeft van ≥ 80 en bij wie het interval tussen het einde van een eventueel toegediende chemotherapie in het kader van de primaire behandeling voor de niet gemetastaseerde ziekte en de start van de huidige behandeling ≥ 6 maanden is. Vanaf de tweede behandelingscyclus mag ERBITUX worden gecombineerd met carboplatine indien cisplatine niet wordt verdragen. ERBITUX mag na de chemotherapie in monotherapie als onderhoudsbehandeling worden verdergezet voor zover er geen ziekteprogressie is opgetreden onder de behandeling. 	<ul style="list-style-type: none"> La spécialité fait l'objet d'un remboursement si elle est administrée comme traitement de première ligne en combinaison avec le cisplatine pour le traitement d'un patient atteint d'un carcinome épidermoïde de la tête ou du cou récidivant et/ou métastasé, ayant un Karnovsky Performance ≥ 80 et chez qui l'intervalle entre la fin d'une chimiothérapie éventuellement administrée dans le cadre du traitement primaire de la maladie nonmétastasée et le début du traitement actuel est ≥ 6 mois. Dès le deuxième cycle de traitement, l'ERBITUX peut être associé au carboplatine en cas d'intolérance au cisplatine. Le traitement par l'ERBITUX peut être poursuivi en monothérapie comme traitement d'entretien après l'arrêt de la chimiothérapie pour autant que la maladie n'ait pas progressé malgré le traitement.



Appendix 4.3. Medical literature: search for evidence

Appendix 4.3.1. Search medical literature (systematic reviews)

The search for systematic reviews in MEDLINE, PreMedline and the Cochrane library of systematic reviews (inception to search date) specifically developed for this research question, yielded 68 records (Figure 158). After de-duplication, 46 reviews (2020-2015) of the 68 remaining reviews were screened based on title and abstract, of which 28 were excluded. In total 18 full text articles were assessed for eligibility. Based on full text evaluation, 16 reviews were excluded (Figure 159).



Figure 101 – Head and Neck cancer – Selection of SRs - Study flow

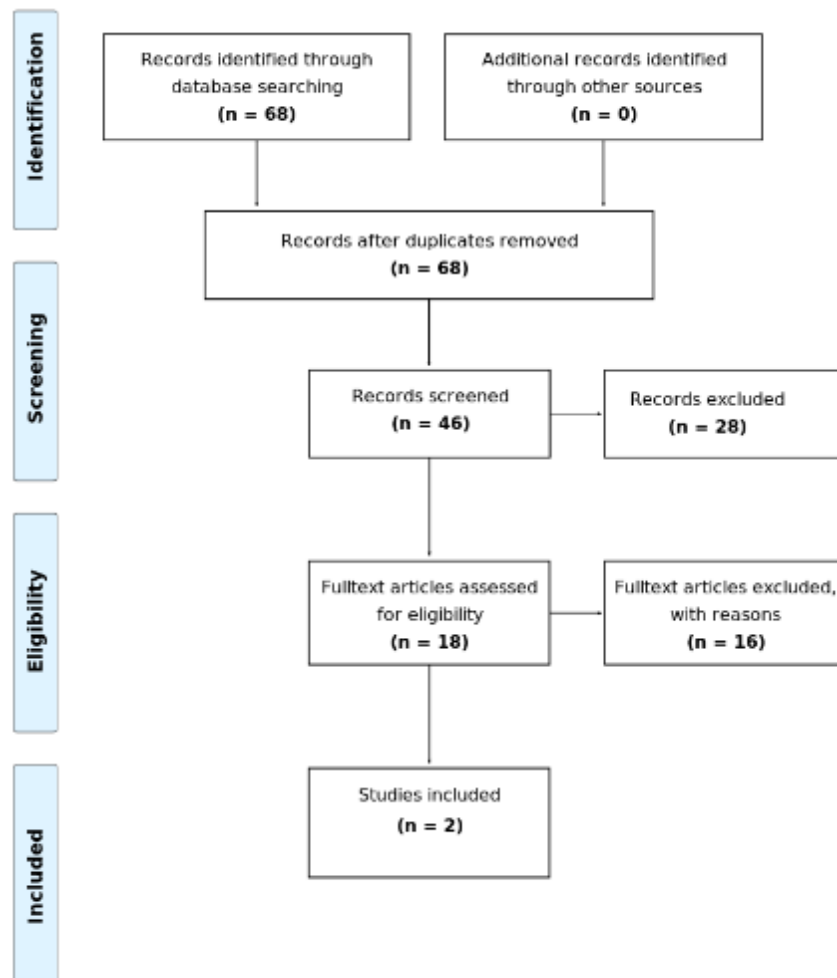



Table 58 – SCC of the H&N: excluded reviews and reason for exclusion

	Year	Publication	Reason for exclusion
1	2019	Zhao, Y. Liu, W. Sun, M. et al. Impact of age on the overall survival benefits of anti-EGFR-containing regimens in head and neck squamous cell carcinoma: A meta-analysis of randomized controlled trials. Crit Rev Oncol Hematol 2019;135:39-46	no separate results for cetuximab
2	2019	Tang, X. He, J. Li, B. et al. Efficacy and Safety of Gefitinib in Patients with Advanced Head and Neck Squamous Cell Carcinoma: A Meta-Analysis of Randomized Controlled Trials. J Oncol 2019; 6273438	no results for cetuximab
3	2019	Suton, P. Skelin, M. Rakusic, Z. et al. Cisplatin-based chemoradiotherapy vs. cetuximab-based bioradiotherapy for p16-positive oropharyngeal cancer: an updated meta-analysis including trials RTOG 1016 and De-ESCALaTE. Eur Arch Otorhinolaryngol 2019;276(5):1275-1281	non-randomized studies included
4	2019	Muratori, L. La Salvia, A. Sperone, P. Di Maio, M. Target therapies in recurrent or metastatic head and neck cancer: state of the art and novel perspectives. A systematic review. Crit Rev Oncol Hematol 2019;139:41-52	searched only 1 database, no critical appraisal
5	2019	El Rassy, E. Assi, T. Bakouny, Z. et al. Comparison of second-line treatments of recurrent and/or metastatic squamous cell carcinoma of the head and neck. Fut Oncol 2019;15(8):909-923	No additional information
6	2018	Xin, Y. Yan, Q. Yang, C. et al. Meta-analysis of the effects of anti-epidermal growth factor receptor on recurrent/metastatic head and neck squamous cell carcinoma. Medicine (Baltimore) 2018;97(51):e13717	wrong outcomes
7	2018	Tian, Y. Lin, J. Tian, Y. et al. Efficacy and safety of anti-EGFR agents administered concurrently with standard therapies for patients with head and neck squamous cell carcinoma: a systematic review and meta-analysis of randomized controlled trials. Int J Cancer 2018;142(11):2198-2206	Included
8	2018	Su, Y. Cui, J. Xu, D. et al. p16(INK4a) status and survival benefit of EGFR inhibitors in head and neck squamous cell cancer: A systematic review and meta-analysis. Crit Rev Oncol Hematol 2018; 124:11-20	no separate results for cetuximab
9	2018	Lala, M. Chirovsky, D. Cheng, J. D. Mayawala, K. Clinical outcomes with therapies for previously treated recurrent/metastatic head-and-neck squamous cell carcinoma (R/M HNSCC): A systematic literature review. Oral Oncol 2018;84:108-120	single-arm trials included
10	2018	Iocca, O. Farcomeni, A. Di Rocco, A. Di Maio, P. et al. Locally advanced squamous cell carcinoma of the head and neck: A systematic review and Bayesian network meta-analysis of the currently available treatment options. Oral Oncol 2018;80:40-51	no separate results for cetuximab
11	2018	Guidi, A. Codeca, C. Ferrari, D. Chemotherapy and immunotherapy for recurrent and metastatic head and neck cancer: a systematic review. Med Oncol 2018;35(3):37	not a systematic review
12	2017	Winquist, E. Agbassi, C. Meyers, B. M. et al. Systemic therapy in the curative treatment of head and neck squamous cell cancer: a systematic review. J Otolaryngol Head Neck Surg 2017;46(1):29	No report of searched databases
13	2017	Kim, B. J. Jeong, J. H. Kim, H. S. Kim, J. H. The role of anti-EGFR agents in patients with locoregionally advanced head and neck cancer: a meta-analysis of randomized trials. Oncotarget 2017;8(60):102371-102380	No description of methodology



Year	Publication	Reason for exclusion
14	2017 Goh, R. M. Syn, N. L. X. Wang, L. et al. Anti-epidermal growth factor receptor (anti-EGFR) agents as adjuncts to conventional treatment for head and neck squamous cell carcinomas. Cochrane Database of Systematic Reviews 2017(3)	Full text could not be obtained
15	2017 Bonomo, P. Loi, M. Desideri, I. et al. Incidence of skin toxicity in squamous cell carcinoma of the head and neck treated with radiotherapy and cetuximab: A systematic review. Crit Rev Oncol Hematol 2017; 120:98-110	wrong outcome
16	2016 Mockelmann, N. Kriegs, M. Lorincz, B. B. et al. Molecular targeting in combination with platinum-based chemoradiotherapy in head and neck cancer treatment. Head Neck 2017;38:E2173-81	searched only 1 database
17	2016 Huang, J. Zhang, J. Shi, C. et al. Survival, recurrence and toxicity of HNSCC in comparison of a radiotherapy combination with cisplatin versus cetuximab: a meta-analysis. BMC Cancer 2016;16:689	no critical appraisal, retrospective studies included
18	2015 Chan KKW, Glenny AM, Weldon JC et al. Interventions for the treatment of oral and oropharyngeal cancers: targeted therapy and immunotherapy (review). Cochrane Database of systematic reviews 2015, issue 12. Art No CD010341	Included

Appendix 4.3.2. Critical appraisal systematic reviews

	Tian 2018 ⁷⁵		Chan 2015 ⁷⁶	
	Score	Rationale/comment	score	Rationale/comment
1. PICO	Y		Y	
2. A priori study design	N		N	
3. Inclusion study designs	Y		Y	
4. Comprehensive literature search	Partial Y	No search of reference lists, no search of trial registers	Partial Y	No search of reference lists mentioned
5. Duplicate study selection	?	Unclear	Y	
6. Duplicate data extraction	Y		Y	
7. List of excluded studies and rationale	N		Y	
8. Characteristics of included studies provided	Y		Y	
9. Assessment of risk of bias	Y		Y	
10. Sources of funding reported	N	funding source of included studies not reported	Y	



	Tian 2018 ⁷⁵		Chan 2015 ⁷⁶	
	Score	Rationale/comment	score	Rationale/comment
11. Appropriate methods to combine findings	Y		Y	
12. Assessment of impact RoB in included studies on results MA	Y		Y	
13. RoB assessment used in interpretation of results and in conclusions	Y		Y	
14. Explanation for and discussion of any observed heterogeneity	Y		Y	
15. Adequate investigation of publication bias and its impact on the results	Y		Y	
16. Potential sources of conflict of interest reported	Y		Y	

Appendix 4.3.3. Search strategy

Appendix 4.3.3.1. Cochrane library of systematic reviews

Date	28/05/2020 19:18:08		
Database	Cochrane@Wiley.com		
Search strategy			
#1	[mh ^"Head and Neck Neoplasms"]		2076
#2	[mh ^"Squamous Cell Carcinoma of Head and Neck"]		159
#3	#1 or #2		2107
#4	((head or neck) NEAR/3 (("squamous cell" NEAR/3 carcinom*) or scc)):ab,ti		1941
#5	hnscc:ab,ti		576
#6	((oral or laryngeal or oropharyngeal) NEAR/3 (("squamous cell" NEAR/3 carcinom*) or scc)):ab,ti		512
#7	#4 or #5 or #6		2489
#8	#2 not #7		44
#9	#3 or #7		3974
#10	[mh ^"cetuximab"]		560
#11	cetuximab:ab,ti		2023
#12	Erbitux:ab,ti		216
#13	C225:ab,ti		26
#14	C-225:ab,ti		3



#15	PQX0D8J21J:ab,ti	0
#16	IMC225:ab,ti	0
#17	CMAB-009:ab,ti	0
#18	CMAB009:ab,ti	7
#19	ABP-494:ab,ti	0
#20	ABP494:ab,ti	0
#21	"205923-56-4":ab,ti	45
#22	#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21	2058
#23	#10 or #22	2108
#24	#9 and #23	474
#25	[mh ^"Epidermal Growth Factor"/AI]	5
#26	(egfr NEAR/5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)):ab,ti	1916
#27	#25 or #26	1920
#28	#9 and #27	117
#29	[mh "Antibodies, Monoclonal"]	12645
#30	(monoclonal NEAR/3 antibod*):ab,ti	8751
#31	#29 or #30	18999
#32	#9 and #31	256
#33	((("new class" or "new classes" or innovative or target*) NEAR/3 (drug? or therapy or therapies or therapeutic* or treatment? or chemotherap*)):ab,ti	11772
#34	#9 and #33	62
#35	#24 or #28 or #32 or #34	645
Comments		

Appendix 4.3.3.2. Medline + PreMedline

Date	May 22, 2020	
Database	Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946 to May 22, 2020>	
Search strategy		
1	"Head and Neck Neoplasms"/	54130
2	"Squamous Cell Carcinoma of Head and Neck"/	5210
3	1 or 2	54788
4	((head or neck) adj3 (squamous cell carcinom* or scc)).ab,ti,kf.	15998
5	hnscc.ab,ti,kf.	8065
6	((oral or laryngeal or oropharyngeal) adj3 (squamous cell carcinom* or scc)).ab,ti,kf.	17584
7	4 or 5 or 6	33001
8	2 not 7	1335
9	3 or 7	74799



10	cetuximab/	4414
11	cetuximab.ab,ti,kf,rn.	7282
12	Erbitux.ab,ti,kf,rn.	345
13	C225.ab,ti,kf,rn.	477
14	C-225.ab,ti,kf,rn.	76
15	PQX0D8J21J.ab,ti,kf,rn.	4415
16	IMC225.ab,ti,kf,rn.	1
17	CMAB-009.ab,ti,kf,rn.	0
18	CMAB009.ab,ti,kf,rn.	3
19	ABP-494.ab,ti,kf,rn.	0
20	ABP494.ab,ti,kf,rn.	0
21	205923-56-4.ab,ti,kf,rn.	1
22	11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21	7656
23	10 or 22	7656
24	9 and 23	1455
25	Epidermal Growth Factor/ai	570
26	(egfr adj5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)).ab,ti,kf.	21833
27	25 or 26	22283
28	9 and 27	1157
29	exp Antibodies, Monoclonal/	234159
30	(monoclonal adj3 antibod*).ab,ti,kf.	195953
31	29 or 30	318585
32	9 and 31	2446
33	((new class* or innovative or target*) adj3 (drug? or therapy or therapies or therapeutic* or treatment? or chemotherap*)).ab,ti,kf.	326596
34	9 and 33	3245
35	24 or 28 or 32 or 34	5958
36	((systematic review or systematic literature review or systematic scoping review or systematic narrative review or systematic qualitative review or systematic evidence review or systematic quantitative review or systematic meta-review or systematic critical review or systematic mixed studies review or systematic mapping review or systematic cochrane review or "systematic search and review" or systematic integrative review).ti. not comment.pt. not (protocol or protocols).ti. not medline.st.) or (Cochrane Database Syst Rev.ja. and review.pt.) or systematic review.pt.	156567
37	meta-analys*.ti.	106988
38	meta-analysis.pt.	114990
39	exp Technology Assessment, Biomedical/	11037
40	health technology assessment.ti,kf.	1908
41	HtA.ti,kf.	590
42	36 or 37 or 38 or 39 or 40 or 41	249374



43	35 and 42	67
Comments		

Appendix 4.4. Economic literature

Appendix 4.4.1. Search economic literature (HTA reports)

The search strategy in CRD's HTA database identified 125 references (Table 59). In a first round, 4 references were selected based on a review of title, keywords and abstract. The 121 remaining references were excluded for the following reasons: intervention (117) and design (4). In a second round, the full text of the four selected references was reviewed. Two references were excluded (design (1), link to two other relevant reports (1)). Two references were retained. These references are indicated in Table 27 with an asterix (*).

Furthermore, in May 2020, the website of the National Institute for Health Research (NIHR) was searched for relevant reports. The following search term was used: cetuximab (23 hits, 5 with a focus on NSCLC, 4 not previously identified).

Finally, also in May 2020, the website of the National Institute for Health and Care Excellence (NICE) was searched. The following search term was used: cetuximab (24 hits, 3 relevant Technology Assessments (TAs), 2 not previously identified).

An overview of the identified references is provided in Table 60.

Table 59 – Search strategy and results for CRD: HTA

Date			
Date covered	All		
Search Strategy	1	MeSH DESCRIPTOR Head and Neck Neoplasms EXPLODE ALL TREES	882
	2	* IN HTA	17351
	3	#1 AND #2	125 references
Note	/		

**Table 60 – Head and neck cancer – Identified HTA reports for the selected drugs**

Selected reports	
Cetuximab	
•	NICE, TA473. August 2017. Cetuximab for treating recurrent or metastatic squamous cell cancer of the head and neck. ^β
	○ Head and neck cancer (squamous cell carcinoma) cetuximab (review of TA 172) [ID1016] → no link to full report, only to NICE TA473. ^α
•	NICE, TA145. June 2008. Cetuximab for the treatment of locally advanced squamous cell cancer of the head and neck. ^β
	○ Griffin S, Walker S, Sculpher M, White S, Erhorn S, Brent S, Dyker A, Ferrie L, Gilfillan C, Horsley W, Macfarlane K, Thomas S. Cetuximab plus radiotherapy for the treatment of locally advanced squamous cell carcinoma of the head and neck. CHE, University of York & NHS Northern and Yorkshire RDTC. 2009.* ^α
	○ Griffin S, Walker S, Sculpher M, White S, Erhorn S, Brent S, et al. Cetuximab plus radiotherapy for the treatment of locally advanced squamous cell carcinoma of the head and neck. Health Technol Assess 2009;13(Suppl 1 Article 8). ^α
Excluded reports	
•	NICE, TA172. June 2009. Cetuximab for the treatment of recurrent and/or metastatic squamous cell cancer of the head and neck.* ^β
	○ Greenhalgh J, Bagust A, Boland A, Fleeman N, McLead C, Dundar Y, Proudlove C and Shaw R. Cetuximab for metastatic and/or recurrent squamous cell carcinoma of the head and neck (SCCHN): A Single Technology Appraisal. LRiG, The University of Liverpool, 2008. ^α
	○ Greenhalgh J, Bagust A, Boland A, Fleeman N, McLeod C, Dundar Y, et al. Cetuximab for the treatment of recurrent and/or metastatic squamous cell carcinoma of the head and neck. Health Technol Assess 2009;13(Suppl 3 Article 8). ^α
	○ This guidance has been updated and replaced by NICE technology appraisal guidance 473.

* These references were identified in CRD's HTA database. ^α References identified on NIHR's website. ^β References identified on NICE's website.



Appendix 4.4.2. Results economic literature (HTA reports)

Appendix 4.4.2.1. NICE, TA473 (2017): cetuximab

- QoL:
 - “The committee noted that after consultation, the company had estimated utilities based on quality-of-life data from the oral cavity cancer subgroup of the EXTREME trial, rather than the full trial population. It had, however, noted in the first committee meeting that the questionnaire used did not include a measure of adverse events. The data were converted to utilities using an algorithm. The company used the same utility estimates for both treatment arms in the post-progression health state, but different utility estimates for both treatment arms in the pre-progression health state. The ERG considered that the data from the EXTREME trial did not allow for reliable utility estimates for the 2 treatment arms. It stated that there was no justification for not using a common utility estimate for the pre-progression health state. The committee heard from the company that its quality-of-life questionnaire, on which its utility estimates were based, was not mandatory and was most likely to have omitted the most sick patients. When the ERG used a common utility value for both treatment arms, the ICER increased. The committee noted that, contrary to the implications of the company's utility values, adverse events were more frequent for patients having cetuximab than for those having standard therapy in the oral cavity subgroup. The committee concluded that the pre-progression utility value used by the company may have resulted in an ICER for cetuximab that was too low, and that it preferred the approach taken by the ERG.”⁷⁷
- Results:
 - No details on the IC, IE or ICER are presented: “To protect the level of discount, the ICERs including the patient access scheme were considered commercial in confidence and cannot be presented here”⁷⁷
 - “The incremental cost-effectiveness ratios (ICERs) presented by the company for the base-case and pre-planned subgroup analyses were substantially higher than those normally considered to be an acceptable use of NHS resources.”⁷⁷
 - “a commercial access agreement was negotiated with NHS England. This arrangement was sufficient to reduce the ICER so that cetuximab could be recommended as a cost-effective use of NHS resources for the treatment of cancer starting in the oral cavity.”⁷⁷
- Uncertainty/sensitivity:
 - “The committee reviewed the additional cost-effectiveness analyses submitted by the company for additional subgroups based on age (younger than 65 years) and KPS (KPS of 90 or more and KPS of 80 or more). It was aware that the preplanned subgroup analyses in the clinical study presented results for patients with a KPS of 80 or more (rather than 90 or more) and for patients who were younger than 65 years, but subgroups combining age and KPS were not included. The committee noted the concerns raised by the ERG about the validity of the modelled overall survival gains for the additional subgroup and whether the number of patients included was sufficient to provide robust evidence of efficacy. It was therefore not persuaded that the evidence provided by the company supported the predicted life years gained for the combined age and KPS subgroup. On this basis, the committee concluded that the estimates of cost effectiveness for the subgroup of patients who were younger than 65 years with a KPS of 90 or more could not be considered reliable.”⁷⁷



- “The committee noted that the company had based its submission on a subgroup of patients with oral cavity cancer. It also noted that, in its earlier deliberations, it had not been persuaded that the estimate from the subgroup was sufficiently reliable for use in the economic model. ...
- However, the committee noted that the subgroup was small (n=88) compared with the whole trial population (n=442), adding to the uncertainty inherent when considering estimates of effectiveness based on subgroup data. ...
- The committee concluded that it was possible that cetuximab might have greater benefits in oral cavity tumours but that the evidence in support of this was limited.”⁷⁷
- Conclusions:
 - “The committee concluded that there remained considerable uncertainty around the results of the company's analyses, and that it was plausible that the true cost-effectiveness estimate for cetuximab plus platinum-based chemotherapy would be even higher than that presented by the company.”⁷⁷
 - “The committee discussed the most plausible incremental cost-effectiveness ratio (ICER) for cetuximab plus platinum-based chemotherapy compared with platinum-based chemotherapy alone. To protect the level of discount, the ICERs including the patient access scheme were considered commercial in confidence and cannot be presented here. Based on the clinical- and cost-effectiveness analyses, including the discount in the revised patient access scheme, the committee considered that the most plausible ICER for cetuximab plus platinum-based chemotherapy compared with platinum-based therapy alone was above the range that would normally be considered cost effective if the end-of-life criteria apply and so could not recommend it for routine use. A subsequently negotiated commercial access agreement reduced this ICER to the extent that cetuximab could be recommended as a cost-effective use of NHS resources for the treatment of cancer starting in the oral cavity.”⁷⁷
- (Confidential) prices:
 - “The company focused on the subgroup of patients with oral cavity cancer from the EXTREME trial, and cost-effectiveness analyses using a patient access scheme that provides cetuximab at a reduced cost. After consultation, the company submitted additional 5-year follow-up data for this subgroup of patients, and a revised patient access scheme with a further discount. The level of discount is commercial in confidence.”⁷⁷



Reference Costs (list prices & remarks)	Population, Intervention & comparator IC, IE and ICERs	Remarks on use of generic utility instrument (e.g. EQ- 5D) to measure impact on QoL in economic evaluations	Most uncertain variables or important variables in sensitivity analysis
Cetuximab			
NICE, TA473 (2017) ⁷⁷	<p>Patients with recurrent or metastatic squamous cell cancer of the head and neck. Cancer Drugs Fund reconsideration: included only the oral cavity cancer subgroup. Cetuximab plus platinum-based chemotherapy compared with platinum-based chemotherapy alone.</p>		
<p>List prices, negotiated discounts are hidden. List price of cetuximab is £178.10 for a 5mg/ml 20-ml vial and £890.50 for a 5 mg/ml 100-ml vial.</p>	<p>The incremental cost-effectiveness ratios (ICERs) presented by the company for the base-case and pre-planned subgroup analyses were substantially higher than those normally considered to be an acceptable use of NHS resources.</p> <p>The most plausible ICER for cetuximab plus platinum-based chemotherapy compared with platinum-based therapy alone was above the range that would normally be considered cost effective if the end-of-life criteria apply. In addition, the uncertainties around this estimate, principally arising from the reliability of the estimation of clinical effectiveness in the subgroup, were too great to allow it to recommended cetuximab for routine use.</p> <p>A commercial access agreement was negotiated with NHS England. This arrangement was sufficient to reduce the ICER so that cetuximab could be recommended as a cost-effective use of NHS resources for the treatment of cancer starting in the oral cavity.</p> <p>To protect the level of discount, the ICERs including the patient access scheme were considered commercial in confidence and cannot be presented here.</p>	No generic utility instrument is used in the underlying EXTREME trial.	Efficacy data



Appendix 4.4.2.2. NICE, TA145 (2008): cetuximab

- QoL:
 - “Locoregional control can have a significant effect on health-related quality of life as the majority of these cancers arise in the airway and mouth leading to difficulty swallowing etc. The submission states that disease-specific health-related quality of Life (HRQoL) instruments (EQ5D, QLQC-30 with Head & Neck module) were used to collect HRQoL data. However, there is no reference to HRQoL assessment in the published paper, although details of HRQoL assessment are provided in the clinical trial protocol.”⁷⁸⁷⁹
 - “The submission states that a HRQoL questionnaire (QLQ)C30/H&N35 was completed at randomisation, before starting the fourth week of radiotherapy, eight weeks following the completion of radiotherapy, and at the next two 4-month follow-up evaluations. The published paper makes no reference to a HRQoL questionnaire, although details of HRQoL assessment are provided in the clinical trial protocol.”⁷⁸ To date any HRQoL findings from the Bonner et al study remain unpublished.”⁸⁰⁷⁹
 - “HRQoL in terms of utility values for the health states was estimated from a study of oncology nurses in the UK using the EQ-5D. Fifty nursing staff from oncology centres around the UK were recruited for the study and screened to ensure they were suitable to act as proxies for the patients The nurses were asked to complete the EQ-5D’s 5-dimensional classification system⁸¹ for each health state which was described to them to reflect their judgement about a patient’s HRQoL when experiencing each health state. Utility values were derived based on the ‘UK social values’.”⁸²
 - The study aimed to estimate utility values for a series of health states describing major side effects and post-treatment outcomes that may be experienced by patients undergoing treatment for stage III and IV head and neck cancer. Seven health states for the acute phase were identified which described different grades of the acute toxicities (these were based on the National Cancer Institute common toxicity criteria⁸³). Two health states were identified that described toxicities post treatment; however, these were then excluded from the economic model.”⁷⁹
 - “The base-case model includes 9 health states which have been valued using the EQ-5D instrument using oncology nurses as a proxy for patients. The ERG has concerns that these health states might not fully capture the HRQoL experience of patients.”⁷⁹
 - “it is reported in the manufacturer’s submission that, at least with respect to the acute health states, these only cover 68% of adverse events experienced and do not take account of patients having more than one adverse event at a time.”⁷⁹ ... “this implies that the adverse events are utility independent of one another.
 - been excluded.”⁷⁹
- Results:
 - “In the base-case analysis, treatment with cetuximab plus radiotherapy instead of radiotherapy alone increased costs by approximately £6,626 and QALYs by 1.6 per patient, giving an ICER of £6,390 per additional QALY.”⁷⁹
 - “The manufacturer’s analysis gave ICERs for cetuximab in combination with radiotherapy versus radiotherapy alone of £13,151 and £4,467 per additional QALY gained for patients with Karnofsky performance-status scores of 100% and 90%, respectively. For patients with Karnofsky performance-status scores of 70%, radiotherapy alone dominated cetuximab in combination with radiotherapy (that is, radiotherapy alone was more effective in terms of QALYs gained and was less expensive). For patients with Karnofsky performance-status scores of 80% and less than 70%, the



manufacturer reported ICERs for cetuximab in combination with radiotherapy versus radiotherapy alone of £58,200 and £37,000 per additional QALY gained, respectively.”⁸⁴

- Uncertainty/sensitivity:
 - “the ERG identified a series of issues and uncertainties about the methods for extrapolation of the trial data, assessment of health-related quality of life (HRQoL), and estimation of resource use and costs. The ERG concluded that the methods used were probably appropriate but was unable to determine, in the majority of cases, the likely influence of using alternative methods on the results of the economic model. However, the ERG concluded that altering the method of extrapolation would be unlikely to cause the ICER to increase to above £20,000.”⁸⁴
 - “the cost-effectiveness estimates might not be directly applicable to the population specified in the manufacturer's decision problem (that is, patients for whom chemoradiotherapy is considered inappropriate). This was because the clinical study on which the economic analysis was based included a substantial proportion of patients for whom chemoradiotherapy would be considered suitable.”⁸⁴
 - “Although the majority of the issues identified by the ERG could be clarified by additional research, it is worth stressing that it would require large changes in parameter values to result in cetuximab plus radiotherapy not being cost-effective.”⁷⁹
- Conclusions:
 - “The Committee considered the ICERs presented by the manufacturer for each Karnofsky performance-status score subgroup separately. It noted that the ICERs for patients with a score of 90% or greater were favourable and similar to the overall estimate in the base case. The Committee was persuaded that although there was uncertainty about the number of patients within the subgroups who would have met the criteria to receive chemoradiotherapy, cetuximab in combination with radiotherapy is cost effective for patients with a Karnofsky performance-status score of 90% or greater and for whom chemoradiotherapy is not an option. However, for those with a Karnofsky performance-status score of 80% or less, the HR for survival did not favour cetuximab and therefore the ICERs were unfavourable. The Committee therefore was unable to recommend cetuximab for people with low performance status.”⁸⁴
 - “Cetuximab in combination with radiotherapy is recommended as a treatment option only for patients with locally advanced squamous cell cancer of the head and neck whose Karnofsky performance-status score is 90% or greater and for whom all forms of platinum-based chemoradiotherapy treatment are contraindicated.”⁸⁴
- (Confidential) prices:
 - No reference is made to confidential discounts.



Reference Costs (list prices & remarks)	Population, Intervention & comparator IC, IE and ICERs					Remarks on use of generic utility instrument (e.g. EQ- 5D) to measure impact on QoL in economic evaluations	Most uncertain variables or important variables in sensitivity analysis	
Cetuximab								
NICE, TA145 (2008) ⁸⁴ Griffin et al. (2009)	Patients with locally advanced squamous-cell carcinoma of the head and neck (LA SCCHN) for which chemoradiotherapy is not considered an appropriate option. Cetuximab plus radiotherapy compared with radiotherapy alone.							
List prices: the acquisition cost of cetuximab is £136.50 for a 5-mg/ml, 20-ml vial (excluding VAT).	Results of the incremental analysis (with list prices):					No generic utility instrument was used in the underlying trial. A separate study among nursing staff from oncology centres has been set up to estimate utilities for health states, using the EQ-5D instrument.	extrapolation of the trial data, assessment of health-related quality of life (HRQoL), and estimation of resource use and costs.	
		Costs	IC	QALYs	IE			ICER
	Radiotherapy	£7195		2.8163				
	Cet.+ RT	£13,820	£6,626	3.8532	1.26			£6,390
	Results according to the Karnofsky performance-status scores:							
	-	100%: £13,151						
	-	90%: £4,467						
	-	80%: £58,200						
	-	Less than 70%: £37,000						

Cet.+ RT: Cetuximab plus radiotherapy.



APPENDIX 5. MELANOMA

Appendix 5.1. BCR data

Appendix 5.1.1. Descriptive statistics

Appendix 5.1.1.1. Malignant melanoma of the skin, exploration

Table 61 – Malignant melanoma of the skin (2004-2017): Frequency table of patient and tumour characteristics

Characteristic	Total	Incidence period		
		2004-2008	2009-2013	2014-2017
Overall	31,657	8,222	11,311	12,124
Gender				
Male	13,085 (41.3)	3,306 (40.2)	4,693 (41.5)	5,086 (41.9)
Female	18,572 (58.7)	4,916 (59.8)	6,618 (58.5)	7,038 (58.1)
Age at diagnosis (year)				
<50 years	10,573 (33.4)	3,060 (37.2)	3,912 (34.6)	3,601 (29.7)
50-59 years	6,027 (19.0)	1,480 (18.0)	2,093 (18.5)	2,454 (20.2)
60-69 years	5,996 (18.9)	1,421 (17.3)	2,067 (18.3)	2,508 (20.7)
70-79 years	5,350 (16.9)	1,389 (16.9)	1,923 (17.0)	2,038 (16.8)
80+ years	3,711 (11.7)	872 (10.6)	1,316 (11.6)	1,523 (12.6)
WHO - Performance Status				
0 – Asymptomatic	10,261 (32.4)	2,339 (28.4)	3,305 (29.2)	4,617 (38.1)
1 – Symptomatic but completely ambulatory	6,778 (21.4)	1,079 (13.1)	2,884 (25.5)	2,815 (23.2)
2 – Symptomatic, <50% in bed during the day	256 (0.8)	109 (1.3)	71 (0.6)	76 (0.6)
3 – Symptomatic, >50% in bed, but not bedbound	60 (0.2)	18 (0.2)	21 (0.2)	21 (0.2)
4 – Bedbound	99 (0.3)	6 (0.1)	6 (0.1)	87 (0.7)
Not reported	14,203 (44.9)	4,671 (56.8)	5,024 (44.4)	4,508 (37.2)
Combined stage				



is	13 (0.0)	0 (0.0)	0 (0.0)	13 (0.1)
I	19,943 (63.0)	4,460 (54.2)	6,712 (59.3)	8,771 (72.3)
II	4,785 (15.1)	1,280 (15.6)	1,687 (14.9)	1,818 (15.0)
III	1,787 (5.6)	437 (5.3)	639 (5.6)	711 (5.9)
IV	619 (2.0)	223 (2.7)	216 (1.9)	180 (1.5)
X	3,734 (11.8)	1,645 (20.0)	1,782 (15.8)	307 (2.5)
NA	776 (2.5)	177 (2.2)	275 (2.4)	324 (2.7)

Note: the values between parentheses are column percentages.

Table 62 – Malignant melanoma of the skin (2004-2017): Frequency table of patient and tumour characteristics (cut-off point: 2011)

Characteristic	Incidence period		
	Total	2004-2010	2012-2017
Overall	29 474	12 252	17 222
Gender			
Male	12 149 (41.2)	4 903 (40.0)	7 246 (42.1)
Female	17 325 (58.8)	7 349 (60.0)	9 976 (57.9)
Age at diagnosis (year)			
<50 years	9 810 (33.3)	4 520 (36.9)	5 290 (30.7)
50-59 years	5 650 (19.2)	2 197 (17.9)	3 453 (20.0)
60-69 years	5 583 (18.9)	2 122 (17.3)	3 461 (20.1)
70-79 years	4 992 (16.9)	2 088 (17.0)	2 904 (16.9)
80+ years	3 439 (11.7)	1325 (10.8)	2 114 (12.3)
WHO - Performance Status			
0 – Asymptomatic	9 650 (32.7)	3 536 (28.9)	6 114 (35.5)
1 – Symptomatic but completely ambulatory	6 125 (20.8)	2 048 (16.7)	4 077 (23.7)
2 – Symptomatic, <50% in bed during the day	242 (0.8)	132 (1.1)	110 (0.6)
3 – Symptomatic, >50% in bed, but not bedbound	52 (0.2)	23 (0.2)	29 (0.2)
4 – Bedbound	96 (0.3)	7 (0.1)	89 (0.5)



Not reported	13 309 (45.2)	6 506 (53.1)	6 803 (39.5)
Combined stage			
is	13 (0.0)	0 (0.0)	13 (0.1)
I	18 757 (63.6)	6 769 (55.2)	11 988 (69.6)
II	4 442 (15.1)	1 868 (15.2)	2 584 (15.0)
III	1 666 (5.7)	652 (5.3)	1 014 (5.9)
IV	576 (2.0)	316 (2.6)	260 (1.5)
X	3 281 (11.1)	2 364 (19.3)	917 (5.3)
NA	728 (2.5)	283 (2.3)	446 (2.6)

Note: the values between parentheses are column percentages.


Table 63 – Malignant melanoma of the skin (2004-2017), Combined stage I, Frequency table of patient and tumour characteristics

Characteristic	Total	Incidence period		
		2004-2008	2009-2013	2014-2017
Overall	19,943	4,460	6,712	8,771
Gender				
Male	7,694 (38.6)	1,611 (36.1)	2,604 (38.8)	3,479 (39.7)
Female	12,249 (61.4)	2,849 (63.9)	4,108 (61.2)	5,292 (60.3)
Age at diagnosis (year)				
<50 years	7,670 (38.5)	1,974 (44.3)	2,735 (40.7)	2,961 (33.8)
50-59 years	4,117 (20.6)	874 (19.6)	1,319 (19.7)	1,924 (21.9)
60-69 years	3,791 (19.0)	740 (16.6)	1,211 (18.0)	1,840 (21.0)
70-79 years	2,909 (14.6)	615 (13.8)	960 (14.3)	1,334 (15.2)
80+ years	1,456 (7.3)	257 (5.8)	487 (7.3)	712 (8.1)
WHO - Performance Status				
0 – Asymptomatic	6,949 (34.8)	1,444 (32.4)	2,132 (31.8)	3,373 (38.5)
1 – Symptomatic but completely ambulatory	3,837 (19.2)	495 (11.1)	1,570 (23.4)	1,772 (20.2)
2 – Symptomatic, <50% in bed during the day	67 (0.3)	43 (1.0)	7 (0.1)	17 (0.2)
3 – Symptomatic, >50% in bed, but not bedbound	3 (0.0)	0 (0.0)	2 (0.0)	1 (0.0)
4 – Bedbound	59 (0.3)	0 (0.0)	2 (0.0)	57 (0.6)
Not reported	9,028 (45.3)	2,478 (55.6)	2,999 (44.7)	3,551 (40.5)

Note: the values between parentheses are column percentages.

Table 64 – Malignant melanoma of the skin (2004-2017), Combined stage I, Frequency table of patient and tumour characteristics (cut-off point: 2011)

Characteristic	Total	Incidence period	
		2004-2010	2012-2017
Overall	18 757	6 769	11 988
Gender			
Male	7 219 (38.5)	2 456 (36.3)	4 763 (39.7)



Female	11 538 (61.5)	4 313 (63.7)	7 225 (60.3)
Age at diagnosis (year)			
<50 years	7 171 (38.2)	2 983 (44.1)	4 188 (34.9)
50-59 years	3 895 (20.8)	1 293 (19.1)	2 602 (21.7)
60-69 years	3 589 (19.1)	1 157 (17.1)	2 432 (20.3)
70-79 years	2 741 (14.6)	933 (13.8)	1 808 (15.1)
80+ years	1 361 (7.3)	403 (6.0)	958 (8.0)
WHO - Performance Status			
0 – Asymptomatic	6 575 (35.1)	2 232 (33.0)	4 343 (36.2)
1 – Symptomatic but completely ambulatory	3 507 (18.7)	984 (14.5)	2 523 (21.0)
2 – Symptomatic, <50% in bed during the day	65 (0.3)	46 (0.7)	19 (0.2)
3 – Symptomatic, >50% in bed, but not bedbound	1 (0.0)	0 (0.0)	1 (0.0)
4 – Bedbound	58 (0.3)	1 (0.0)	57 (0.5)
Not reported	8 551 (45.6)	3 506 (51.8)	5 045 (42.1)

Note: the values between parentheses are column percentages.


Table 65 – Malignant melanoma of the skin (2004-2017), Combined stage II, Frequency table of patient and tumour characteristics

Characteristic	Total	Incidence period		
		2004-2008	2009-2013	2014-2017
Overall	4,785	1,280	1,687	1,818
Gender				
Male	2,198 (45.9)	605 (47.3)	771 (45.7)	822 (45.2)
Female	2,587 (54.1)	675 (52.7)	916 (54.3)	996 (54.8)
Age at diagnosis (year)				
<50 years	791 (16.5)	244 (19.1)	267 (15.8)	280 (15.4)
50-59 years	675 (14.1)	177 (13.8)	245 (14.5)	253 (13.9)
60-69 years	905 (18.9)	230 (18.0)	323 (19.1)	352 (19.4)
70-79 years	1,109 (23.2)	323 (25.2)	412 (24.4)	374 (20.6)
80+ years	1,305 (27.3)	306 (23.9)	440 (26.1)	559 (30.7)
WHO - Performance Status				
0 – Asymptomatic	1,624 (33.9)	407 (31.8)	542 (32.1)	675 (37.1)
1 – Symptomatic but completely ambulatory	1,352 (28.3)	228 (17.8)	556 (33.0)	568 (31.2)
2 – Symptomatic, <50% in bed during the day	53 (1.1)	25 (2.0)	13 (0.8)	15 (0.8)
3 – Symptomatic, >50% in bed, but not bedbound	15 (0.3)	4 (0.3)	3 (0.2)	8 (0.4)
4 – Bedbound	20 (0.4)	1 (0.1)	0 (0.0)	19 (1.0)
Not reported	1,721 (36.0)	615 (48.0)	573 (34.0)	533 (29.3)

Note: the values between parentheses are column percentages.



Table 66 – Malignant melanoma of the skin (2004-2017), Combined stage II, Frequency table of patient and tumour characteristics (cut-off point: 2011)

Characteristic	Total	Incidence period	
		2004-2010	2012-2017
Overall	4 452	1 868	2 584
Gender			
Male	2 047 (46.0)	859 (46.0)	1 188 (46.0)
Female	2 405 (54.0)	1 009 (54.0)	1 396 (54.0)
Age at diagnosis (year)			
<50 years	734 (16.5)	343 (18.4)	391 (15.1)
50-59 years	635 (14.3)	262 (14.0)	373 (14.4)
60-69 years	833 (18.7)	327 (17.5)	506 (19.6)
70-79 years	1 031 (23.2)	492 (26.3)	539 (20.9)
80+ years	1 219 (27.4)	444 (23.8)	775 (30.0)
WHO - Performance Status			
0 – Asymptomatic	1 515 (34.0)	594 (31.8)	921 (35.6)
1 – Symptomatic but completely ambulatory	1 223 (27.5)	414 (22.2)	809 (31.3)
2 – Symptomatic, <50% in bed during the day	50 (1.1)	32 (1.7)	18 (0.7)
3 – Symptomatic, >50% in bed, but not bedbound	13 (0.3)	4 (0.2)	9 (0.3)
4 – Bedbound	20 (0.4)	1 (0.1)	19 (0.7)
Not reported	1 631 (36.6)	823 (44.1)	808 (31.3)

Note: the values between parentheses are column percentages.


Table 67 – Malignant melanoma of the skin (2004-2017), Combined stage III, Frequency table of patient and tumour characteristics

Characteristic	Total	Incidence period		
		2004-2008	2009-2013	2014-2017
Overall	1,787	437	639	711
Gender				
Male	893 (50.0)	221 (50.6)	319 (49.9)	353 (49.6)
Female	894 (50.0)	216 (49.4)	320 (50.1)	358 (50.4)
Age at diagnosis (year)				
<50 years	540 (30.2)	163 (37.3)	188 (29.4)	189 (26.6)
50-59 years	363 (20.3)	86 (19.7)	139 (21.8)	138 (19.4)
60-69 years	370 (20.7)	88 (20.1)	125 (19.6)	157 (22.1)
70-79 years	342 (19.1)	58 (13.3)	128 (20.0)	156 (21.9)
80+ years	172 (9.6)	42 (9.6)	59 (9.2)	71 (10.0)
WHO - Performance Status				
0 – Asymptomatic	890 (49.8)	215 (49.2)	297 (46.5)	378 (53.2)
1 – Symptomatic but completely ambulatory	525 (29.4)	102 (23.3)	221 (34.6)	202 (28.4)
2 – Symptomatic, <50% in bed during the day	17 (1.0)	4 (0.9)	5 (0.8)	8 (1.1)
3 – Symptomatic, >50% in bed, but not bedbound	3 (0.2)	1 (0.2)	1 (0.2)	1 (0.1)
4 – Bedbound	2 (0.1)	0 (0.0)	0 (0.0)	2 (0.3)
Not reported	350 (19.6)	115 (26.3)	115 (18.0)	120 (16.9)

Note: the values between parentheses are column percentages.



Table 68 – Malignant melanoma of the skin (2004-2017), Combined stage III, Frequency table of patient and tumour characteristics (cut-off point: 2011)

Characteristic	Total	Incidence period	
		2004-2010	2012-2017
Overall	1 666	652	1 014
Gender			
Male	830 (49.8)	327 (50.2)	503 (49.6)
Female	836 (50.2)	325 (49.8)	511 (50.4)
Age at diagnosis (year)			
<50 years	502 (30.1)	229 (35.1)	273 (26.9)
50-59 years	339 (20.3)	131 (20.1)	208 (20.5)
60-69 years	343 (20.6)	124 (19.0)	219 (21.6)
70-79 years	320 (19.2)	102 (15.6)	218 (21.5)
80+ years	162 (9.7)	66 (10.1)	96 (9.5)
WHO - Performance Status			
0 – Asymptomatic	840 (50.4)	307 (47.1)	533 (52.6)
1 – Symptomatic but completely ambulatory	474 (28.5)	182 (27.9)	292 (28.8)
2 – Symptomatic, <50% in bed during the day	17 (1.0)	6 (0.9)	11 (1.1)
3 – Symptomatic, >50% in bed, but not bedbound	3 (0.2)	1 (0.2)	2 (0.2)
4 – Bedbound	2 (0.1)	0 (0.0)	0 (0.0)
Not reported	330 (19.8)	156 (23.9)	174 (17.2)

Note: the values between parentheses are column percentages.


Table 69 – Malignant melanoma of the skin (2004-2017), Combined stage IV, Frequency table of patient and tumour characteristics

Characteristic	Total	Incidence period		
		2004-2008	2009-2013	2014-2017
Overall	619	223	216	180
Gender				
Male	356 (57.5)	116 (52.0)	128 (59.3)	112 (62.2)
Female	263 (42.5)	107 (48.0)	88 (40.7)	68 (37.8)
Age at diagnosis (year)				
<50 years	128 (20.7)	54 (24.2)	52 (24.1)	22 (12.2)
50-59 years	112 (18.1)	40 (17.9)	36 (16.7)	36 (20.0)
60-69 years	121 (19.5)	49 (22.0)	37 (17.1)	35 (19.4)
70-79 years	144 (23.3)	56 (25.1)	51 (23.6)	37 (20.6)
80+ years	114 (18.4)	24 (10.8)	40 (18.5)	50 (27.8)
WHO - Performance Status				
0 – Asymptomatic	159 (25.7)	67 (30.0)	39 (18.1)	53 (29.4)
1 – Symptomatic but completely ambulatory	265 (42.8)	80 (35.9)	111 (51.4)	74 (41.1)
2 – Symptomatic, <50% in bed during the day	46 (7.4)	15 (6.7)	17 (7.9)	14 (7.8)
3 – Symptomatic, >50% in bed, but not bedbound	22 (3.6)	8 (3.6)	8 (3.7)	6 (3.3)
4 – Bedbound	3 (0.5)	1 (0.4)	1 (0.5)	1 (0.6)
Not reported	124 (20.0)	52 (23.3)	40 (18.5)	32 (17.8)

Note: the values between parentheses are column percentages.



Table 70 – Malignant melanoma of the skin (2004-2017), Combined stage IV, Frequency table of patient and tumour characteristics (cut-off point: 2011)

Characteristic	Total	Incidence period	
		2004-2010	2012-2017
Overall	576	316	260
Gender			
Male	328 (56.9)	170 (53.8)	158 (60.8)
Female	248 (43.1)	146 (46.2)	102 (39.2)
Age at diagnosis (year)			
<50 years	121 (21.0)	76 (24.1)	45 (17.3)
50-59 years	105 (18.2)	54 (17.1)	51 (19.6)
60-69 years	109 (18.9)	61 (19.3)	48 (18.5)
70-79 years	135 (23.4)	81 (25.6)	54 (20.8)
80+ years	106 (18.4)	44 (13.9)	62 (23.8)
WHO - Performance Status			
0 – Asymptomatic	153 (26.6)	85 (26.9)	68 (26.2)
1 – Symptomatic but completely ambulatory	243 (42.2)	126 (39.9)	117 (45.0)
2 – Symptomatic, <50% in bed during the day	42 (7.3)	20 (6.3)	22 (8.5)
3 – Symptomatic, >50% in bed, but not bedbound	20 (3.5)	11 (3.5)	9 (3.5)
4 – Bedbound	3 (0.5)	1 (0.3)	2 (0.8)
Not reported	115 (20.0)	73 (23.1)	42 (16.2)

Note: the values between parentheses are column percentages.


Table 71 – Malignant melanoma of the skin (2004-2017), Combined stage NA, Frequency table of patient and tumour characteristics

Characteristic	Total	Incidence period		
		2004-2008	2009-2013	2014-2017
Overall	776	177	275	324
Gender				
Male	436 (56.2)	102 (57.6)	155 (56.4)	179 (55.2)
Female	340 (43.8)	75 (42.4)	120 (43.6)	145 (44.8)
Age at diagnosis (year)				
<50 years	146 (18.8)	34 (19.2)	65 (23.6)	47 (14.5)
50-59 years	148 (19.1)	38 (21.5)	51 (18.5)	59 (18.2)
60-69 years	168 (21.6)	41 (23.2)	56 (20.4)	71 (21.9)
70-79 years	189 (24.4)	42 (23.7)	60 (21.8)	87 (26.9)
80+ years	125 (16.1)	22 (12.4)	43 (15.6)	60 (18.5)
WHO - Performance Status				
0 – Asymptomatic	110 (14.2)	15 (8.5)	27 (9.8)	68 (21.0)
1 – Symptomatic but completely ambulatory	263 (33.9)	34 (19.2)	94 (34.2)	135 (41.7)
2 – Symptomatic, <50% in bed during the day	48 (6.2)	11 (6.2)	21 (7.6)	16 (4.9)
3 – Symptomatic, >50% in bed, but not bedbound	13 (1.7)	2 (1.1)	6 (2.2)	5 (1.5)
4 – Bedbound	9 (1.2)	3 (1.7)	3 (1.1)	3 (0.9)
Not reported	333 (42.9)	112 (63.3)	124 (45.1)	97 (29.9)

Note: the values between parentheses are column percentages.



Table 72 – Malignant melanoma of the skin (2004-2017), Combined stage NA, Frequency table of patient and tumour characteristics (cut-off point: 2011)

Characteristic	Total	Incidence period	
		2004-2010	2012-2017
Overall	729	283	446
Gender			
Male	411 (56.4)	162 (57.2)	249 (55.8)
Female	318 (43.6)	121 (42.8)	197 (44.2)
Age at diagnosis (year)			
<50 years	135 (18.5)	57 (20.1)	78 (17.5)
50-59 years	138 (18.9)	62 (21.9)	76 (17.0)
60-69 years	156 (21.4)	63 (22.3)	93 (20.9)
70-79 years	182 (25.0)	62 (21.9)	120 (26.9)
80+ years	118 (16.2)	39 (13.8)	79 (17.7)
WHO - Performance Status			
0 – Asymptomatic	106 (14.5)	26 (9.2)	80 (17.9)
1 – Symptomatic but completely ambulatory	247 (33.9)	70 (24.7)	177 (39.7)
2 – Symptomatic, <50% in bed during the day	46 (6.3)	15 (5.3)	31 (7.0)
3 – Symptomatic, >50% in bed, but not bedbound	11 (1.5)	3 (1.1)	8 (1.8)
4 – Bedbound	7 (1.0)	3 (1.1)	4 (0.9)
Not reported	312 (42.8)	166 (58.7)	146 (32.7)

Note: the values between parentheses are column percentages.



Appendix 5.1.1.2. Malignant melanoma of the skin, Observed and Relative Survival graphs

Malignant melanoma of the skin (2004-2017)

Figure 102 – Malignant melanoma of the skin (2004-2017), Kaplan-Meier graphs observed survival by incidence period

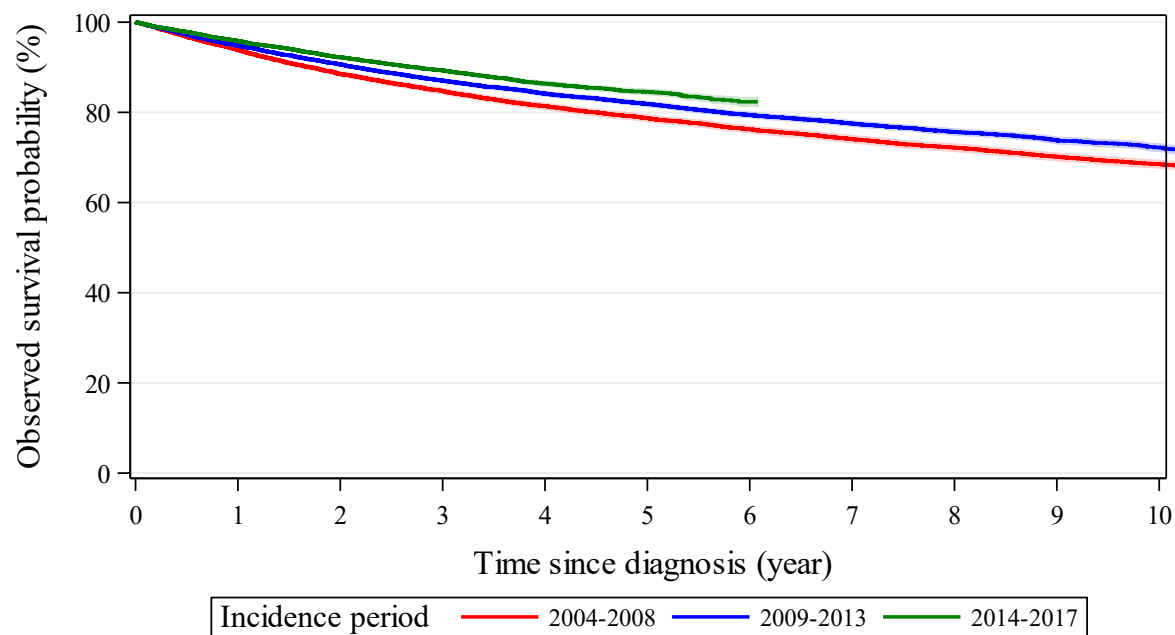




Figure 103 – Malignant melanoma of the skin (2004-2017), Kaplan-Meier graphs observed survival by incidence period (cut-off point: 2011)

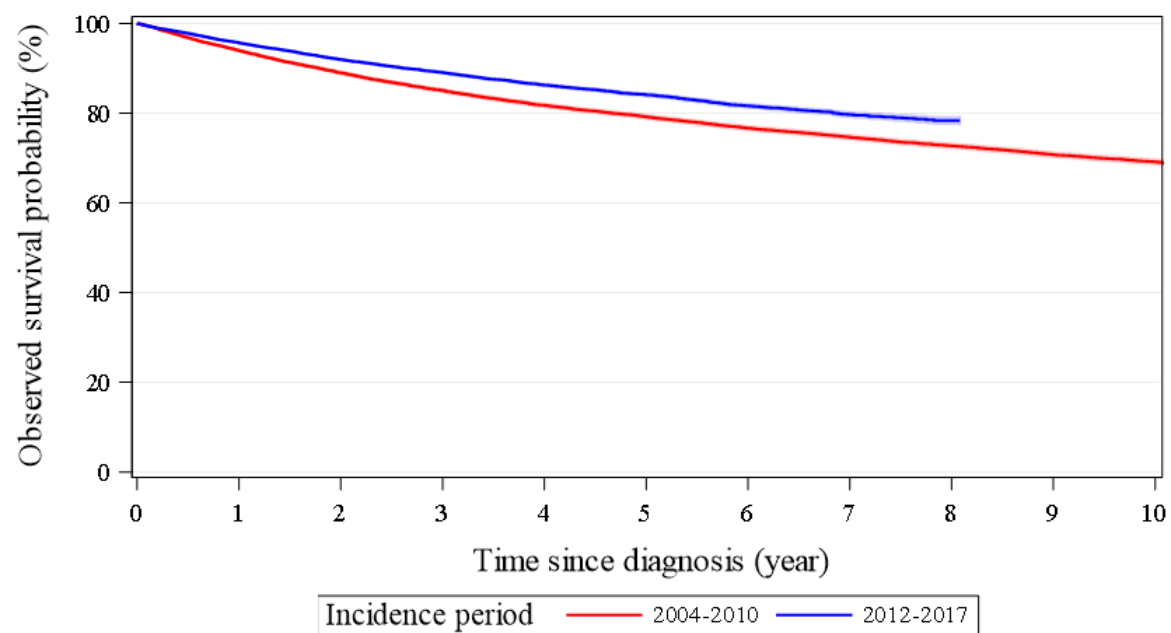




Figure 104 – Malignant melanoma of the skin (2004-2017), relative survival graphs by incidence period

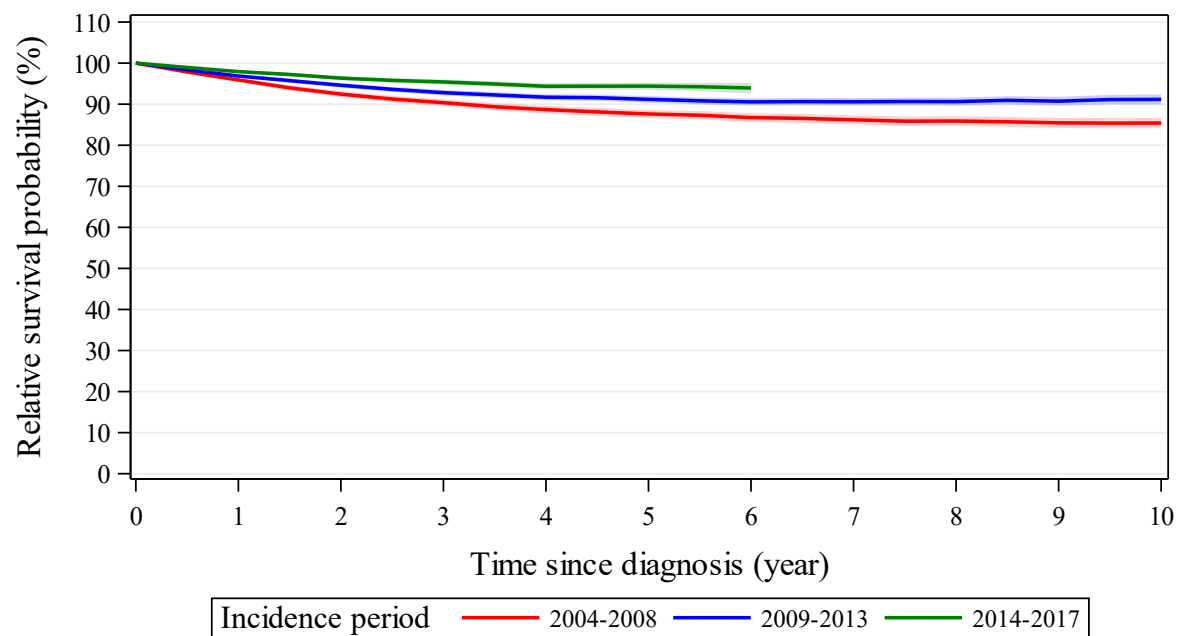
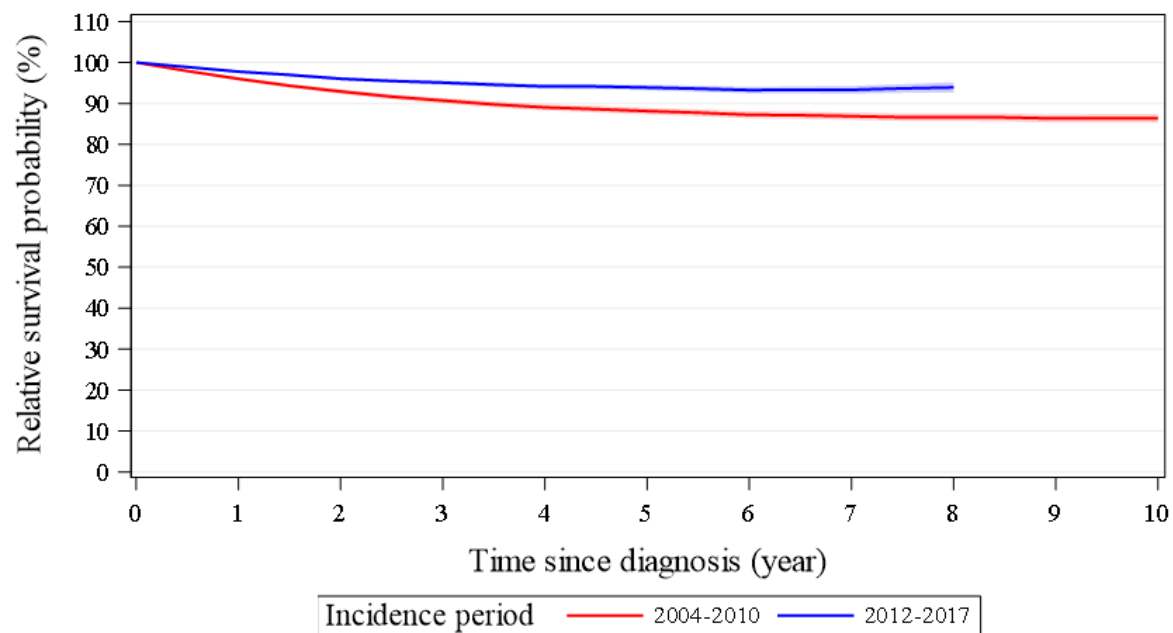




Figure 105 – Malignant melanoma of the skin (2004-2017), relative survival graphs by incidence period (cut-off point: 2011)



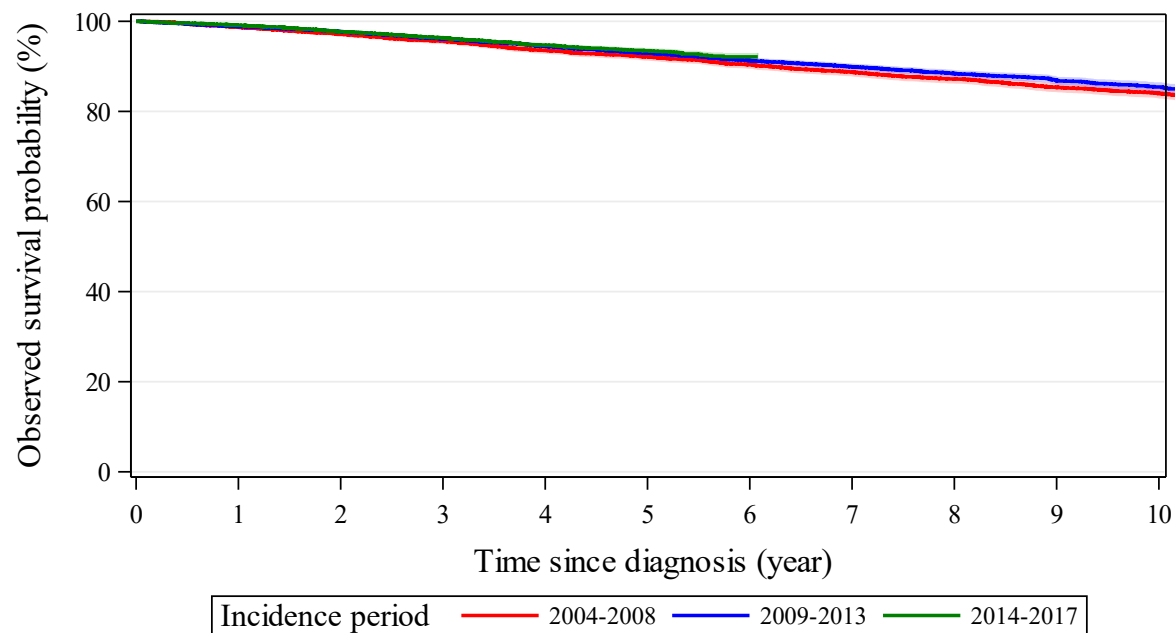
**Malignant melanoma of the skin, combined stage I (2004-2017)****Figure 106 – Malignant melanoma of the skin (2004-2017), combined stage I, Kaplan-Meier graphs observed survival by incidence period**



Figure 107 – Malignant melanoma of the skin (2004-2017), combined stage I, Kaplan-Meier graphs observed survival by incidence period (cut-off point: 2011)

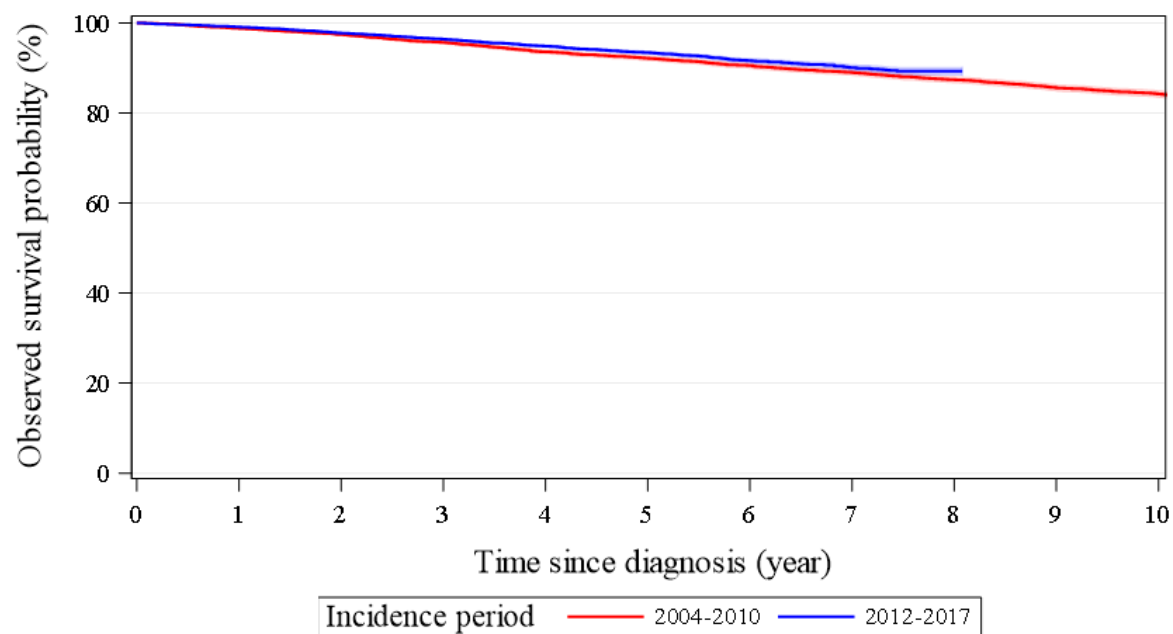




Figure 108 – Malignant melanoma of the skin (2004-2017), combined stage I, relative survival graphs by incidence period

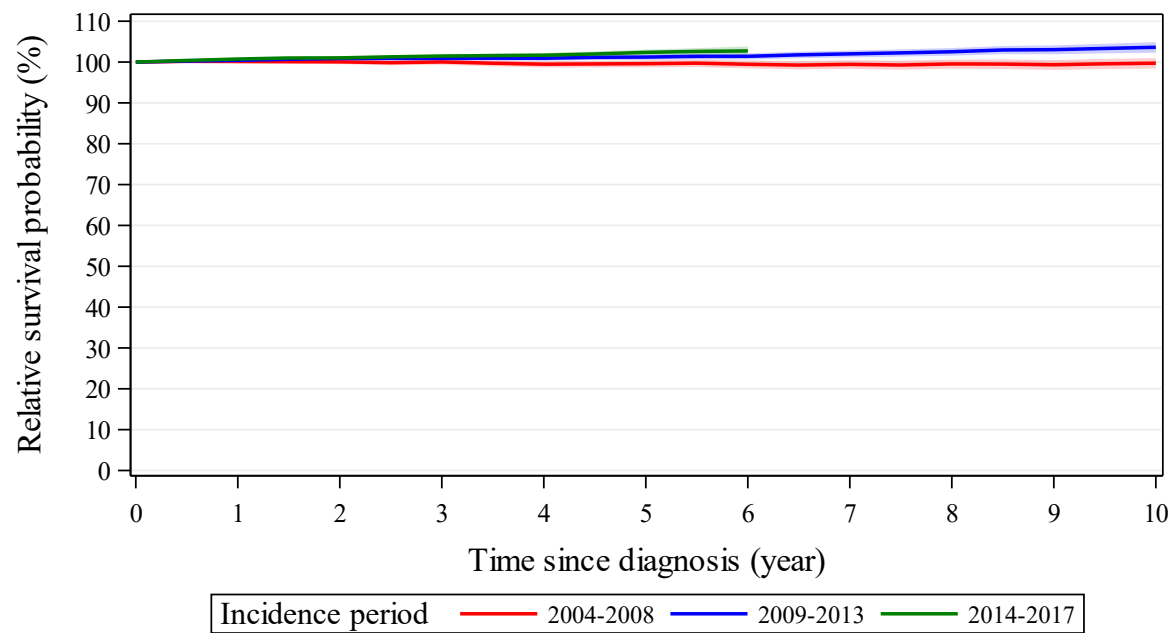
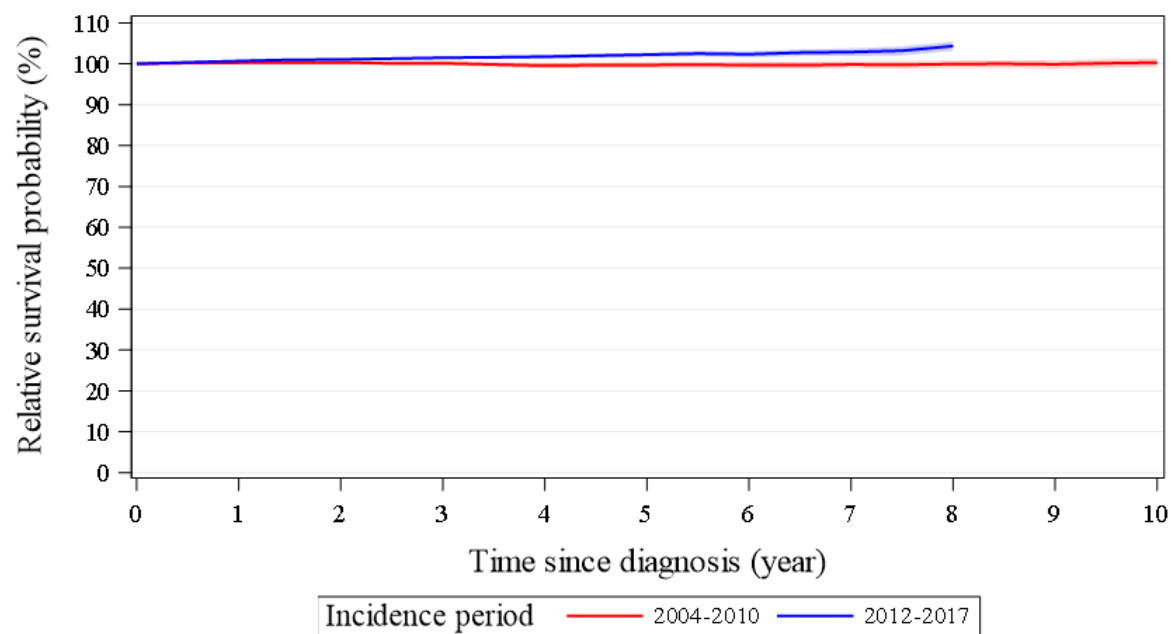




Figure 109 – Malignant melanoma of the skin (2004-2017), combined stage I, relative survival graphs by incidence period (cut-off point: 2011)



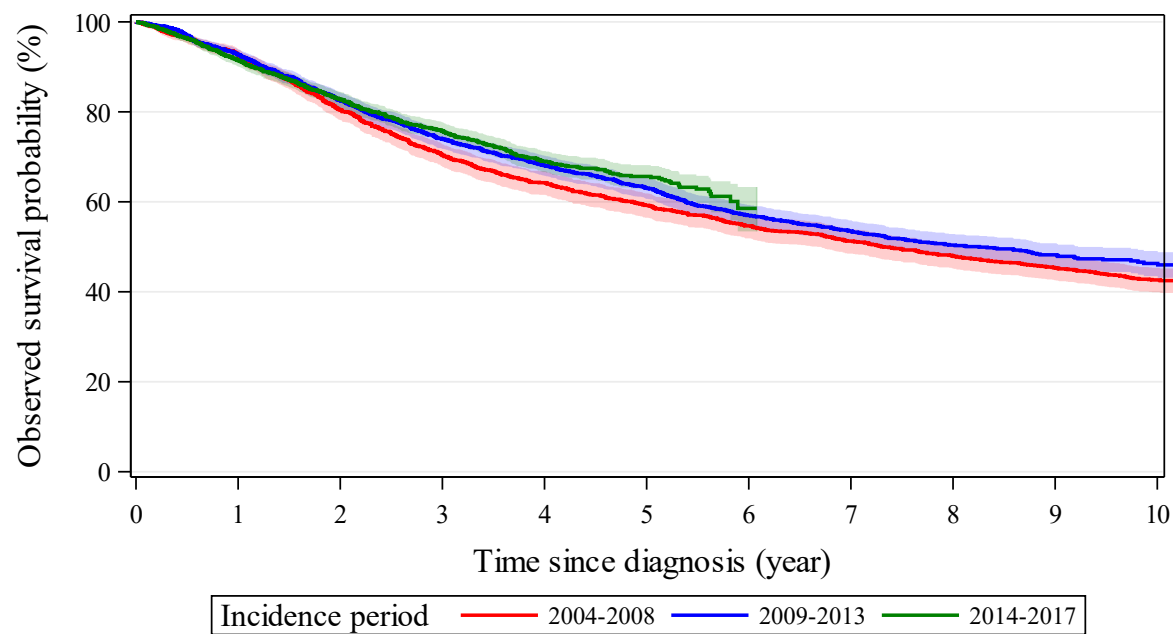
**Malignant melanoma of the skin, combined stage II (2004-2017)****Figure 110 – Malignant melanoma of the skin (2004-2017), combined stage II, Kaplan-Meier graphs observed survival by incidence period**



Figure 111 – Malignant melanoma of the skin (2004-2017), combined stage II, Kaplan-Meier graphs observed survival by incidence period (cut-off point: 2011)

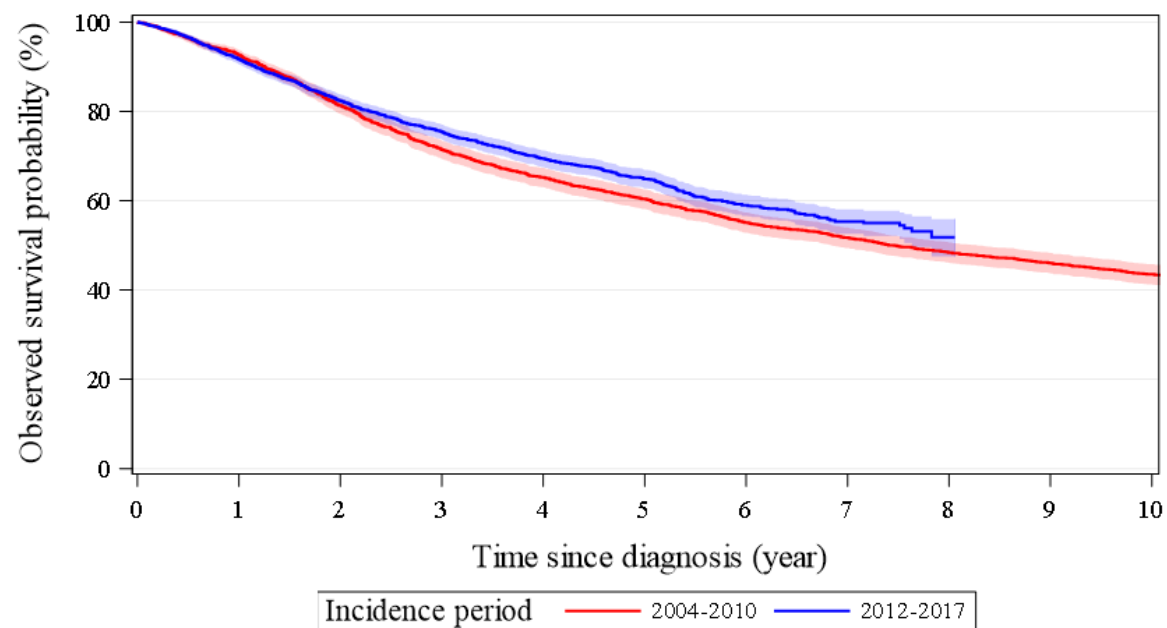


Figure 112 – Malignant melanoma of the skin (2004-2017), combined stage II, relative survival graphs by incidence period

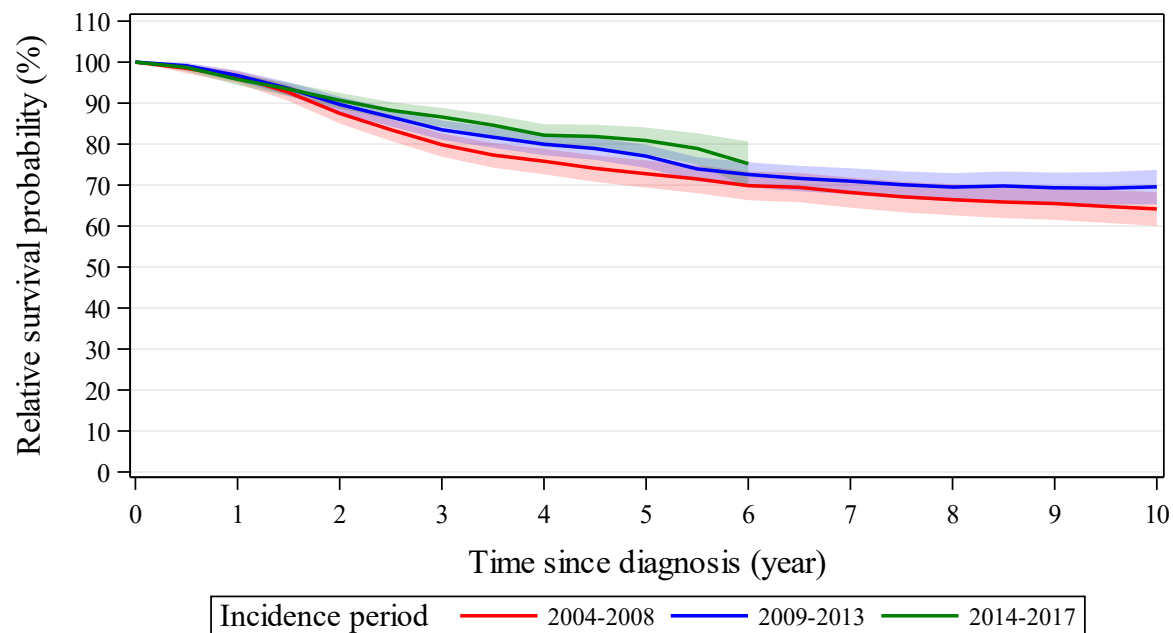
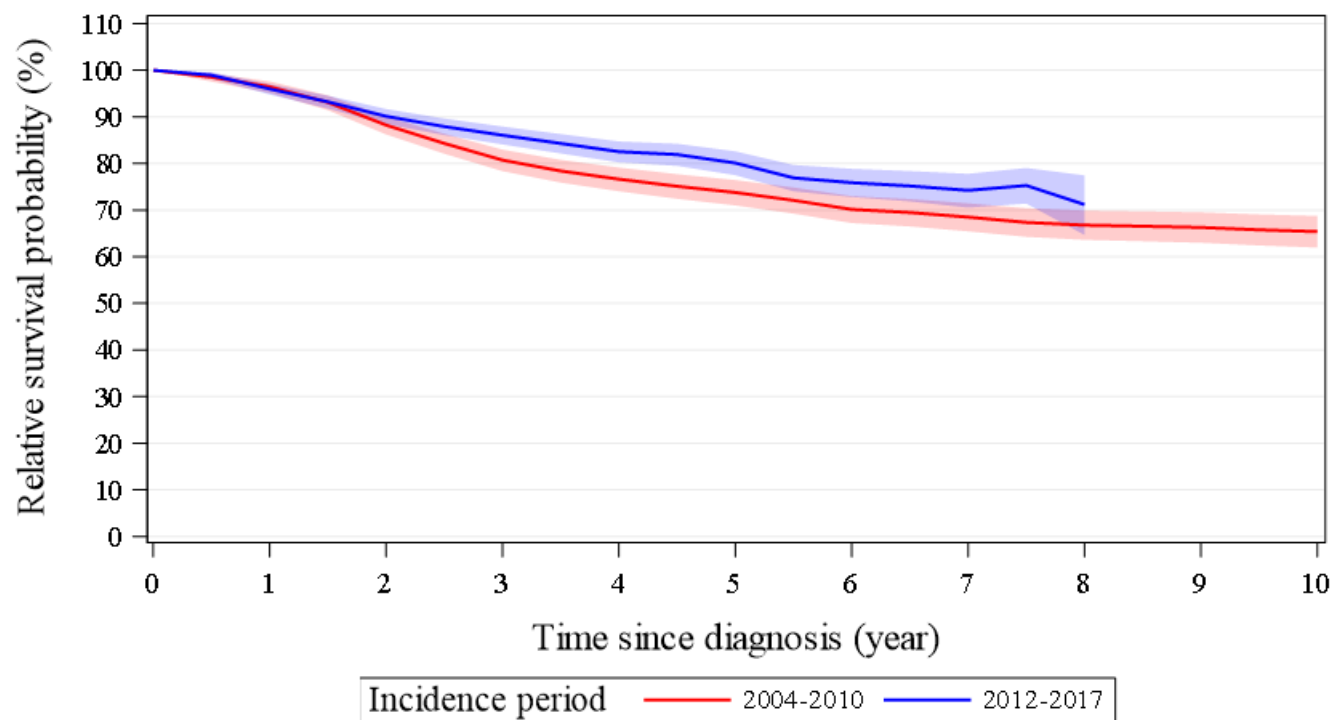




Figure 113 – Malignant melanoma of the skin (2004-2017), combined stage II, relative survival graphs by incidence period



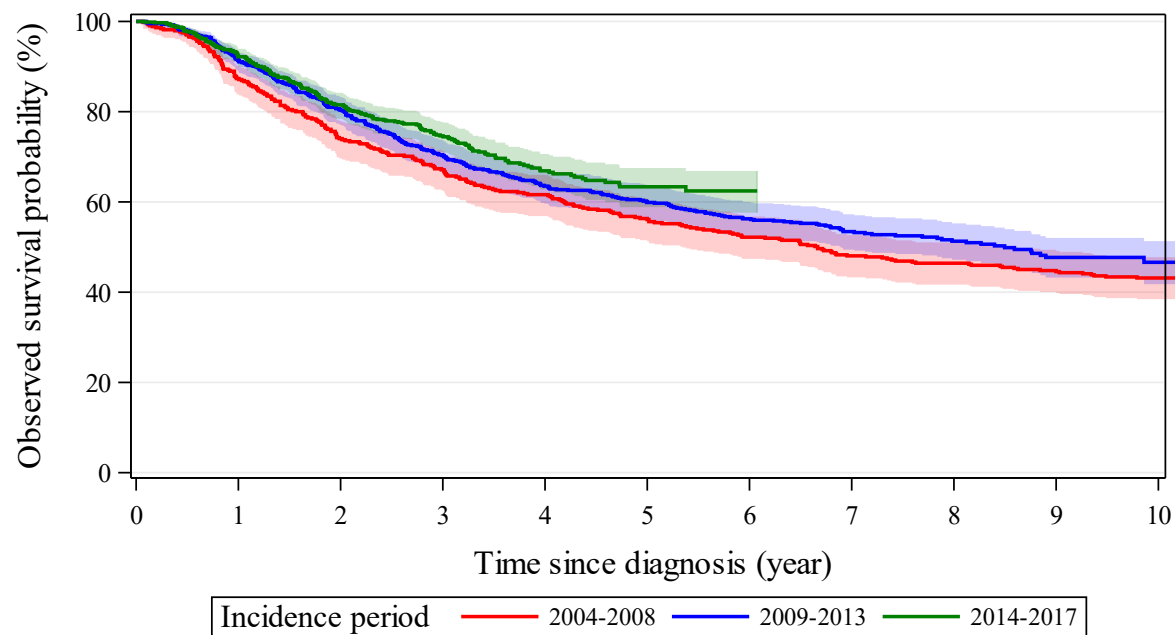
**Malignant melanoma of the skin, combined stage III (2004-2017)****Figure 114 – Malignant melanoma of the skin (2004-2017), combined stage III, Kaplan-Meier graphs observed survival by incidence period**



Figure 115 – Malignant melanoma of the skin (2004-2017), combined stage III, Kaplan-Meier graphs observed survival by incidence period (cut-off point: 2011)

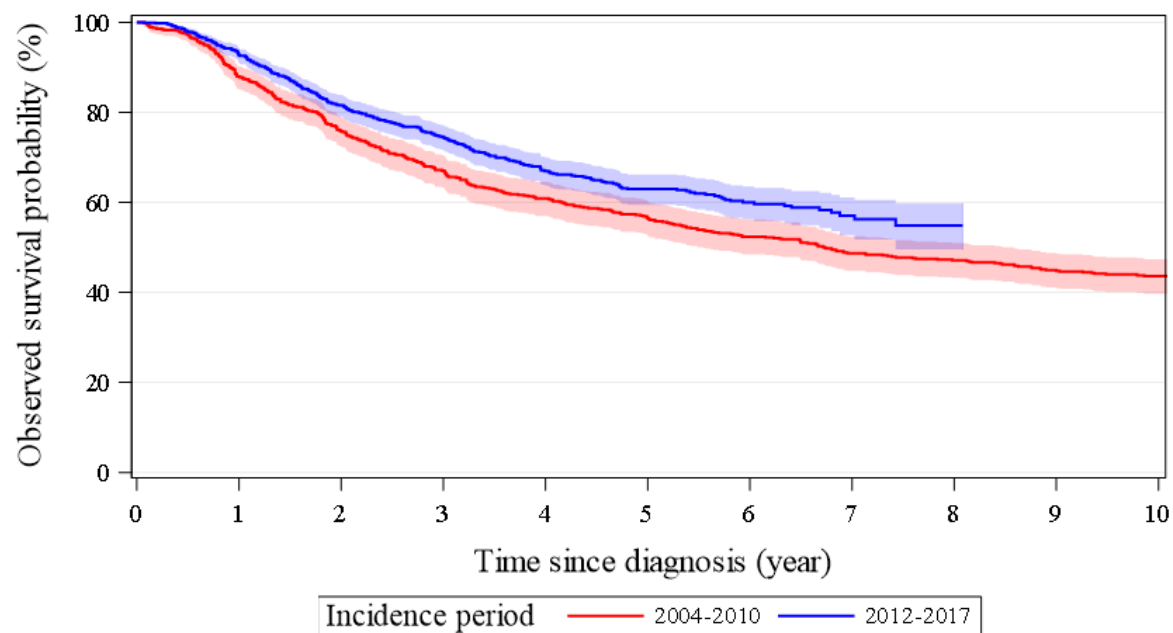




Figure 116 – Malignant melanoma of the skin (2004-2017), combined stage III, relative survival graphs by incidence period

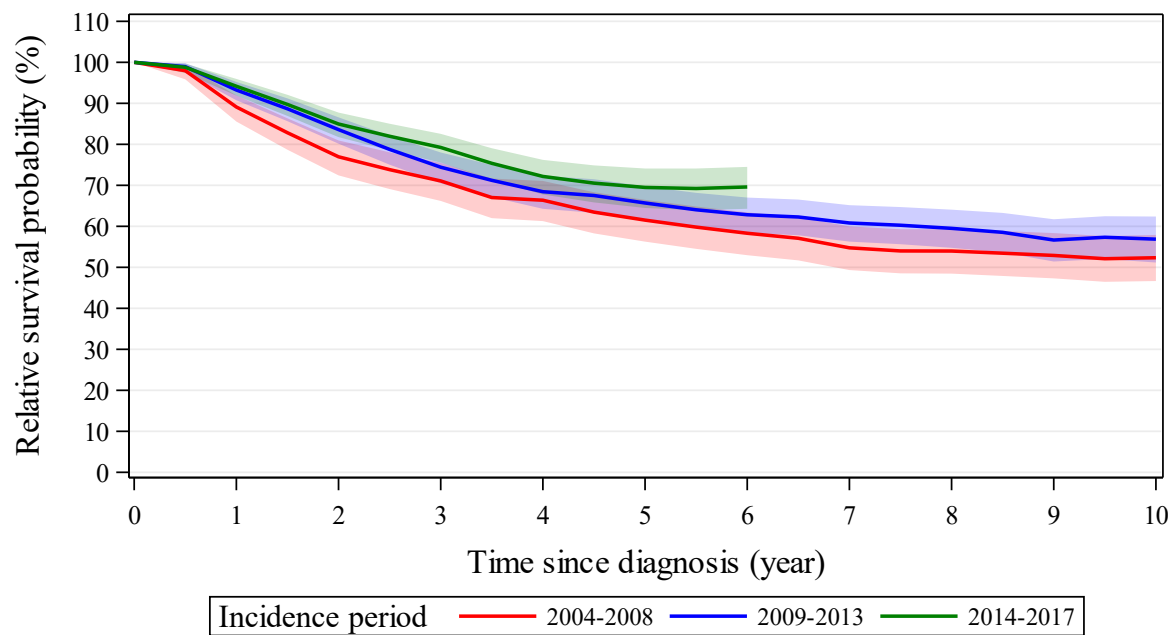
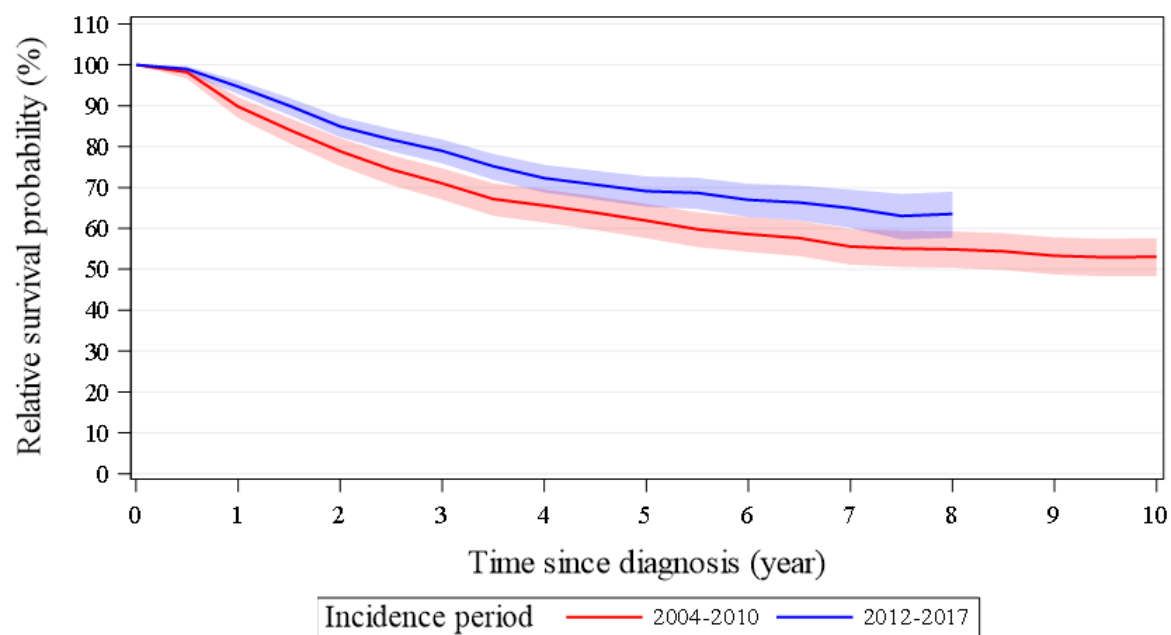




Figure 117 – Malignant melanoma of the skin (2004-2017), combined stage III, relative survival graphs by incidence period (cut-off point: 2011)



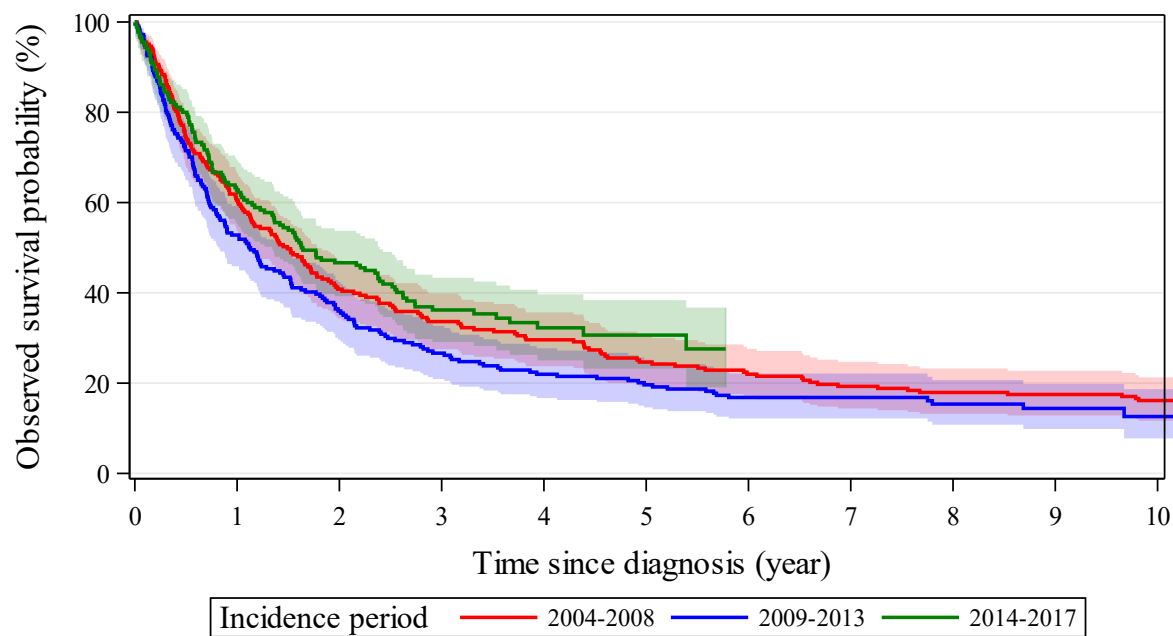
**Malignant melanoma of the skin, combined stage IV (2004-2017)****Figure 118 – Malignant melanoma of the skin (2004-2017), combined stage IV, Kaplan-Meier graphs observed survival by incidence period**



Figure 119 – Malignant melanoma of the skin (2004-2017), combined stage IV, Kaplan-Meier graphs observed survival by incidence period (cut-off point: 2011)

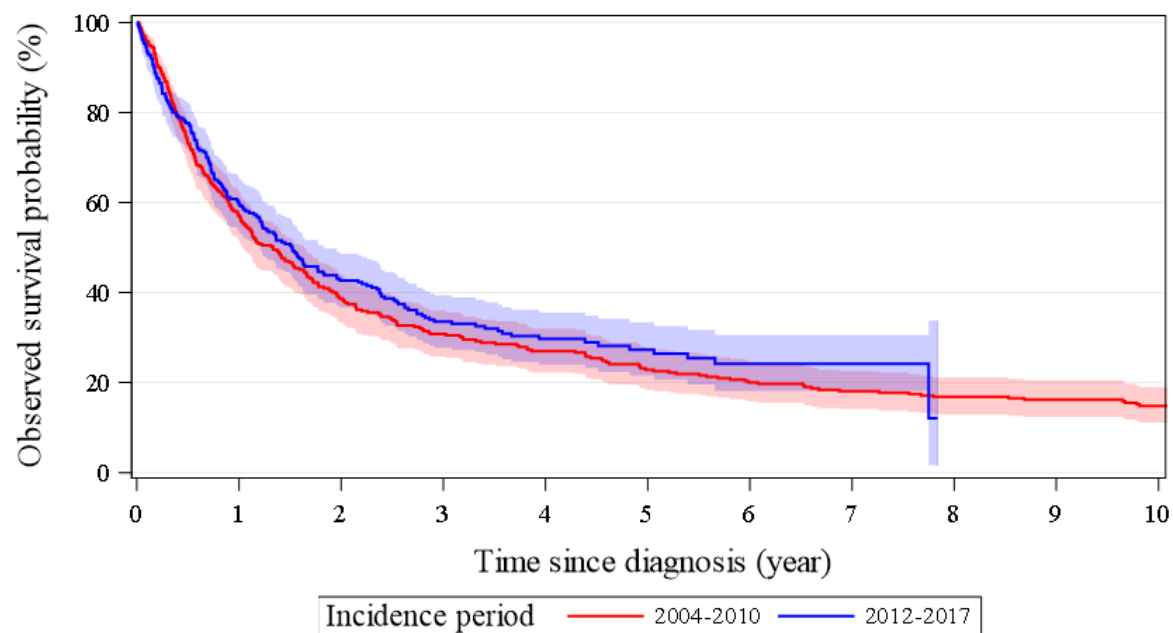




Figure 120 – Malignant melanoma of the skin (2004-2017), combined stage IV, relative survival graphs by incidence period

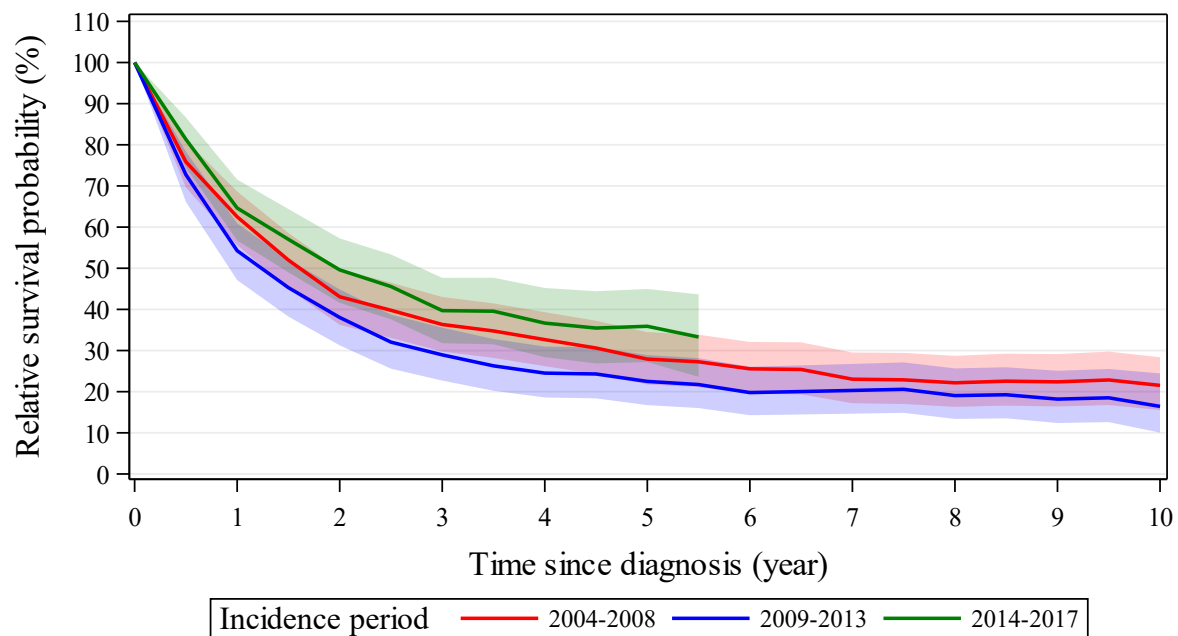
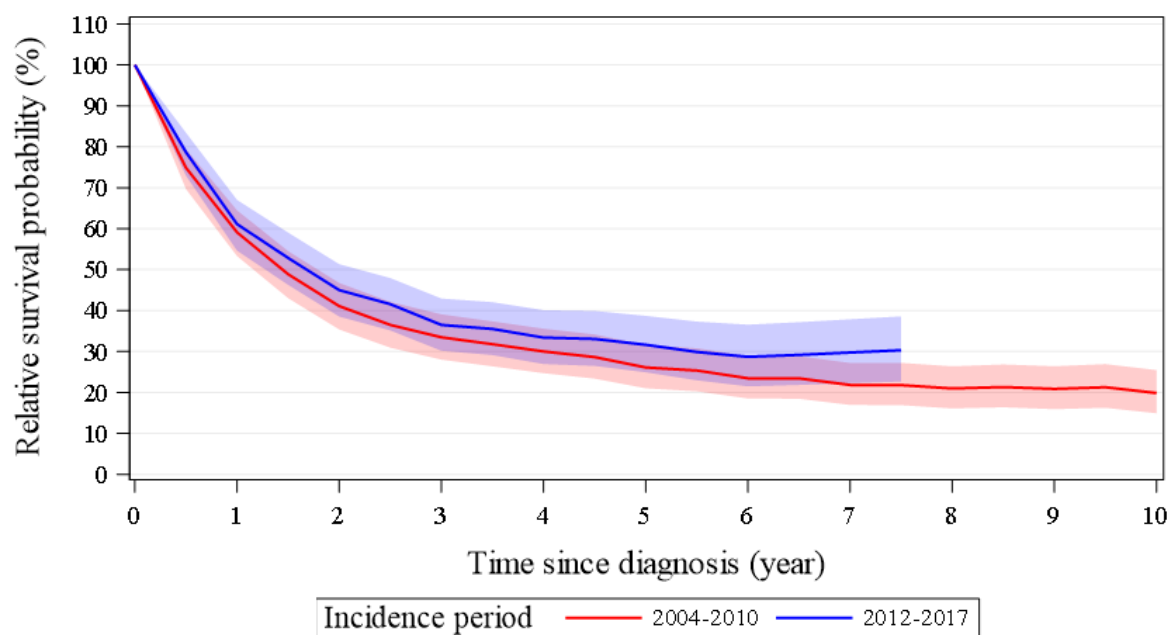




Figure 121 – Malignant melanoma of the skin (2004-2017), combined stage IV, relative survival graphs by incidence period (cut-off point: 2011)



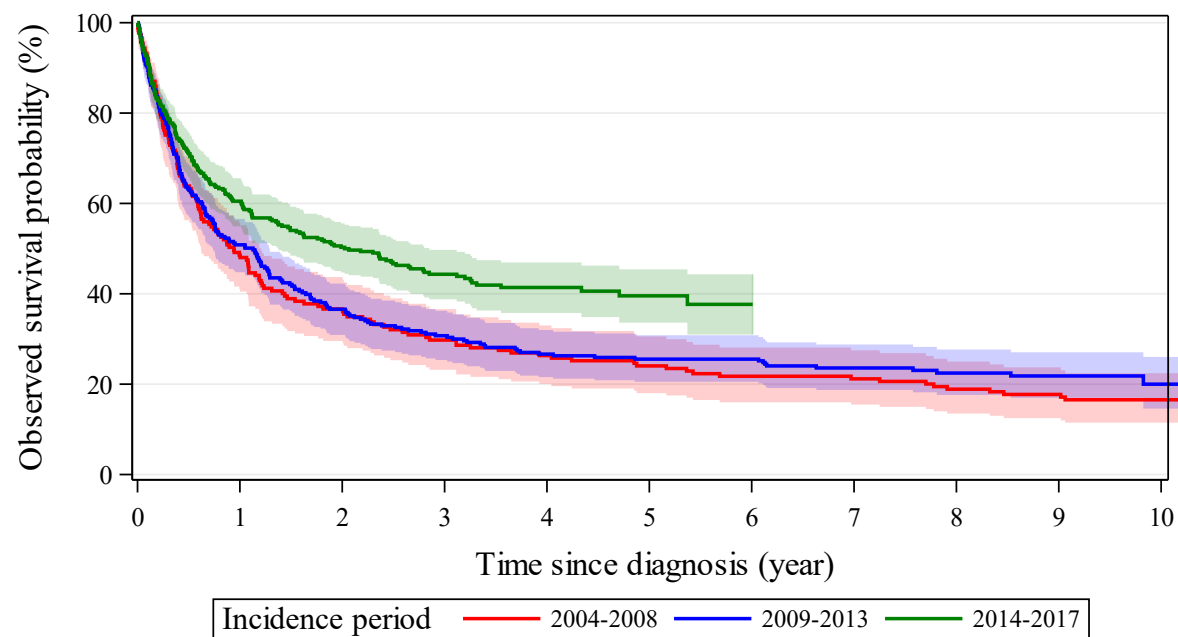
**Malignant melanoma of the skin, combined stage NA (2004-2017)****Figure 122 – Malignant melanoma of the skin (2004-2017), combined stage NA, Kaplan-Meier graphs observed survival by incidence period**



Figure 123 – Malignant melanoma of the skin (2004-2017), combined stage NA, Kaplan-Meier graphs observed survival by incidence period (cut-off point: 2011)

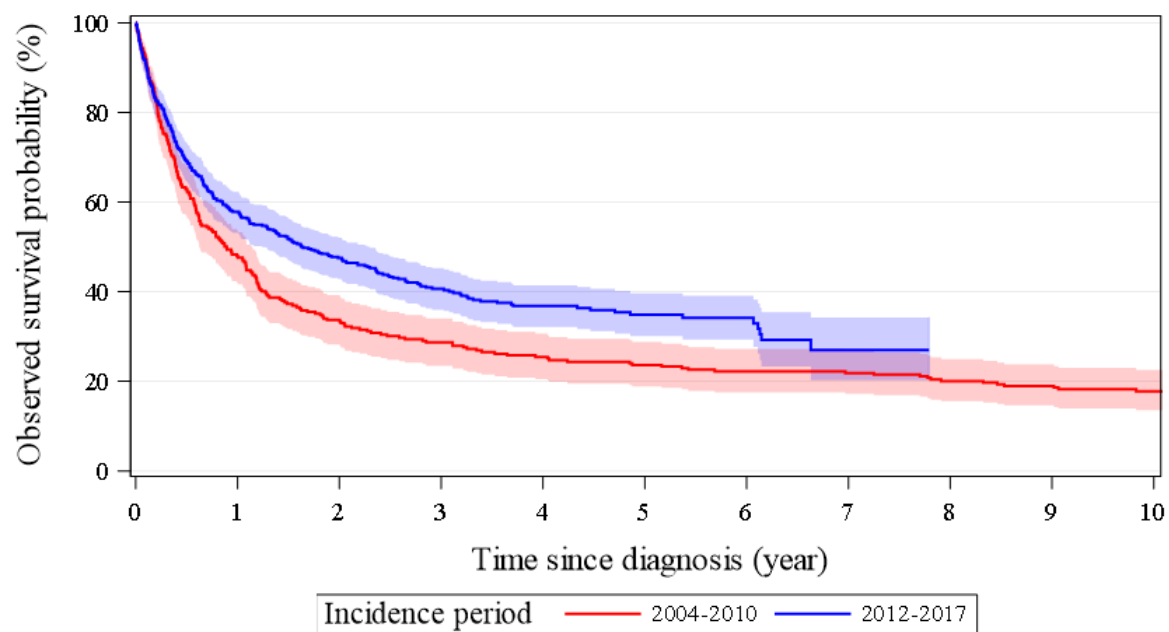




Figure 124 – Malignant melanoma of the skin (2004-2017), combined stage NA, relative survival graphs by incidence period

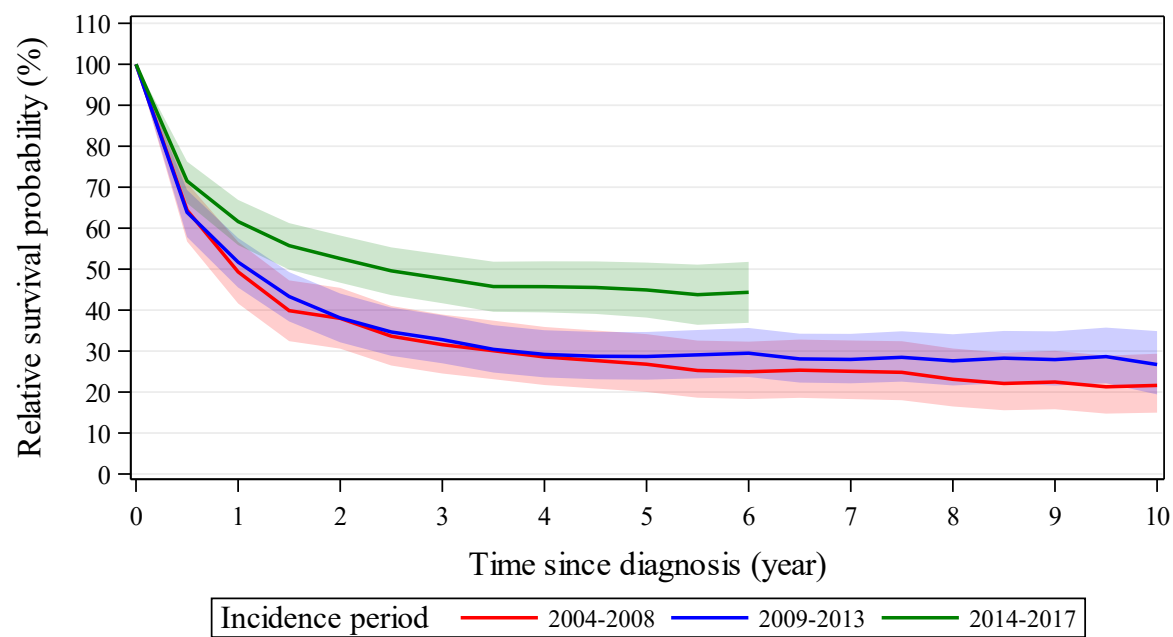
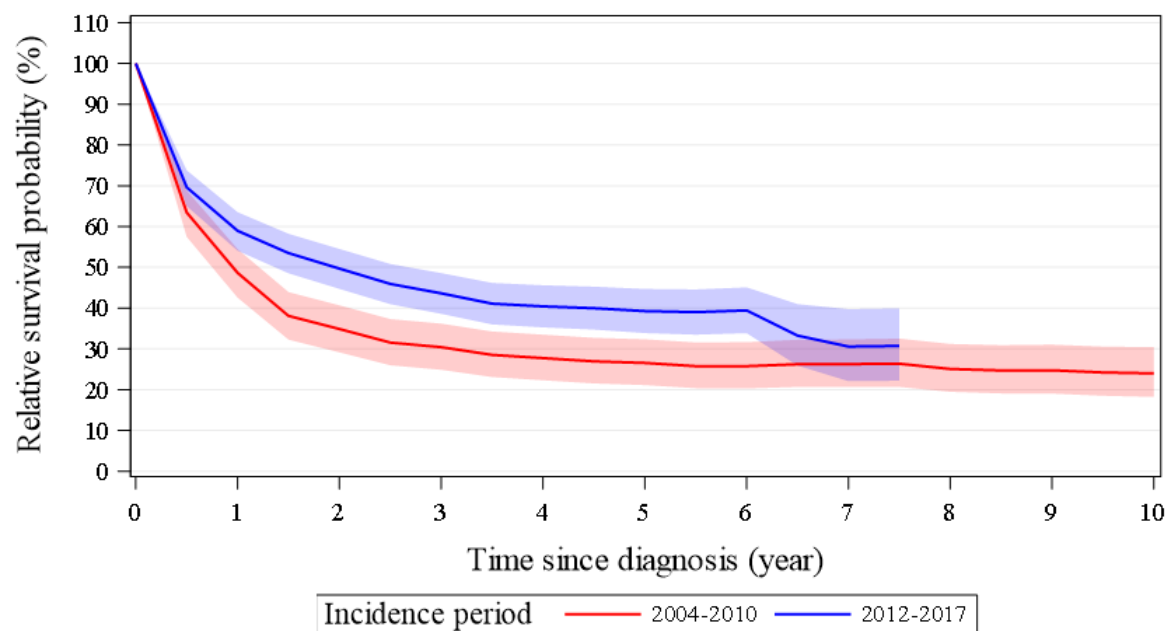




Figure 125 – Malignant melanoma of the skin (2004-2017), combined stage NA, relative survival graphs by incidence period (cut-off point: 2011)

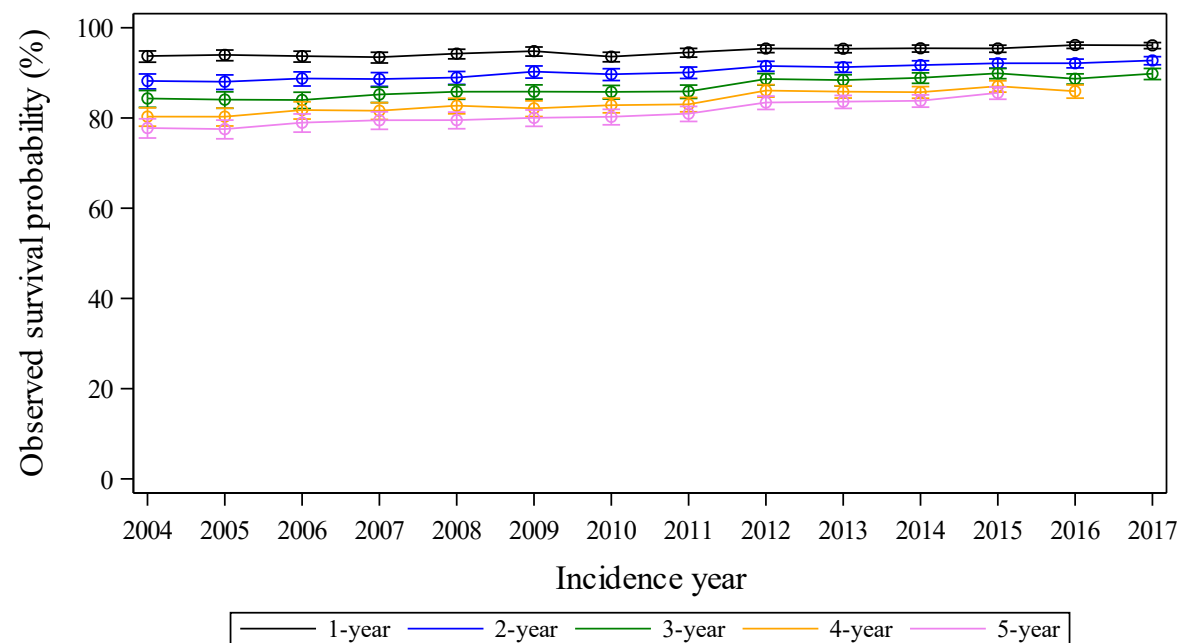




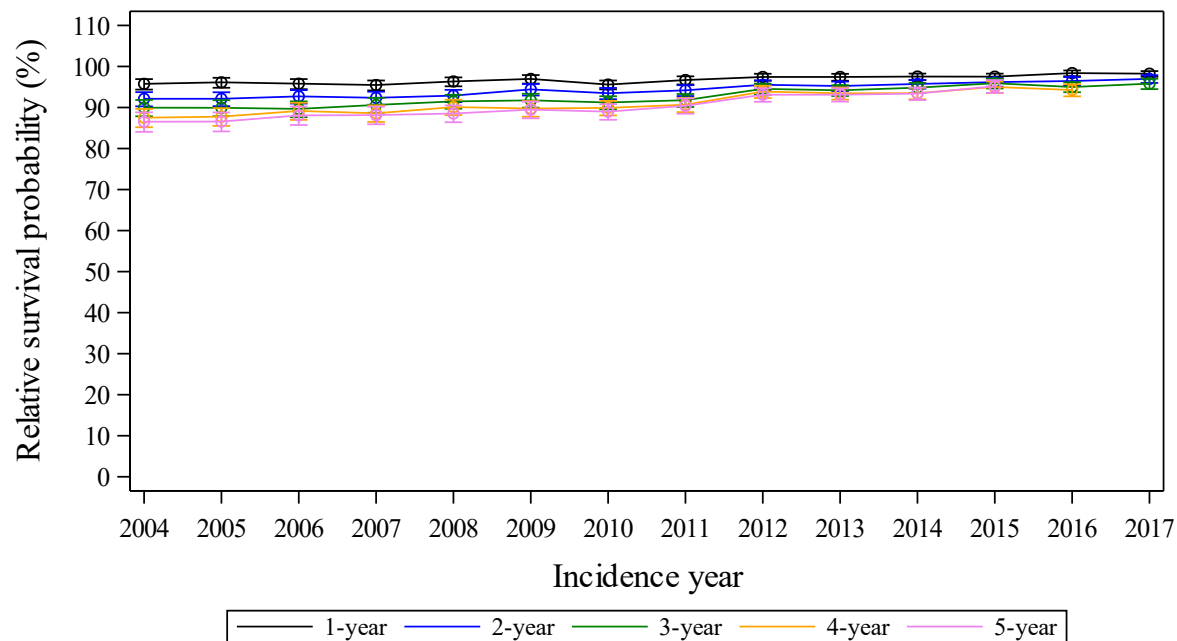
Appendix 5.1.1.3. Malignant melanoma of the skin, time trend Observed and Relative Survival

Malignant melanoma of the skin (2004-2017)

Figure 126 – Malignant melanoma of the skin (2004-2017), time trend observed survival with incidence year



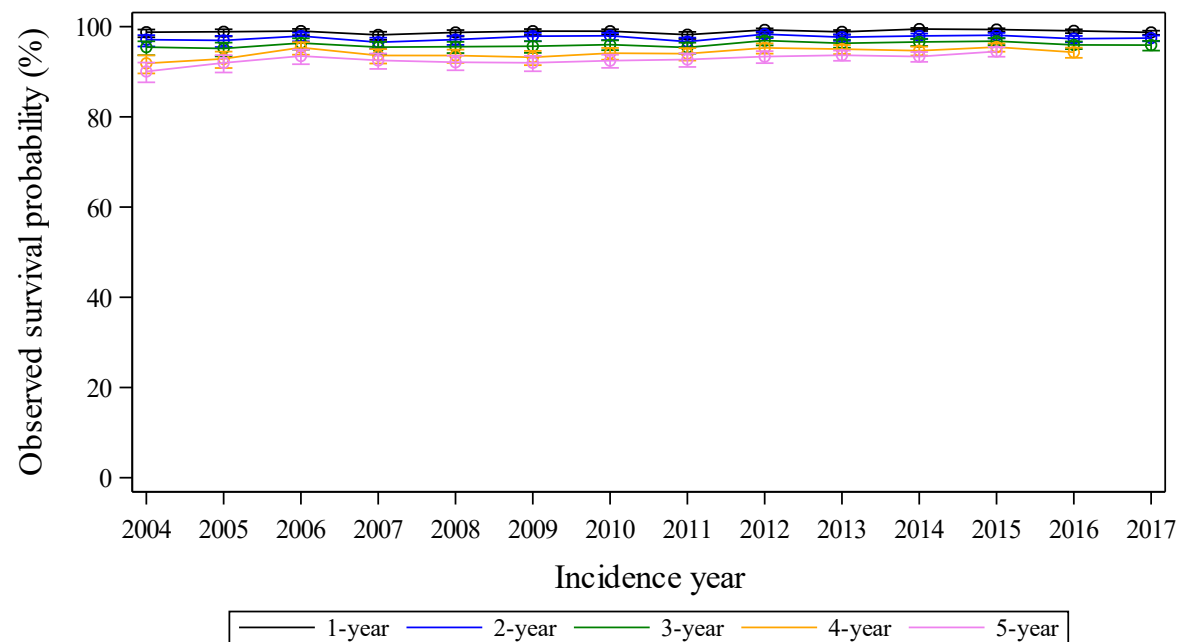
Note: the error bars represent the 95% CI.

**Figure 127 – Malignant melanoma of the skin (2004-2017), time trend relative survival with incidence year**

Note: the error bars represent the 95% CI.

Figure 128 – Malignant melanoma of the skin (2004-2017), Median time observed survival

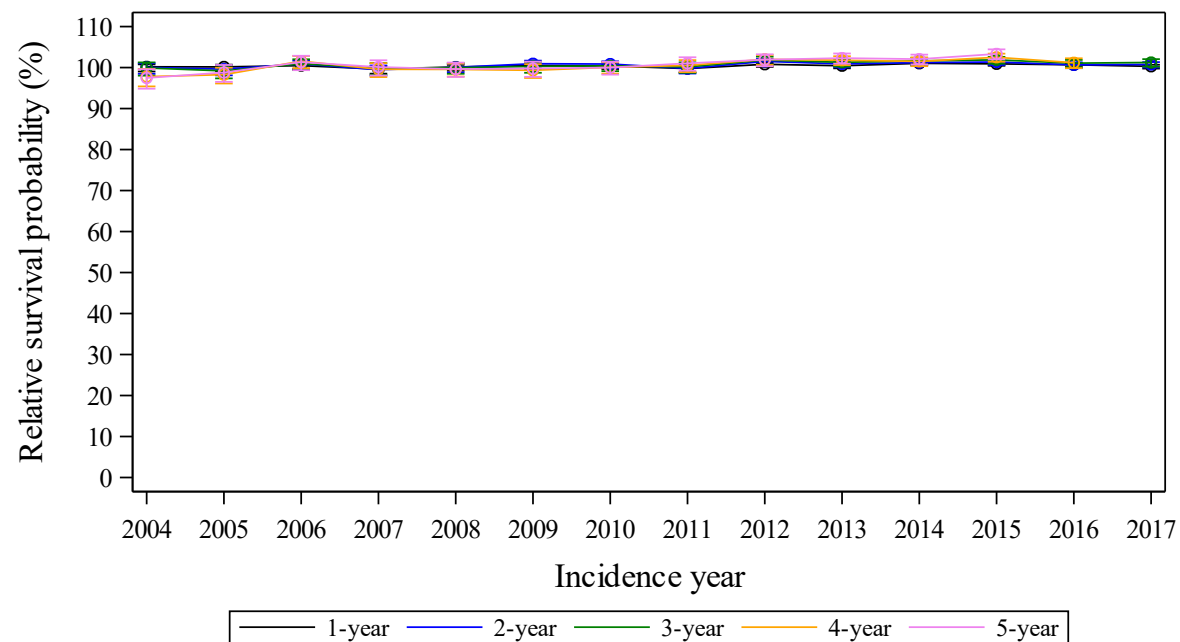
No data points to plot, as survival curves remain above 50% and the median survival time can therefore not be determined.

**Malignant melanoma of the skin, combined stage I (2004-2017)****Figure 129 – Malignant melanoma of the skin (2004-2017), combined stage I, time trend observed survival with incidence year**

Note: the error bars represent the 95% CI.



Figure 130 – Malignant melanoma of the skin (2004-2017), combined stage I, time trend relative survival with incidence year



Note: the error bars represent the 95% CI.

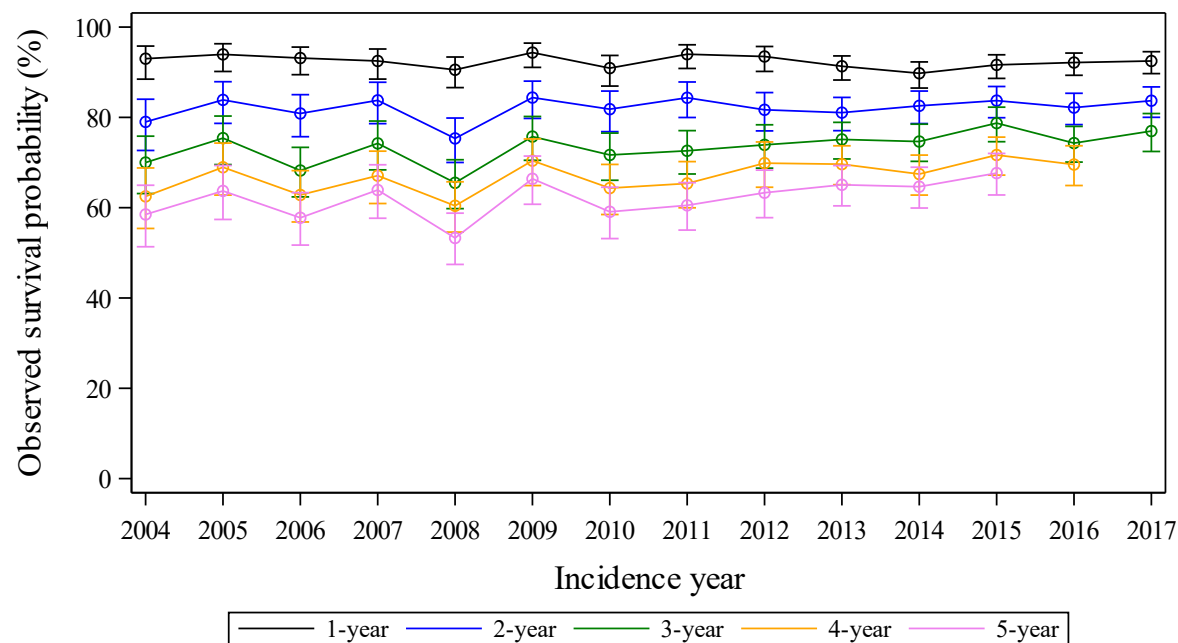


Figure 131 – Malignant melanoma of the skin (2004-2017), combined stage I, median time observed survival

No data points to plot, as survival curves remain above 50% and the median survival time can therefore not be determined.

Malignant melanoma of the skin, combined stage II (2004-2017)

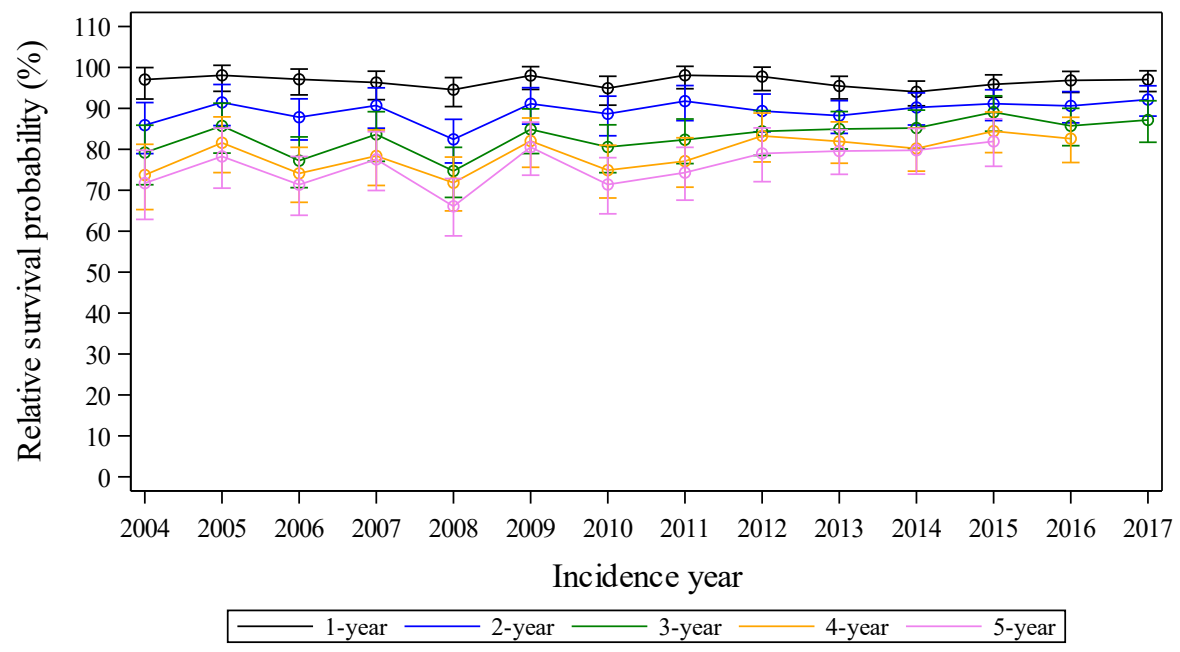
Figure 132 – Malignant melanoma of the skin (2004-2017), combined stage II, time trend observed survival with incidence year



Note: the error bars represent the 95% CI.



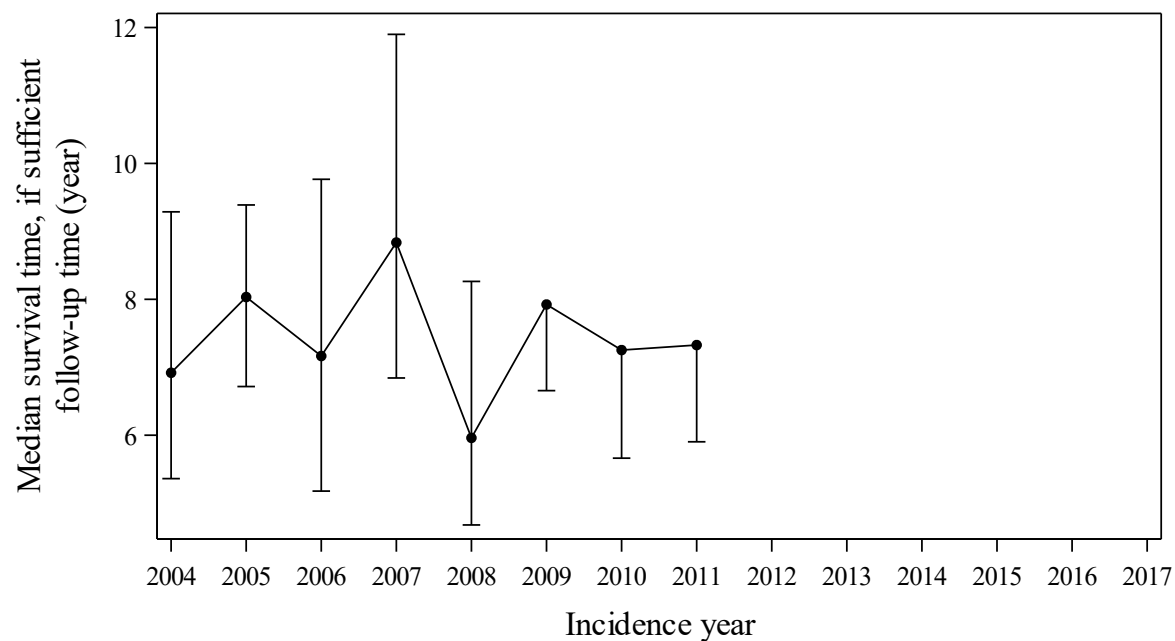
Figure 133 – Malignant melanoma of the skin (2004-2017), combined stage II, time trend relative survival with incidence year



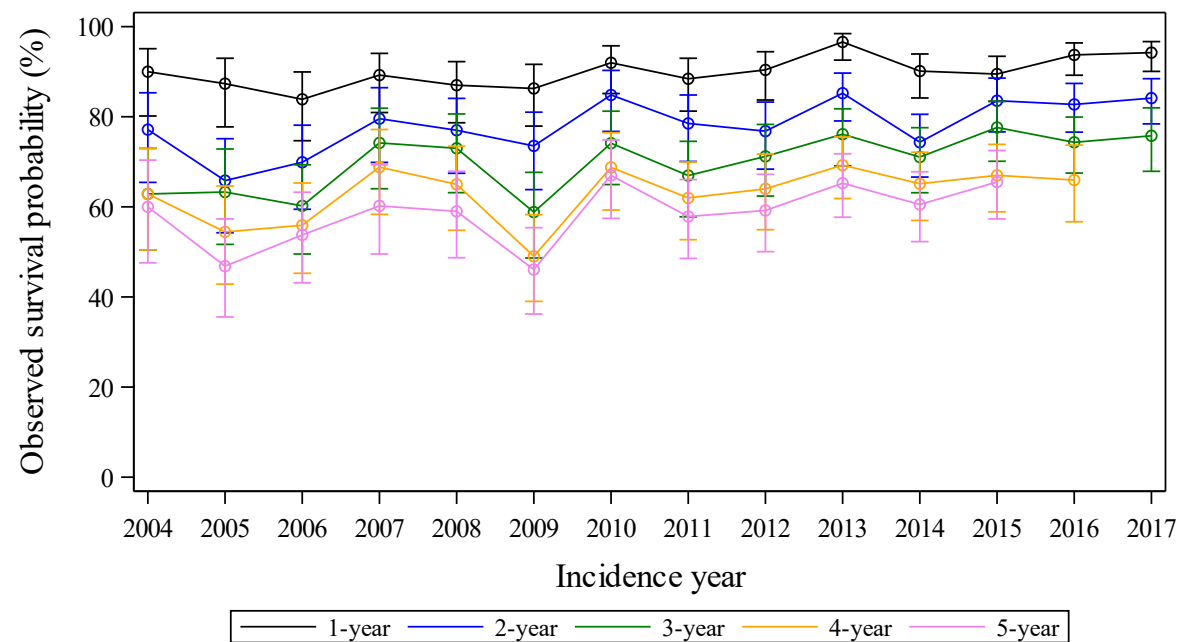
Note: the error bars represent the 95% CI.



Figure 134 – Malignant melanoma of the skin (2004-2017), combined stage II, median time observed survival



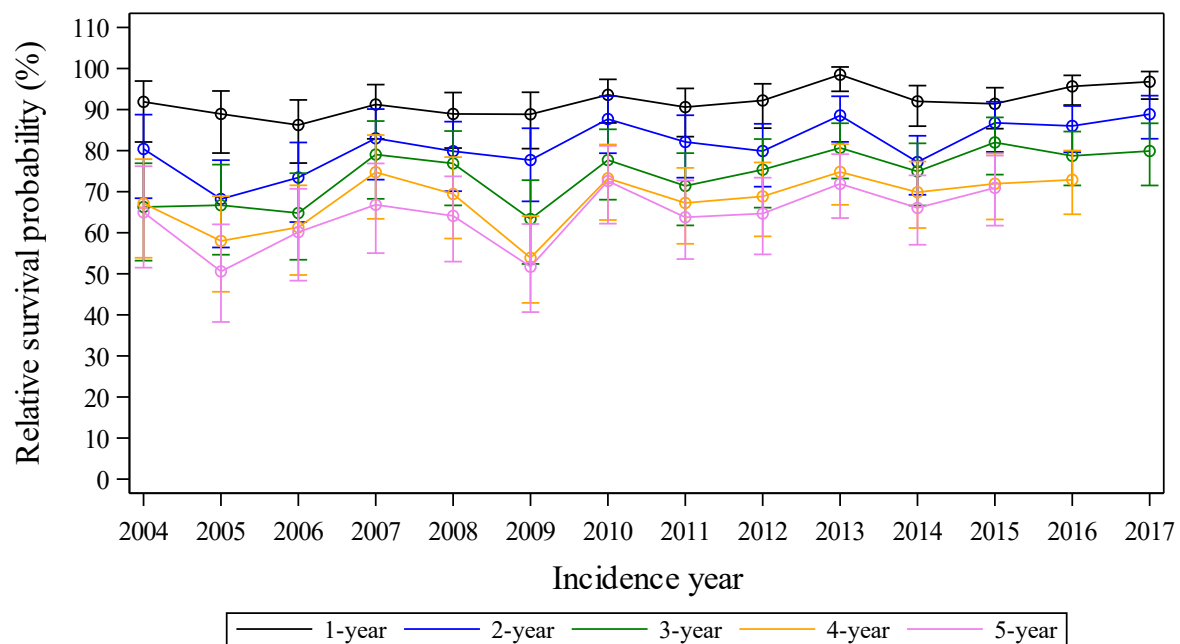
Note: the error bars represent the 95% CI. When the upper error is not plotted, the upper limit could not be determined with the follow-up available.

**Malignant melanoma of the skin, combined stage III (2004-2017)****Figure 135 – Malignant melanoma of the skin (2004-2017), combined stage III, time trend observed survival with incidence year**

Note: the error bars represent the 95% CI.



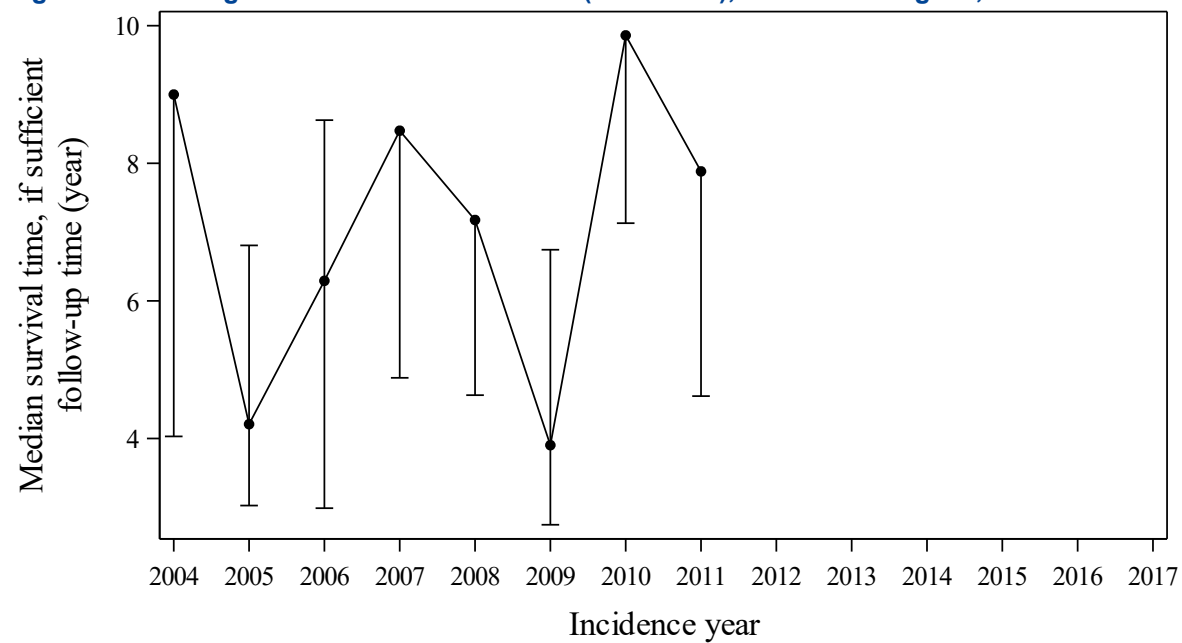
Figure 136 – Malignant melanoma of the skin (2004-2017), combined stage III, time trend relative survival with incidence year



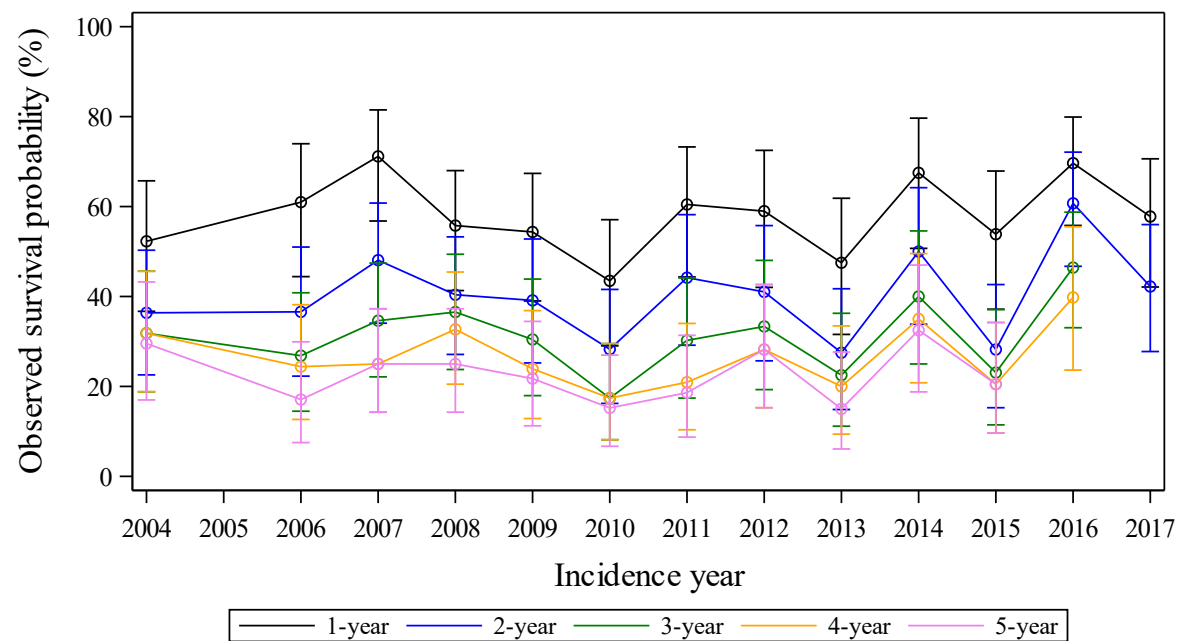
Note: the error bars represent the 95% CI.



Figure 137 – Malignant melanoma of the skin (2004-2017), combined stage III, median time observed survival



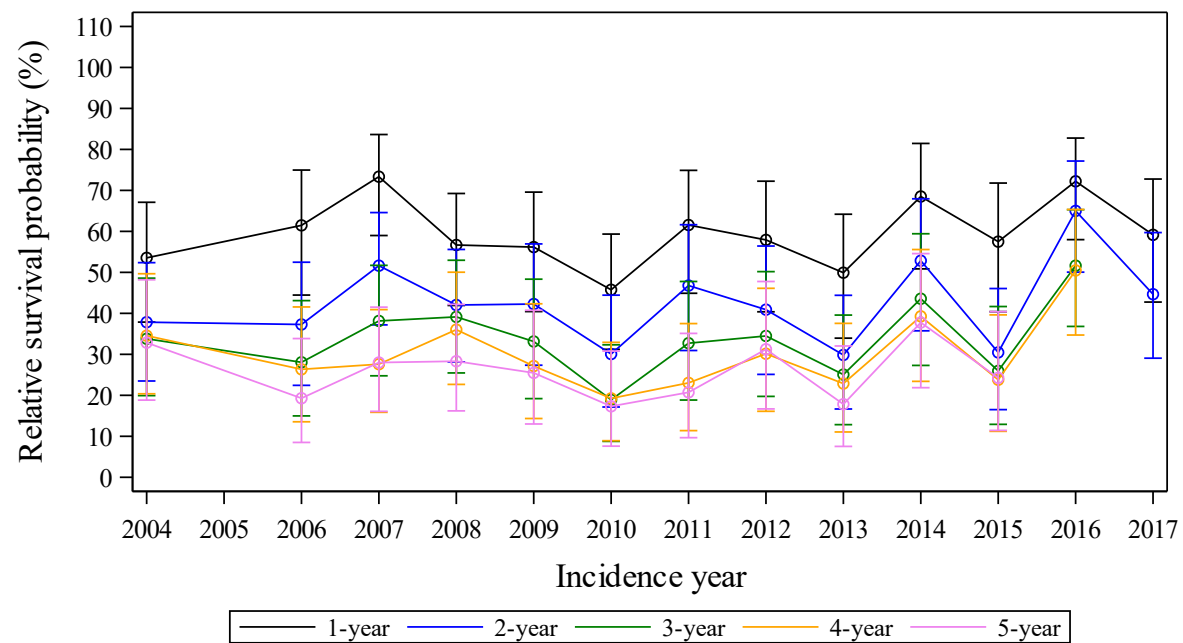
Note: the error bars represent the 95% CI. When the upper error is not plotted, the upper limit could not be determined with the follow-up available.

**Malignant melanoma of the skin, combined stage IV (2004-2017)****Figure 138 – Malignant melanoma of the skin (2004-2017), combined stage IV, time trend observed survival with incidence year**

Note: the error bars represent the 95% CI.

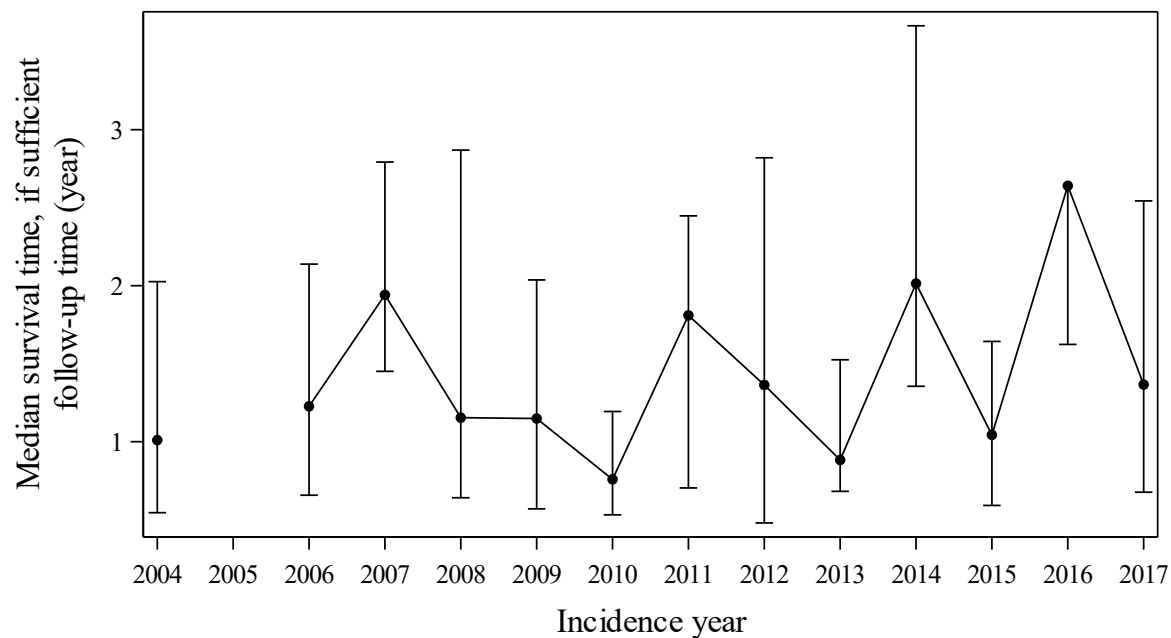


Figure 139 – Malignant melanoma of the skin (2004-2017), combined stage IV, time trend relative survival with incidence year

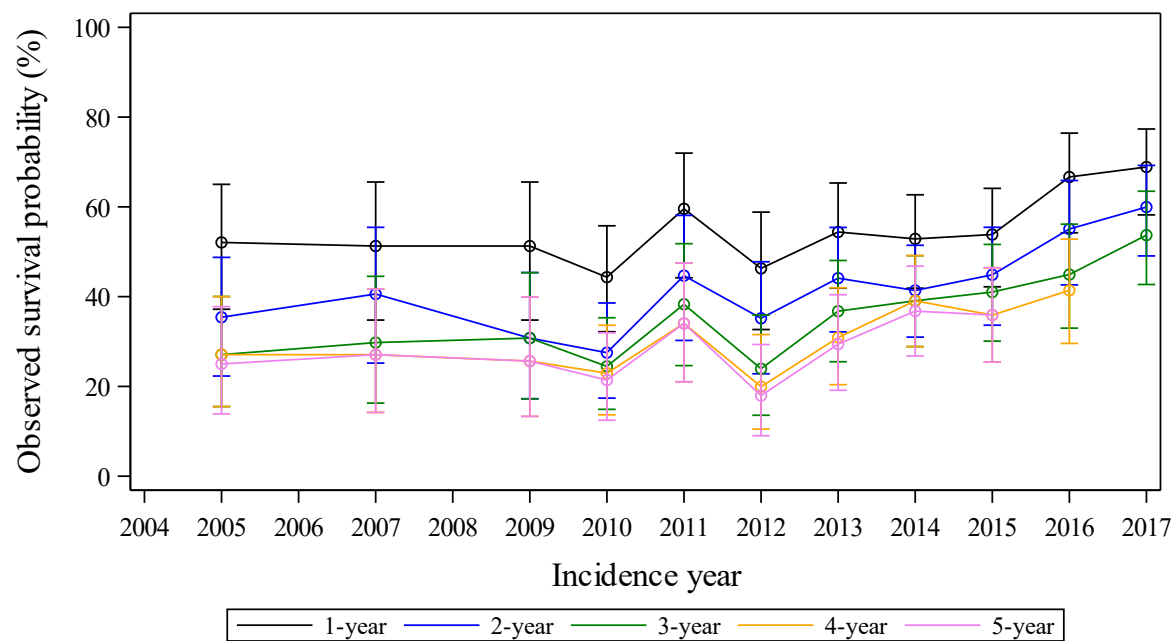


Note: the error bars represent the 95% CI.

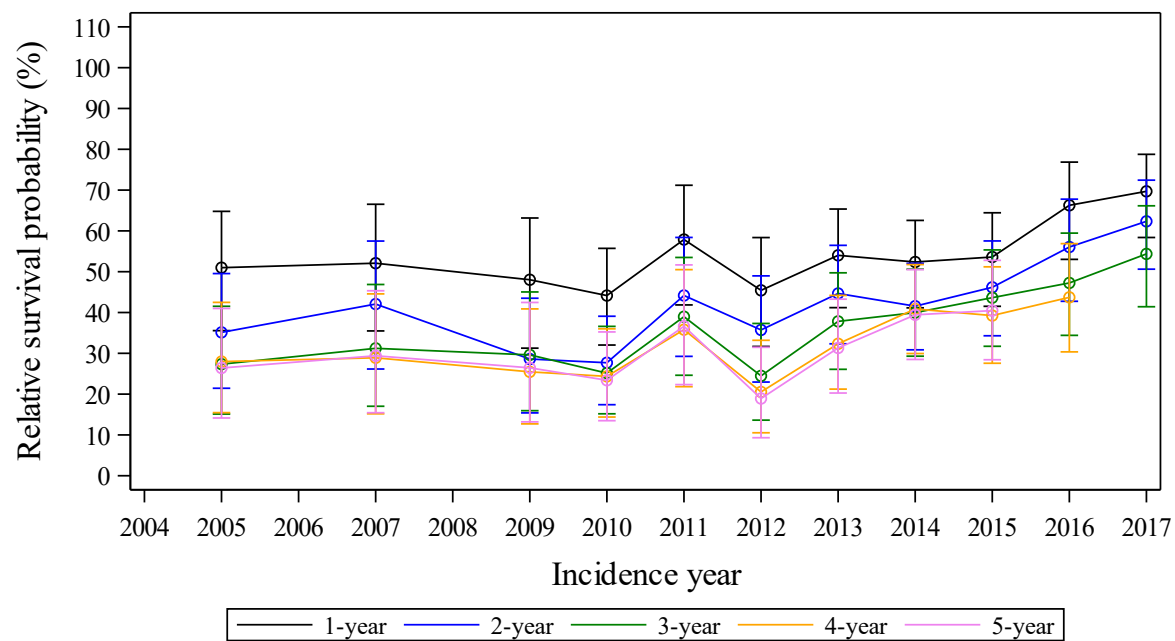
Figure 140 – Malignant melanoma of the skin (2004-2017), combined stage IV, median time observed survival



Note: the error bars represent the 95% CI. When the upper error is not plotted, the upper limit could not be determined with the follow-up available.

**Malignant melanoma of the skin, combined stage NA (2004-2017)****Figure 141 – Malignant melanoma of the skin (2004-2017), combined stage NA, time trend observed survival with incidence year**

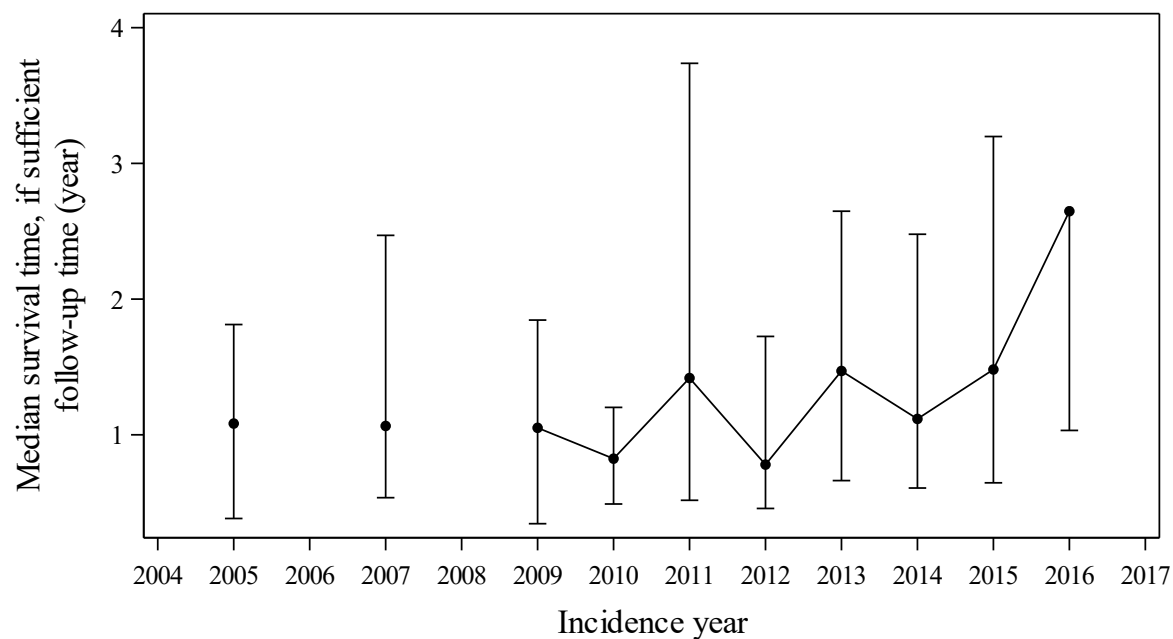
Note: the error bars represent the 95% CI.

**Figure 142 – Malignant melanoma of the skin (2004-2017), combined stage NA, time trend relative survival with incidence year**

Note: the error bars represent the 95% CI.



Figure 143 – Malignant melanoma of the skin (2004-2017), combined stage NA, median time observed survival



Note: the error bars represent the 95% CI. When the upper error is not plotted, the upper limit could not be determined with the follow-up available.



Appendix 5.1.1.4. Malignant melanoma of the skin, time trend tables Observed and Relative Survival

Table 73 – Malignant melanoma of the skin (2004-2017), time trend observed survival with incidence year

Unadjusted observed survival, %													
Characteristic	N at risk	1 year		2 year		3 year		4 year		5 year		Median survival time (year)	
		%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI	T	95% CI
All													
2004	1,467	93.7	[92.4, 94.9]	88.2	[86.4, 89.8]	84.3	[82.4, 86.1]	80.3	[78.2, 82.2]	77.8	[75.6, 79.8]	>16	
2005	1,563	94.0	[92.7, 95.1]	88.0	[86.3, 89.5]	84.1	[82.2, 85.8]	80.3	[78.2, 82.2]	77.5	[75.4, 79.5]	>15	
2006	1,575	93.7	[92.4, 94.8]	88.8	[87.1, 90.2]	84.0	[82.1, 85.7]	81.8	[79.8, 83.6]	79.0	[76.9, 80.9]	>14	
2007	1,673	93.5	[92.2, 94.6]	88.6	[87.0, 90.1]	85.2	[83.4, 86.8]	81.6	[79.7, 83.4]	79.5	[77.5, 81.4]	>13	
2008	1,851	94.3	[93.1, 95.2]	89.0	[87.4, 90.3]	85.8	[84.1, 87.3]	82.7	[80.9, 84.4]	79.5	[77.6, 81.3]	>12	
2009	1,873	94.8	[93.7, 95.7]	90.3	[88.8, 91.5]	85.8	[84.2, 87.3]	82.1	[80.3, 83.8]	80.0	[78.1, 81.8]	>11	
2010	2,080	93.6	[92.5, 94.6]	89.7	[88.3, 90.9]	85.8	[84.2, 87.2]	82.8	[81.1, 84.4]	80.3	[78.5, 81.9]	>10	
2011	2,144	94.5	[93.5, 95.4]	90.1	[88.8, 91.3]	85.9	[84.3, 87.3]	83.0	[81.4, 84.6]	81.0	[79.2, 82.6]	>9	
2012	2,435	95.4	[94.5, 96.2]	91.5	[90.3, 92.6]	88.6	[87.3, 89.8]	86.1	[84.6, 87.4]	83.4	[81.9, 84.8]	>8	
2013	2,559	95.3	[94.5, 96.1]	91.3	[90.1, 92.3]	88.4	[87.1, 89.6]	85.8	[84.4, 87.1]	83.6	[82.1, 85.0]	>7	
2014	2,815	95.5	[94.6, 96.2]	91.7	[90.6, 92.7]	88.9	[87.7, 90.0]	85.7	[84.4, 87.0]	83.8	[82.4, 85.1]	>6	
2015	2,747	95.4	[94.6, 96.1]	92.1	[91.1, 93.1]	89.9	[88.7, 91.0]	87.0	[85.7, 88.2]	85.6	[84.1, 86.9]	>5	
2016	2,981	96.2	[95.4, 96.8]	92.1	[91.1, 93.0]	88.7	[87.5, 89.8]	85.9	[84.4, 87.3]	no FU	—	>4	
2017	3,235	96.1	[95.4, 96.7]	92.7	[91.8, 93.6]	89.8	[88.5, 91.0]	no FU	—	no FU	—	>3	
Combined Stage I													
2004	725	98.8	[97.6, 99.4]	97.1	[95.6, 98.1]	95.4	[93.7, 96.7]	91.9	[89.6, 93.6]	90.1	[87.7, 92.0]	>16	
2005	785	98.9	[97.8, 99.4]	96.9	[95.5, 97.9]	95.2	[93.4, 96.5]	92.9	[90.8, 94.5]	92.0	[89.8, 93.7]	>15	
2006	907	99.0	[98.1, 99.5]	97.9	[96.7, 98.7]	96.4	[94.9, 97.4]	95.4	[93.8, 96.6]	93.5	[91.7, 94.9]	>14	
2007	923	98.2	[97.1, 98.9]	96.5	[95.1, 97.5]	95.4	[93.9, 96.6]	93.6	[91.8, 95.0]	92.5	[90.6, 94.0]	>13	
2008	1,081	98.7	[97.8, 99.2]	97.1	[95.9, 98.0]	95.5	[94.1, 96.6]	93.6	[92.0, 94.9]	92.1	[90.3, 93.6]	>12	



2009	991	99.0	[98.1, 99.5]	97.9	[96.8, 98.6]	95.7	[94.2, 96.8]	93.2	[91.5, 94.6]	92.0	[90.1, 93.5]	>11
2010	1,278	99.0	[98.3, 99.4]	98.0	[97.0, 98.6]	96.0	[94.8, 96.9]	94.1	[92.7, 95.3]	92.5	[90.9, 93.8]	>10
2011	1,171	98.2	[97.3, 98.8]	96.7	[95.5, 97.6]	95.4	[94.0, 96.4]	94.0	[92.5, 95.2]	92.7	[91.1, 94.1]	>9
2012	1,362	99.3	[98.6, 99.6]	98.3	[97.5, 98.9]	96.9	[95.8, 97.7]	95.3	[94.0, 96.3]	93.4	[91.9, 94.6]	>8
2013	1,796	98.8	[98.2, 99.2]	97.7	[96.8, 98.3]	96.3	[95.3, 97.1]	95.0	[93.9, 95.9]	93.7	[92.4, 94.7]	>7
2014	2,032	99.5	[99.0, 99.7]	97.9	[97.2, 98.5]	96.6	[95.7, 97.3]	94.7	[93.6, 95.6]	93.4	[92.2, 94.4]	>6
2015	1,990	99.3	[98.9, 99.6]	98.1	[97.4, 98.6]	96.8	[95.9, 97.5]	95.5	[94.4, 96.3]	94.5	[93.3, 95.5]	>5
2016	2,126	99.1	[98.5, 99.4]	97.3	[96.5, 97.9]	95.9	[95.0, 96.7]	94.3	[93.1, 95.3]	no FU	—	>4
2017	2,407	98.7	[98.2, 99.1]	97.5	[96.7, 98.0]	95.9	[94.7, 96.8]	no FU	—	no FU	—	>3
Combined Stage II												
2004	200	93.0	[88.5, 95.8]	79.0	[72.7, 84.0]	70.0	[63.1, 75.8]	62.5	[55.4, 68.8]	58.5	[51.3, 65.0]	6.9 [5.4, 9.3]
2005	248	94.0	[90.2, 96.3]	83.9	[78.7, 87.9]	75.4	[69.5, 80.3]	69.0	[62.8, 74.3]	63.7	[57.4, 69.3]	8.0 [6.7, 9.4]
2006	277	93.1	[89.5, 95.6]	80.9	[75.7, 85.0]	68.2	[62.4, 73.4]	62.8	[56.8, 68.2]	57.8	[51.7, 63.3]	7.2 [5.2, 9.8]
2007	254	92.5	[88.5, 95.1]	83.8	[78.6, 87.8]	74.2	[68.4, 79.2]	67.1	[60.9, 72.5]	63.9	[57.7, 69.5]	8.8 [6.8, 11.9]
2008	296	90.5	[86.6, 93.4]	75.3	[70.0, 79.9]	65.5	[59.8, 70.6]	60.4	[54.6, 65.7]	53.3	[47.4, 58.8]	6.0 [4.7, 8.3]
2009	301	94.4	[91.1, 96.5]	84.4	[79.8, 88.0]	75.7	[70.5, 80.2]	70.4	[64.9, 75.2]	66.4	[60.8, 71.4]	7.9 [6.7, .]
2010	286	90.9	[86.9, 93.7]	81.8	[76.8, 85.8]	71.7	[66.1, 76.5]	64.3	[58.5, 69.6]	59.1	[53.2, 64.5]	7.3 [5.7, .]
2011	333	94.0	[90.8, 96.1]	84.3	[80.0, 87.8]	72.6	[67.5, 77.1]	65.4	[60.0, 70.2]	60.5	[55.0, 65.5]	7.3 [5.9, .]
2012	323	93.5	[90.2, 95.7]	81.7	[77.0, 85.5]	73.9	[68.8, 78.4]	69.9	[64.5, 74.6]	63.3	[57.8, 68.3]	>8
2013	439	91.3	[88.3, 93.6]	81.1	[77.1, 84.4]	75.1	[70.8, 78.9]	69.6	[65.1, 73.7]	65.1	[60.4, 69.3]	>7
2014	430	89.8	[86.5, 92.3]	82.6	[78.6, 85.8]	74.7	[70.3, 78.5]	67.4	[62.8, 71.6]	64.6	[59.9, 69.0]	>6
2015	442	91.6	[88.6, 93.9]	83.7	[79.9, 86.8]	78.7	[74.6, 82.3]	71.7	[67.2, 75.6]	67.7	[62.8, 72.0]	>5
2016	471	92.1	[89.3, 94.2]	82.2	[78.4, 85.3]	74.3	[70.1, 78.0]	69.6	[64.9, 73.7]	no FU	—	>4
2017	466	92.5	[89.7, 94.5]	83.7	[80.0, 86.7]	77.0	[72.4, 80.9]	no FU	—	no FU	—	>3
Combined Stage III												
2004	70	90.0	[80.2, 95.1]	77.1	[65.4, 85.3]	62.9	[50.4, 73.0]	62.9	[50.4, 73.0]	60.0	[47.6, 70.4]	9.0 [4.0, .]
2005	79	87.3	[77.8, 93.0]	65.8	[54.3, 75.1]	63.3	[51.7, 72.8]	54.4	[42.8, 64.6]	46.8	[35.6, 57.3]	4.2 [3.0, 6.8]
2006	93	83.9	[74.7, 89.9]	69.9	[59.5, 78.1]	60.2	[49.5, 69.3]	55.9	[45.2, 65.3]	53.8	[43.1, 63.3]	6.3 [3.0, 8.6]



2005	48	52.1	[37.2, 65.0]	35.4	[22.3, 48.8]	27.1	[15.5, 40.0]	27.1	[15.5, 40.0]	25.0	[13.9, 37.8]	1.1	[0.4, 1.8]
2006	33	N<35	—	N<35	—	N<35	—	N<35	—	N<35	—	N<35	—
2007	39	51.3	[34.8, 65.5]	40.6	[25.2, 55.5]	29.8	[16.3, 44.5]	27.1	[14.2, 41.7]	27.1	[14.2, 41.7]	1.1	[0.5, 2.5]
2008	24	N<35	—	N<35	—	N<35	—	N<35	—	N<35	—	N<35	—
2009	39	51.3	[34.8, 65.5]	30.8	[17.3, 45.4]	30.8	[17.3, 45.4]	25.6	[13.3, 39.9]	25.6	[13.3, 39.9]	1.1	[0.3, 1.8]
2010	67	44.3	[32.2, 55.8]	27.5	[17.4, 38.6]	24.5	[14.9, 35.3]	22.9	[13.7, 33.6]	21.4	[12.5, 31.9]	0.8	[0.5, 1.2]
2011	47	59.6	[44.2, 72.0]	44.7	[30.2, 58.1]	38.3	[24.6, 51.8]	34.0	[21.0, 47.5]	34.0	[21.0, 47.5]	1.4	[0.5, 3.7]
2012	54	46.3	[32.7, 58.8]	35.2	[22.8, 47.8]	23.9	[13.6, 35.9]	19.9	[10.5, 31.6]	17.9	[9.0, 29.3]	0.8	[0.5, 1.7]
2013	68	54.4	[41.9, 65.3]	44.1	[32.2, 55.4]	36.8	[25.5, 48.1]	30.9	[20.4, 42.0]	29.4	[19.1, 40.4]	1.5	[0.7, 2.6]
2014	87	52.9	[41.9, 62.7]	41.4	[31.0, 51.4]	39.1	[28.9, 49.1]	39.1	[28.9, 49.1]	36.8	[26.8, 46.8]	1.1	[0.6, 2.5]
2015	78	53.8	[42.2, 64.1]	44.9	[33.6, 55.5]	41.0	[30.1, 51.6]	35.9	[25.5, 46.4]	35.9	[25.5, 46.4]	1.5	[0.6, 3.2]
2016	69	66.7	[54.2, 76.4]	55.1	[42.6, 65.9]	44.9	[33.0, 56.1]	41.4	[29.6, 52.8]	no FU	—	2.6	[1.0, .]
2017	90	68.9	[58.2, 77.4]	60.0	[49.1, 69.2]	53.7	[42.7, 63.5]	no FU	—	no FU	—	>3	

Survival results based on small number of persons initially at risk (N<35) can be too variable to be practically meaningful and are therefore not reported.


Table 74 – Malignant melanoma of the skin (2004-2017), time trend relative survival with incidence year

Unadjusted relative survival, %											
Characteristic	N at risk	%	1 year	%	2 year	%	3 year	%	4 year	%	5 year
			95% CI		95% CI		95% CI		95% CI		95% CI
All											
2004	1,467	95.8	[94.4, 96.9]	92.1	[90.3, 93.7]	90.0	[87.9, 91.8]	87.5	[85.2, 89.6]	86.5	[84.1, 88.8]
2005	1,563	96.1	[94.8, 97.2]	92.1	[90.3, 93.7]	89.9	[87.9, 91.8]	87.8	[85.5, 89.8]	86.6	[84.2, 88.8]
2006	1,575	95.8	[94.5, 96.9]	92.7	[91.0, 94.2]	89.7	[87.6, 91.5]	89.2	[87.0, 91.1]	88.1	[85.7, 90.2]
2007	1,673	95.5	[94.2, 96.6]	92.4	[90.7, 93.9]	90.6	[88.7, 92.3]	88.6	[86.5, 90.5]	88.1	[85.9, 90.2]
2008	1,851	96.3	[95.2, 97.3]	92.9	[91.3, 94.3]	91.5	[89.7, 93.1]	90.1	[88.1, 91.9]	88.5	[86.4, 90.5]
2009	1,873	97.0	[95.8, 97.9]	94.4	[92.9, 95.7]	91.7	[90.0, 93.4]	89.7	[87.8, 91.6]	89.5	[87.4, 91.4]
2010	2,080	95.6	[94.4, 96.6]	93.5	[92.0, 94.8]	91.2	[89.5, 92.7]	89.9	[88.1, 91.6]	89.0	[87.0, 90.8]
2011	2,144	96.7	[95.6, 97.6]	94.2	[92.8, 95.4]	91.8	[90.1, 93.3]	90.7	[88.9, 92.3]	90.4	[88.5, 92.2]
2012	2,435	97.4	[96.5, 98.2]	95.5	[94.3, 96.6]	94.5	[93.1, 95.8]	93.9	[92.3, 95.3]	93.1	[91.4, 94.7]
2013	2,559	97.4	[96.5, 98.2]	95.2	[94.0, 96.3]	94.2	[92.8, 95.5]	93.5	[91.9, 94.9]	93.1	[91.4, 94.6]
2014	2,815	97.5	[96.7, 98.3]	95.7	[94.6, 96.7]	94.8	[93.5, 96.0]	93.5	[92.0, 94.8]	93.4	[91.8, 94.9]
2015	2,747	97.5	[96.6, 98.3]	96.2	[95.1, 97.2]	95.9	[94.6, 97.1]	95.0	[93.6, 96.3]	95.2	[93.5, 96.7]
2016	2,981	98.4	[97.6, 99.0]	96.5	[95.4, 97.4]	95.0	[93.7, 96.2]	94.3	[92.7, 95.7]	no FU	—
2017	3,235	98.2	[97.5, 98.9]	97.0	[96.0, 97.9]	95.8	[94.5, 97.0]	no FU	—	no FU	—
Combined Stage I											
2004	725	100.2	[99.1, 100.8]	100.0	[98.5, 101.1]	99.9	[98.0, 101.3]	97.8	[95.4, 99.7]	97.5	[94.8, 99.6]
2005	785	100.2	[99.1, 100.7]	99.6	[98.1, 100.6]	99.2	[97.4, 100.5]	98.3	[96.1, 100.0]	98.8	[96.5, 100.6]
2006	907	100.5	[99.6, 101.0]	100.9	[99.7, 101.7]	100.9	[99.4, 102.0]	101.6	[99.9, 102.8]	101.3	[99.4, 102.9]
2007	923	99.7	[98.5, 100.4]	99.5	[98.0, 100.5]	99.9	[98.3, 101.1]	99.6	[97.7, 101.1]	100.1	[98.1, 101.8]
2008	1,081	100.1	[99.3, 100.7]	100.1	[98.8, 100.9]	100.0	[98.5, 101.1]	99.6	[97.8, 101.0]	99.6	[97.7, 101.2]
2009	991	100.5	[99.6, 101.0]	101.0	[99.8, 101.7]	100.3	[98.7, 101.4]	99.3	[97.5, 100.8]	99.8	[97.7, 101.4]
2010	1,278	100.4	[99.7, 100.8]	100.9	[99.9, 101.5]	100.4	[99.1, 101.4]	100.1	[98.5, 101.3]	100.0	[98.3, 101.4]
2011	1,171	99.8	[98.8, 100.4]	99.8	[98.6, 100.7]	100.2	[98.7, 101.3]	100.5	[98.9, 101.8]	101.0	[99.2, 102.5]



2012	1,362	100.8	[100.2, 101.2]	101.5	[100.6, 102.1]	101.8	[100.7, 102.7]	102.0	[100.7, 103.1]	101.9	[100.3, 103.2]
2013	1,796	100.5	[99.8, 100.9]	100.9	[100.1, 101.5]	101.3	[100.3, 102.1]	101.8	[100.6, 102.8]	102.3	[101.0, 103.4]
2014	2,032	101.1	[100.6, 101.3]	101.2	[100.5, 101.8]	101.6	[100.7, 102.4]	101.5	[100.4, 102.5]	102.1	[100.8, 103.2]
2015	1,990	100.9	[100.4, 101.2]	101.4	[100.6, 101.9]	101.9	[101.0, 102.6]	102.5	[101.4, 103.4]	103.3	[102.0, 104.4]
2016	2,126	100.7	[100.2, 101.0]	100.7	[99.9, 101.3]	101.1	[100.1, 101.9]	101.2	[99.9, 102.3]	no FU	—
2017	2,407	100.3	[99.8, 100.7]	100.8	[100.0, 101.3]	101.2	[100.2, 102.1]	no FU	—	no FU	—
Combined Stage II											
2004	200	97.0	[92.3, 100.0]	85.9	[78.9, 91.4]	79.2	[71.3, 85.9]	73.7	[65.3, 81.2]	71.7	[62.9, 79.8]
2005	248	98.1	[94.2, 100.5]	91.4	[85.8, 95.8]	85.7	[79.1, 91.3]	81.6	[74.3, 87.9]	78.3	[70.5, 85.2]
2006	277	97.1	[93.3, 99.6]	87.8	[82.3, 92.3]	77.2	[70.6, 83.0]	74.1	[67.1, 80.5]	71.4	[63.9, 78.2]
2007	254	96.3	[92.1, 99.1]	90.7	[85.2, 95.0]	83.6	[77.1, 89.2]	78.4	[71.2, 84.7]	77.5	[69.9, 84.3]
2008	296	94.6	[90.4, 97.5]	82.4	[76.7, 87.3]	74.7	[68.2, 80.5]	71.8	[65.0, 78.1]	66.1	[58.9, 72.9]
2009	301	98.0	[94.6, 100.2]	91.1	[86.1, 95.1]	84.9	[79.0, 89.9]	82.0	[75.6, 87.6]	80.5	[73.7, 86.6]
2010	286	94.9	[90.8, 97.8]	88.7	[83.3, 93.0]	80.6	[74.3, 86.0]	74.9	[68.1, 81.0]	71.4	[64.2, 78.0]
2011	333	98.1	[94.8, 100.3]	91.8	[87.0, 95.6]	82.3	[76.5, 87.4]	77.1	[70.8, 82.8]	74.3	[67.6, 80.5]
2012	323	97.8	[94.3, 100.1]	89.4	[84.3, 93.5]	84.4	[78.5, 89.5]	83.3	[76.9, 88.9]	79.0	[72.1, 85.2]
2013	439	95.5	[92.3, 97.8]	88.2	[83.9, 91.9]	85.0	[80.1, 89.2]	81.9	[76.6, 86.7]	79.6	[73.9, 84.8]
2014	430	94.0	[90.6, 96.7]	90.2	[85.9, 93.8]	85.2	[80.2, 89.6]	80.2	[74.7, 85.2]	79.8	[73.9, 85.1]
2015	442	95.9	[92.7, 98.2]	91.1	[87.0, 94.5]	89.1	[84.4, 93.1]	84.4	[79.2, 89.1]	81.9	[75.9, 87.4]
2016	471	96.8	[93.9, 99.0]	90.6	[86.5, 94.1]	85.7	[80.9, 90.0]	82.6	[76.8, 87.8]	no FU	—
2017	466	97.0	[94.1, 99.2]	92.2	[88.1, 95.5]	87.2	[81.7, 91.9]	no FU	—	no FU	—
Combined Stage III											
2004	70	91.9	[82.1, 96.9]	80.4	[68.4, 88.8]	66.3	[53.2, 76.9]	67.1	[53.9, 77.9]	65.0	[51.5, 76.2]
2005	79	88.9	[79.4, 94.5]	68.2	[56.4, 77.7]	66.7	[54.6, 76.6]	58.0	[45.6, 68.9]	50.6	[38.3, 62.0]
2006	93	86.2	[77.0, 92.3]	73.4	[62.6, 82.0]	64.8	[53.4, 74.5]	61.3	[49.7, 71.5]	60.2	[48.3, 70.7]
2007	93	91.2	[82.9, 96.1]	83.0	[72.9, 90.1]	79.0	[68.3, 87.2]	74.7	[63.4, 83.8]	66.8	[55.0, 76.9]
2008	100	88.9	[80.6, 94.1]	79.8	[70.1, 87.0]	76.9	[66.7, 84.8]	69.4	[58.6, 78.4]	64.1	[53.0, 73.7]
2009	102	88.8	[80.5, 94.2]	77.7	[67.6, 85.4]	63.3	[52.4, 72.8]	53.9	[42.9, 64.0]	51.7	[40.7, 62.1]



2010	113	93.6	[86.7, 97.3]	87.7	[79.4, 93.3]	77.7	[68.0, 85.2]	73.2	[63.1, 81.5]	72.6	[62.2, 81.2]
2011	121	90.6	[83.4, 95.1]	82.1	[73.4, 88.6]	71.4	[61.8, 79.4]	67.2	[57.3, 75.8]	63.8	[53.6, 72.7]
2012	125	92.2	[85.5, 96.3]	79.9	[71.2, 86.5]	75.4	[66.1, 82.8]	68.8	[59.1, 77.1]	64.7	[54.7, 73.4]
2013	176	98.5	[94.4, 100.4]	88.6	[82.1, 93.2]	80.7	[73.2, 86.7]	74.8	[66.8, 81.6]	71.9	[63.6, 79.1]
2014	152	92.0	[85.9, 95.8]	77.2	[69.2, 83.6]	74.9	[66.6, 81.8]	69.9	[61.1, 77.3]	66.1	[57.1, 74.0]
2015	153	91.4	[85.3, 95.3]	86.8	[79.7, 91.9]	82.0	[74.2, 88.1]	71.9	[63.2, 79.3]	70.9	[61.7, 78.8]
2016	193	95.6	[91.1, 98.3]	86.0	[79.6, 90.9]	78.7	[71.5, 84.6]	72.9	[64.5, 80.0]	no FU	—
2017	209	96.8	[92.5, 99.2]	88.9	[82.9, 93.4]	79.9	[71.5, 86.6]	no FU	—	no FU	—
Combined Stage IV											
2004	44	53.5	[37.9, 67.1]	37.8	[23.5, 52.4]	33.8	[19.9, 48.6]	34.6	[20.4, 49.7]	32.8	[18.8, 48.2]
2005	34	N<35	—	N<35	—	N<35	—	N<35	—	N<35	—
2006	41	61.5	[44.5, 75.0]	37.3	[22.4, 52.5]	28.1	[15.0, 43.1]	26.3	[13.5, 41.6]	19.3	[8.5, 33.8]
2007	52	73.3	[59.0, 83.6]	51.6	[37.2, 64.6]	38.1	[24.8, 51.7]	27.6	[15.9, 40.9]	28.0	[16.1, 41.5]
2008	52	56.7	[41.9, 69.2]	42.0	[28.2, 55.6]	39.1	[25.5, 53.0]	36.0	[22.7, 50.0]	28.3	[16.2, 42.2]
2009	46	56.2	[40.4, 69.6]	42.3	[27.3, 56.9]	33.1	[19.2, 48.3]	27.1	[14.3, 42.3]	25.5	[13.0, 40.7]
2010	46	45.7	[31.2, 59.3]	30.1	[17.1, 44.4]	18.9	[8.8, 32.3]	19.2	[8.9, 32.9]	17.3	[7.6, 30.8]
2011	43	61.6	[44.9, 74.9]	46.8	[30.9, 61.6]	32.7	[18.8, 47.8]	23.0	[11.4, 37.5]	20.7	[9.7, 35.1]
2012	39	57.9	[40.4, 72.2]	40.9	[25.1, 56.4]	34.5	[19.7, 50.2]	30.1	[16.1, 46.1]	31.2	[16.7, 47.8]
2013	40	49.9	[33.9, 64.2]	29.8	[16.7, 44.4]	25.1	[12.8, 39.6]	22.9	[11.1, 37.6]	17.8	[7.5, 32.0]
2014	40	68.5	[50.8, 81.5]	52.8	[35.7, 67.9]	43.6	[27.3, 59.4]	39.3	[23.4, 55.6]	37.8	[21.9, 54.6]
2015	39	57.5	[40.4, 71.8]	30.5	[16.5, 46.1]	26.0	[12.9, 41.7]	23.8	[11.2, 39.6]	24.3	[11.4, 40.4]
2016	56	72.2	[58.0, 82.8]	65.0	[50.0, 77.2]	51.6	[36.8, 65.3]	50.5	[34.7, 65.3]	no FU	—
2017	45	59.2	[42.8, 72.8]	44.7	[29.1, 59.7]	no FU	—	no FU	—	no FU	—
Combined Stage NA											
2004	33	N<35	—	N<35	—	N<35	—	N<35	—	N<35	—
2005	48	51.0	[35.5, 64.8]	35.1	[21.4, 49.5]	27.3	[15.1, 41.5]	28.0	[15.5, 42.5]	26.4	[14.1, 41.0]
2006	33	N<35	—	N<35	—	N<35	—	N<35	—	N<35	—
2007	39	52.1	[35.5, 66.5]	42.1	[26.1, 57.5]	31.2	[17.0, 46.9]	28.9	[15.2, 44.6]	29.4	[15.4, 45.3]



2008	24	N<35	—	N<35	—	N<35	—	N<35	—	N<35	—
2009	39	48.0	[31.3, 63.1]	28.6	[15.4, 43.5]	29.6	[15.9, 45.0]	25.5	[12.7, 40.9]	26.4	[13.2, 42.5]
2010	67	44.1	[32.0, 55.7]	27.7	[17.4, 39.1]	25.1	[15.2, 36.6]	24.3	[14.4, 36.0]	23.4	[13.5, 35.2]
2011	47	57.9	[41.8, 71.2]	44.2	[29.2, 58.4]	39.0	[24.6, 53.5]	35.8	[21.8, 50.5]	36.6	[22.3, 51.7]
2012	54	45.4	[31.7, 58.4]	35.7	[22.9, 49.0]	24.5	[13.6, 37.3]	20.5	[10.5, 33.2]	18.9	[9.3, 31.5]
2013	68	54.0	[41.2, 65.3]	44.7	[32.3, 56.4]	37.8	[26.1, 49.7]	32.3	[21.2, 44.2]	31.3	[20.3, 43.3]
2014	87	52.4	[41.1, 62.6]	41.5	[30.8, 52.0]	40.0	[29.3, 50.6]	40.9	[29.9, 51.7]	39.4	[28.5, 50.5]
2015	78	53.6	[41.5, 64.4]	46.2	[34.3, 57.5]	43.6	[31.7, 55.3]	39.2	[27.6, 51.2]	40.5	[28.4, 52.8]
2016	69	66.3	[53.0, 76.8]	56.0	[42.7, 67.8]	47.2	[34.4, 59.4]	43.7	[30.3, 56.9]	no FU	—
2017	90	69.7	[58.4, 78.8]	62.3	[50.6, 72.4]	54.4	[41.4, 66.1]	no FU	—	no FU	—

Survival results based on small number of persons initially at risk (N<35) can be too variable to be practically meaningful and are therefore not reported.



Appendix 5.2. Reimbursement criteria for selected drugs

Table 75 – BRAF and MEK inhibitors in Melanoma

Drug	Trade name	Date reimbursement	start	Indication NI	Indication Fr
Vemurafenib	Zelboraf	1/4/2013		De specialiteit komt voor vergoeding in aanmerking indien ze wordt toegediend in monotherapie in het kader van de behandeling van een volwassen patiënt met een gevorderd (niet reseceerbare of gemetastaseerd) melanoom dat positief is voor de BRAF V600-mutatie zoals aangetoond door middel van een gevalideerde test uitgevoerd in een laboratorium met ervaring, dat de validiteit van de analyse kan garanderen.	La spécialité fait l'objet d'un remboursement si elle est administrée en monothérapie dans le cadre du traitement d'un patient adulte atteint d'un mélanome avancé (non résécable ou métastatique) porteur d'une mutation BRAF V600, comme démontré par un test validé et effectué dans un laboratoire expérimenté pouvant garantir la validation des procédures d'analyse.
Dabrafenib	Tafinlar	1/5/2014		De specialiteit komt voor vergoeding in aanmerking indien zij wordt toegediend in monotherapie in het kader van de behandeling van een volwassen patiënt met een gevorderd (niet reseceerbare of gemetastaseerd) melanoom dat positief is voor de BRAFV600-mutatie.	La spécialité fait l'objet d'un remboursement si elle est administrée en monothérapie dans le cadre du traitement d'un patient adulte atteint d'un mélanome avancé (non résécable ou métastatique) porteur d'une mutation BRAFV600.
		1/2/2017		Deze paragraaf 140208 van hoofdstuk VIII vervangt paragraaf 8560000 van hoofdstuk IV voor de vergoeding van dabrafenib in combinatietherapie bij gevorderd melanoom. De specialiteit komt voor vergoeding in aanmerking indien ze wordt toegediend in het kader van de behandeling van een volwassen patiënt met een gevorderd (niet reseceerbare of gemetastaseerd) melanoom dat positief is voor de BRAFV600-mutatie.	Ce paragraphe 140208 du chapitre VIII remplace le paragraphe 8560000 du chapitre IV pour le remboursement de dabrafenib en combithérapie dans le mélanome avancé. A titre transitoire, les autorisations § 8560000 qui ont été délivrées pour le dabrafenib avant l'entrée en vigueur de la présente réglementation, peuvent conserver leur validité conformément aux dispositions énoncées dans ces autorisations. La spécialité fait l'objet d'un remboursement si elle est administrée dans le cadre du traitement d'un patient adulte atteint d'un mélanome avancé (non résécable ou métastatique) porteur d'une mutation BRAFV600.
		1/8/2019		De specialiteit komt voor vergoeding in aanmerking indien ze wordt toegediend in combinatie met trametinib voor de adjuvante behandeling van een volwassen patiënt, na complete resectie van een stadium III melanoom dat positief is voor de BRAFV600-mutatie zoals aangetoond door middel	La spécialité fait l'objet d'un remboursement si elle est administrée en combinaison avec le trametinib pour le traitement adjuvant d'un patient adulte, après résection complète d'un mélanome de stade III, porteur d'une mutation BRAFV600, comme démontré par un test validé et effectué dans un



			van een gevalideerde test uitgevoerd in een laboratorium met ervaring, dat de validiteit van de analyse kan garanderen.	laboratoire expérimenté pouvant garantir la validation des procédures d'analyse.
Trametinib	Mekinist	1/2/2017	De specialiteit komt voor vergoeding in aanmerking indien ze wordt toegediend in combinatie met dabrafenib voor de behandeling van een volwassen patiënt met een gevorderd (niet reseceerbare of gemetastaseerd) melanoom dat positief is voor de BRAFV600-mutatie zoals aangetoond door middel van een gevalideerde test uitgevoerd in een laboratorium met ervaring, dat de validiteit van de analyse kan garanderen.	La spécialité fait l'objet d'un remboursement si elle est administrée en combinaison avec le dabrafenib pour le traitement d'un patient adulte atteint d'un mélanome avancé (non résécable ou métastatique) porteur d'une mutation BRAFV600, comme démontré par un test validé et effectué dans un laboratoire expérimenté pouvant garantir la validation des procédures d'analyse.

Table 76 – Immunotherapy in Melanoma

Drug	Trade name	Date reimbursement	start	Indication NI	Indication Fr
Ipilimumab	Yervoy	1/6/2012		De specialiteit komt voor vergoeding in aanmerking indien ze wordt toegediend voor de behandeling van een patiënt die minstens 18 jaar is, met Eastern Cooperative Oncology Group (ECOG) performance van 0 of 1, die lijdt aan een gevorderd (niet reseceerbare of gemetastaseerd) melanoom.	La spécialité fait l'objet d'un remboursement si elle est administrée pour le traitement d'un patient âgé d'au moins 18 ans, ayant un indice de performance Eastern Cooperative Oncology Group (ECOG) 0 ou 1, atteint d'un mélanome avancé (non résécable ou métastatique).
Nivolumab	Opdivo	1/4/2016		behandeling van gevorderd (inoperabel of gemetastaseerd) melanoom bij volwassenen (monotherapie)	traitement des patients adultes atteints d'un mélanome avancé (non résécable ou métastatique) (monothérapie)
		1/1/2017		behandeling van gevorderd (inoperabel of gemetastaseerd) melanoom bij volwassenen (in combinatie met ipilimumab)	traitement des patients adultes atteints d'un mélanome avancé (non résécable ou métastatique) (en association à l'ipilimumab)
		1/9/2018		Adjuvante behandeling van melanoom bij volwassenen waarbij de lymfeklieren betrokken zijn of in geval van gemetastaseerde ziekte waarbij volledige resectie is uitgevoerd (monotherapie)	traitement adjuvant des patients adultes atteints d'un mélanome avec atteinte des ganglions lymphatiques ou une maladie métastatique, et ayant subi une résection complète (monothérapie)
Pembrolizumab	Keytruda	1/5/2016		de behandeling van gevorderd (inoperabel of gemetastaseerd) melanoom bij volwassenen (monotherapie)	le traitement des patients adultes atteints d'un mélanome avancé (non résécable ou métastatique) (monothérapie)
		1/1/2019		adjuvante behandeling bij volwassenen met stadium III-melanoom waarbij lymfeklieren	le traitement adjuvant des patients adultes atteints d'un mélanome de stade III avec atteinte



betrokken zijn en bij wie complete resectie heeft plaatsgevonden (monotherapie)	ganglionnaire, ayant eu une résection complète (monothérapie)
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Appendix 5.3. Medical literature: search for evidence

Appendix 5.3.1. Search medical literature (systematic reviews)

The search for systematic reviews in MEDLINE, PreMedline and the Cochrane library of systematic reviews (inception to search date) specifically developed for this research question, yielded 139 records (Figure 220). After de-duplication, the 119 most recent records of the 137 remaining records were screened based on title and abstract, of which 86 were excluded. In total 33 full text articles were assessed for eligibility. Based on full text evaluation, 30 reviews were excluded (Figure 221).

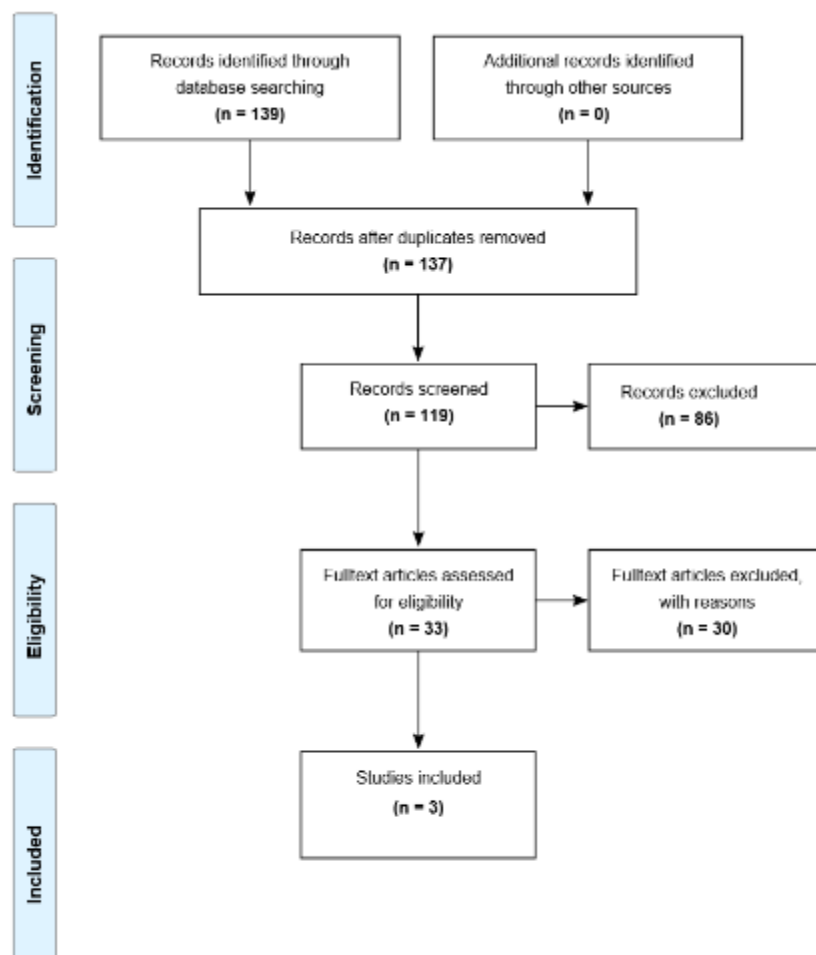
**Figure 144 – Melanoma: Selection of SRs - Study flow**

**Table 77 – Melanoma: excluded reviews and reason for exclusion**

	Year	Publication	Reason for exclusion
1	2020	Zhou, X. Yao, Z. Yang, H. et al. Are immune-related adverse events associated with the efficacy of immune checkpoint inhibitors in patients with cancer? A systematic review and meta-analysis. BMC Med 2020; 18(1):87	Wrong research question
2	2020	van Opijnen, M. P. Dirven, L. Coremans, I. E. M. et al. The impact of current treatment modalities on the outcomes of patients with melanoma brain metastases: A systematic review Int J Cancer 2020;146(6):1479-1489	No critical appraisal, no meta-analysis
3	2020	Silvinato, A. Bernardo, W. M. Floriano, I. Advanced melanoma in adults: Pembrolizumab as a treatment option. Rev Assoc Med Bras 2020;66(2):100-107	Not a systematic review
4	2020	Li, J. Kan, H. Zhao, L. et al. Immune checkpoint inhibitors in advanced or metastatic mucosal melanoma: a systematic review. Ther Adv Med Oncol 2020;12	Wrong population
5	2020	Gorry, C. McCullagh, L. Barry, M. Economic Evaluation of Systemic Treatments for Advanced Melanoma: A Systematic Review. Value Health 2020;23(1):52-60	No full HTA report with primary economic evaluation
6	2019	Zhang, R. Li, X. You, Z. et al. A large scale meta analysis identifies common adverse events with checkpoint inhibitors vs chemotherapy in melanoma patients. Int Immunopharmacol 2019;74:105691	wrong outcomes
7	2019	Zhang, B. Zhou, Y. L. Chen, X. et al. Efficacy and safety of CTLA-4 inhibitors combined with PD-1 inhibitors or chemotherapy in patients with advanced melanoma Int Immunopharmacol 2019;68:131-136	Single-arm studies included, no meta-analysis
8	2019	Yu, Q. Xie, J. Li, J. et al. Clinical outcomes of BRAF plus MEK inhibition in melanoma: A meta-analysis and systematic review Cancer Med 2019;8(12):5414-5424	No additional information
9	2019	Yang, W. Li, S. Yang, Q. Risk of dermatologic and mucosal adverse events associated with PD-1/PD-L1 inhibitors in cancer patients: A meta-analysis of randomized controlled trials Medicine (Baltimore) 2019;98(20):e15731	wrong outcomes
10	2019	Vinal, D. Martinez, D. Espinosa, E. Efficacy of rechallenge with BRAF inhibition therapy in patients with advanced BRAFV600 mutant melanoma Clin Transl Oncol 2019;21(8):1061-1066	Not within reimbursement criteria
11	2019	Rulli, E. Legramandi, L. Salvati, L. Mandala, M. The impact of targeted therapies and immunotherapy in melanoma brain metastases: A systematic review and meta-analysis Cancer 2019;125(21):3776-3789	single-arm studies included
12	2019	Rahouma, M. Karim, N. A. Baudo, M. et al. Cardiotoxicity with immune system targeting drugs: a meta-analysis of anti-PD/PD-L1 immunotherapy randomized clinical trials Immunotherapy 2019;11(8):725-735	wrong outcomes
13	2019	Mincu, R. I. Mahabadi, A. A. Michel, L. et al. Cardiovascular Adverse Events Associated With BRAF and MEK Inhibitors: A Systematic Review and Meta-analysis JAMA netw 2019;2(8):e1988890	wrong outcomes



	Year	Publication	Reason for exclusion
14	2019	Li, J. Gu, J. Efficacy and safety of ipilimumab for treating advanced melanoma: A systematic review and meta-analysis. J Clin Pharm Ther 2019;44(3):420-429	Included
15	2019	Geldof, T. Rawal, S. Dyck, W. V. Huys, I. Comparative and combined effectiveness of innovative therapies in cancer: a literature review J 2019;8(4):205-216	wrong research question
16	2019	Franken, M. G. Leeneman, B. Gheorghe, M. et al. A systematic literature review and network meta-analysis of effectiveness and safety outcomes in advanced melanoma Eur J Cancer 2019;123:58-71	No additional information
17	2019	Chen, P. Chen, F. Zhou, B. The risk of dermatological toxicities of combined BRAF and MEK inhibition versus BRAF inhibition alone in melanoma patients: a systematic review and meta-analysis Cutan 2019;38(2):105-111	wrong outcomes
18	2019	Chen, P. Chen, F. Zhou, B. Systematic review and meta-analysis of prevalence of dermatological toxicities associated with vemurafenib treatment in patients with melanoma Clin Exp Dermatol 2019;44(3):243-251	wrong outcomes
19	2019	An, Q. Liu, Z. Comparative efficacy and safety of combination therapies for advanced melanoma: a network meta-analysis BMC Cancer 2019;19(1):43	Included
20	2018	Xu, C. Chen, Y. P. Du, X. J. et al. Comparative safety of immune checkpoint inhibitors in cancer: systematic review and network meta-analysis BMJ 2018;363:k4226	wrong research question
21	2018	Xie, T. Huang, C. Y. Kang, X. et al. A Network Meta-Analysis of Short and Long-Term Efficacy of Targeted Therapy With Single or Double-Drug Regimens in the Treatment of Stage III/IV Malignant Melanoma Based on 16 Randomized Controlled Trials J Cell Biochem 2019;119(1):640-649	No additional information
22	2018	Tran, A. D. Fogarty, G. Nowak, A. K. et al. A systematic review and meta-analysis of utility estimates in melanoma Br J Dermatol 2018;178(2):384-393	Wrong research question
23	2018	Tandon, P. Bourassa-Blanchette, S. Bishay, K. et al. The Risk of Diarrhea and Colitis in Patients With Advanced Melanoma Undergoing Immune Checkpoint Inhibitor Therapy: A Systematic Review and Meta-Analysis J Immunother 2018;41(3):101-108	wrong outcomes
24	2018	Pasquali, S. Hadjinicolaou, A. V. Chiarion Sileni, V. et al. Systemic treatments for metastatic cutaneous melanoma Cochrane Database Syst Rev 2018;2:CD011123	Included
25	2018	Menshawy, A. Eltonob, A. A. Barkat, S. A. et al. Nivolumab monotherapy or in combination with ipilimumab for metastatic melanoma: systematic review and meta-analysis of randomized-controlled trials Melanoma Res 2018;28(5):371-379	No additional information
26	2018	Li, J. Gu, J. Efficacy and safety of PD-1 inhibitors for treating advanced melanoma: a systematic review and meta-analysis Immunotherapy Immunotherapy 2018;10(15): 1293-1302	No additional information



	Year	Publication	Reason for exclusion
27	2018	Kim, S. Kim, H. T. Suh, H. S. Combination therapy of BRAF inhibitors for advanced melanoma with BRAF V600 mutation: a systematic review and meta-analysis J Dermatolog Treat 2018;29(3):314-321	No additional information
28	2018	Faghfuri, E. Nikfar, S. Niaz, K. et al. Mitogen-activated protein kinase (MEK) inhibitors to treat melanoma alone or in combination with other kinase inhibitors Expert Opin Drug Metab Toxicol 2018;14(3):317-330	Not a systematic review
29	2018	Copley-Merriman, C. Stevinson, K. Liu, F. X. et al. Direct costs associated with adverse events of systemic therapies for advanced melanoma: Systematic literature review Medicine (Baltimore) 2018;97(31):e11736	Wrong outcome
30	2017	Pike, E. Hamidi, V. Saeterdal, I. et al. Multiple treatment comparison of seven new drugs for patients with advanced malignant melanoma: a systematic review and health economic decision model in a Norwegian setting BMJ Open 2017;7(8):e014880	Full HTA report is included in the HE chapter
31	2017	Hao, C. Tian, J. Liu, H. et al. Efficacy and safety of anti-PD-1 and anti-PD-1 combined with anti-CTLA-4 immunotherapy to advanced melanoma: A systematic review and meta-analysis of randomized controlled trials Medicine (Baltimore) 2017;96(26):e7325	No additional information
32	2017	Devji, T. Levine, O. Neupane, B. et al. Systemic Therapy for Previously Untreated Advanced BRAF-Mutated Melanoma: A Systematic Review and Network Meta-Analysis of Randomized Clinical Trials JAMA Oncol 2017;3(3):366-373	No additional information
33	2017	da Silveira Nogueira Lima, J. P. Georgieva, M. Haaland, B. de Lima Lopes, G. A systematic review and network meta-analysis of immunotherapy and targeted therapy for advanced melanoma Cancer Med 2017;6(6):1143-1153	No additional information



Appendix 5.3.2. Melanoma: Critical appraisal systematic reviews

	Pasquali 2018 ⁸⁵		Li 2019 ⁸⁶	
	Score	Rationale/comment	score	Rationale/comment
1. PICO	Y		Y	
2. A priori study design	Y		N	
3. Inclusion study designs	Y		Y	
4. Comprehensive literature search	Y		partial Y	No search of reference lists, trial registers, no consultation of content experts
5. Duplicate study selection	Y		Y	(unclear)
6. Duplicate data extraction	Y		Y	
7. List of excluded studies and rationale	Y		N	
8. Characteristics of included studies provided	Y		Y	
9. Assessment of risk of bias	Y		partial Y	no assessment of selective outcome reporting
10. Sources of funding reported	Y		N	
11. Appropriate methods to combine findings	Y		Y	
12. Assessment of impact RoB in included studies on results MA	Y		N	
13. RoB assessment used in interpretation of results and in conclusions	Y		N	
14. Explanation for and discussion of any observed heterogeneity	Y		Y	
15. Adequate investigation of publication bias and its impact on the results	Y		Y	(too small numbers)
16. Potential sources of conflict of interest reported	Y		Y	



An 2019 ⁸⁷		
	Score	Rationale/comment
1. PICO	Y	
2. A priori study design	N	
3. Inclusion study designs	Y	
4. Comprehensive literature search	Partial yes	No search of trial registries, no consultation of content experts
5. Duplicate study selection	Y	
6. Duplicate data extraction	Y	
7. List of excluded studies and rationale	N	
8. Characteristics of included studies provided	Y	
9. Assessment of risk of bias	Y	
10. Sources of funding reported	N	
11. Appropriate methods to combine findings	Y	
12. Assessment of impact RoB in included studies on results MA	N	
13. RoB assessment used in interpretation of results and in conclusions	N	
14. Explanation for and discussion of any observed heterogeneity	Y	
15. Adequate investigation of publication bias and its impact on the results	N	
16. Potential sources of conflict of interest reported	Y	



Appendix 5.3.3. Search strategy

Appendix 5.3.3.1. Cochrane library of systematic reviews

Date	25/06/2020 09:15:37	
Database	Cochrane@Wiley.com	
Search strategy		
#1	[mh ^"Melanoma"]	1743
#2	[mh ^"Skin neoplasms"]	1521
#3	#1 or #2	2587
#4	[mh ^"Neoplasms, multiple primary"]	78
#5	[mh "neoplasms"]	77268
#6	#4 or #5	77268
#7	neoplasm*:ab,ti	5493
#8	cancer*:ab,ti	137481
#9	carcinoma*:ab,ti	28449
#10	adenocarcinoma*:ab,ti	7391
#11	angiosarcoma*:ab,ti	67
#12	tumour*:ab,ti	11565
#13	tumor*:ab,ti	49313
#14	metast*:ab,ti	37054
#15	malign*:ab,ti	22725
#16	#7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15	187954
#17	[mh "skin"]	4322
#18	skin:ab,ti	44588
#19	cutaneous:ab,ti	7844
#20	nevus:ab,ti	127
#21	nevi:ab,ti	124
#22	dermis:ab,ti	661
#23	epidermis:ab,ti	615
#24	dermato*:ab,ti	9624
#25	corium:ab,ti	6
#26	#18 or #19 or #20 or #21 or #22 or #23 or #24 or #25	55694
#27	(#6 or #16) and #17	324
#28	#6 and #26	3197



Date	25/06/2020 09:15:37	
#29	((neoplasm* or cancer* or carcinoma* or adenocarcinoma* or angiosarcoma* or chrondosarcoma* or sarcoma* or teratoma* or lymphoma* or blastoma* or carcinogenesis or tumour* or tumor* or metast* or malign*) NEAR/5 (skin or cutaneous or nevus or nevi or dermis or epidermis or dermato* or corium)):ab,ti	2879
#30	#27 or #28 or #29	5198
#31	#3 or #30	6690
#32	pembrolizumab:ab,ti	1354
#33	lambrolizumab:ab,ti	2
#34	keytruda:ab,ti	69
#35	"mk 3475":ab,ti	270
#36	mk3475:ab,ti	5
#37	"sch 900475":ab,ti	2
#38	sch900475:ab,ti	9
#39	"1374853-91-4":ab,ti	101
#40	DPT003T46P:ab,ti	0
#41	#32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40	1366
#42	[mh ^"nivolumab"]	395
#43	Nivolumab:ab,ti	1566
#44	"bms 936558":ab,ti	121
#45	bms936558:ab,ti	36
#46	"mdx 1106":ab,ti	16
#47	mdx1106:ab,ti	22
#48	"ono 4538":ab,ti	61
#49	ono4538:ab,ti	0
#50	opdivo:ab,ti	85
#51	"cmab 819":ab,ti	0
#52	cmab819:ab,ti	0
#53	"946414-94-4":ab,ti	81
#54	31YO63LBSN:ab,ti	0
#55	#43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54	1587
#56	#42 or #55	1604
#57	[mh ^"Ipilimumab"]	156
#58	ipilimumab:ab,ti	1067
#59	yervoy:ab,ti	56



Date	25/06/2020 09:15:37	
#60	strentarga:ab,ti	0
#61	"mdx 010":ab,ti	23
#62	mdx10:ab,ti	0
#63	"mdx ctla 4":ab,ti	1
#64	"bms 734016":ab,ti	56
#65	bms734016:ab,ti	27
#66	"mdx 101":ab,ti	0
#67	mdx101:ab,ti	0
#68	"477202-00-9":ab,ti	53
#69	6T8C155666:ab,ti	0
#70	#58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69	1078
#71	#57 or #70	1095
#72	[mh ^"Vemurafenib"]	39
#73	"plx 4032":ab,ti	0
#74	plx4032:ab,ti	12
#75	RO5185426:ab,ti	17
#76	"RO 5185426":ab,ti	0
#77	"rg 7204":ab,ti	0
#78	rg7204:ab,ti	10
#79	vemurafenib:ab,ti	179
#80	zelboraf:ab,ti	13
#81	"r 7204":ab,ti	0
#82	r7204:ab,ti	0
#83	"918504-65-1":ab,ti	11
#84	207SMY3FQT:ab,ti	0
#85	#73 OR #74 OR #75 OR #76 OR #77 OR #78 OR #79 OR #80 OR #81 OR #82 OR #83 OR #84	183
#86	#72 or #85	187
#87	trametinib:ab,ti	221
#88	"1187431-43-1":ab,ti	4
#89	"gsk 1120212":ab,ti	0
#90	gsk1120212:ab,ti	30
#91	"gsk 1120212b":ab,ti	0
#92	gsk1120212b:ab,ti	2



Date	25/06/2020 09:15:37	
#93	"jtp 74057":ab,ti	0
#94	jtp74057:ab,ti	0
#95	mekinist:ab,ti	7
#96	33E86K87QN:ab,ti	0
#97	#87 OR #88 OR #89 OR #90 OR #91 OR #92 OR #93 OR #94 OR #95 OR #96	235
#98	dabrafenib:ab,ti	187
#99	"gsk 2118436":ab,ti	0
#100	gsk2118436:ab,ti	14
#101	"gsk 2118436a":ab,ti	0
#102	gsk2118436a:ab,ti	0
#103	"gsk 2118436b":ab,ti	0
#104	gsk2118436b:ab,ti	0
#105	tafinlar:ab,ti	7
#106	"1195765-45-7":ab,ti	4
#107	"1195768-06-9":ab,ti	3
#108	QGP4HA4G1B:ab,ti	0
#109	#98 OR #99 OR #100 OR #101 OR #102 OR #103 OR #104 OR #105 OR #106 OR #107 OR #108	192
#110	#41 or #56 or #71 or #86 or #97 or #109	3500
#111	[mh "CTLA-4 Antigen"/AI]	10
#112	[mh "Programmed Cell Death 1 Receptor"/AI]	25
#113	[mh "Proto-Oncogene Proteins B-raf"/AI]	24
#114	[mh "map kinase kinase kinases"/AI]	36
#115	[mh "Mitogen-Activated Protein Kinases"/AI]	50
#116	[mh "Mitogen-Activated Protein Kinase Kinases"/AI]	23
#117	#112 OR #113 OR #114 OR #115 OR #116	126
#118	((("CTLA-4" or CTLA4 or CD152) NEAR/3 (inhibit* or antagonist? or target* or block* or against or anti or multi-targets or multi-target or multi-targeting or reduc*)):ab,ti	82
#119	((("PD-1" or PD1 or CD279) NEAR/3 (inhibit* or antagonist? or target* or block* or against or anti or multi-targets or multi-target or multi-targeting or reduc*)):ab,ti	200
#120	("programmed cell death" NEAR/3 (inhibit* or antagonist? or target* or block* or against or anti or multi-targets or multi-target or multi-targeting or reduc*)):ab,ti	119
#121	(MEK? NEAR/3 (inhibit* or antagonist? or target* or block* or against or anti or multi-targets or multi-target or multi-targeting or reduc*)):ab,ti	348



Date	25/06/2020 09:15:37	
#122	("Mitogen-activated" NEAR/5 (inhibit* or antagonist? or target* or block* or against or anti or multi-targets or multi-target or multi-targeting or reduc*)):ab,ti	0
#123	(BRAF NEAR/3 (inhibit* or antagonist? or target* or block* or against or anti or multi-targets or multi-target or multi-targeting or reduc*)):ab,ti	264
#124	("B-RAF" NEAR/3 (inhibit* or antagonist? or target* or block* or against or anti or multi-targets or multi-target or multi-targeting or reduc*)):ab,ti	0
#125	#118 OR #119 OR #120 OR #121 OR #122 or #123 OR #124	815
#126	#117 OR #125	899
#127	[mh "Antibodies, Monoclonal"]	12727
#128	[mh ^"Protein Kinase Inhibitors"]	762
#129	[mh "Molecular Targeted Therapy"]	133
#130	#127 or #128 or #129	13507
#131	((("new class" or "new classes" or innovative or target*) NEAR/3 (drug? or therapy or therapies or therapeutic* or treatment? or chemotherap*)):ab,ti	11940
#132	(kinase? NEAR/3 (inhibit* or antagonist? or target* or block* or against or anti or multi-targets or multi-target or multi-targeting or reduc*)):ab,ti	3959
#133	(monoclonal NEAR/3 antibod*):ab,ti	8824
#134	"Molecular Targeted" NEXT/2 therap*:ab,ti	89
#135	#131 or #132 or #133 or #134	23771
#136	#130 or #135	34164
#137	#31 and #110	409
#138	#31 AND #126	137
#139	#31 AND #136	746
#140	#137 OR #138 OR #139	924
#141	#140 with Cochrane Library publication date Between Jan 2017 and Dec 2020, in Cochrane Reviews	9
Comments		

*Appendix 5.3.3.2. Medline + PreMedline*

Date	June 23, 2020	
Database	Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946 to June 23, 2020>	
Search strategy		
1	Melanoma/	84100
2	Skin neoplasms/	120623
3	1 or 2	168796
4	Neoplasms, multiple primary/	25838
5	exp neoplasms/	3332785
6	4 or 5	3332785
7	neoplasm\$.ti,ab.	134881
8	cancer\$.ti,ab.	1761740
9	carcinoma\$.ti,ab.	654715
10	adenocarcinoma\$.ti,ab.	145140
11	angiosarcoma\$.ti,ab.	6095
12	tumour\$.ti,ab.	269338
13	tumor\$.ti,ab.	1434719
14	metast\$.ti,ab.	504016
15	malign\$.ti,ab.	573845
16	7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15	3294353
17	exp skin/	223171
18	skin.ti,ab.	524912
19	cutaneous.ti,ab.	150461
20	nevus.ti,ab.	9788
21	nevi.ti,ab.	7591
22	dermis.ti,ab.	22135
23	epidermis.ti,ab.	38431
24	dermato*.ti,ab.	105816
25	corium.ti,ab.	563
26	18 or 19 or 20 or 21 or 22 or 23 or 24 or 25	720196
27	(6 or 16) and 17	37531
28	6 and 26	139046



Date	June 23, 2020	
29	((neoplasm\$ or cancer\$ or carcinoma\$ or adenocarcinoma\$ or angiosarcoma\$ or chrondosarcoma\$ or sarcoma\$ or teratoma\$ or lymphoma\$ or blastoma\$ or carcinogenesis or tumour\$ or tumor\$ or metast\$ or malign\$) adj5 (skin or cutaneous or nevus or nevi or dermis or epidermis or dermato* or corium)).ti,ab.	77613
30	27 or 28 or 29	171621
31	3 or 30	260832
32	pembrolizumab.ab,ti,kf,rn.	3986
33	lambrolizumab.ab,ti,kf,rn.	23
34	keytruda.ab,ti,kf,rn.	75
35	mk 3475.ab,ti,kf,rn.	50
36	mk3475.ab,ti,kf,rn.	4
37	sch 900475.ab,ti,kf,rn.	2
38	sch900475.ab,ti,kf,rn.	0
39	1374853-91-4.ab,ti,kf,rn.	1
40	DPT003T46P.ab,ti,kf,rn.	1675
41	32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40	4012
42	nivolumab/	2385
43	Nivolumab.ab,ti,kf,rn.	5049
44	bms 936558.ab,ti,kf,rn.	24
45	bms936558.ab,ti,kf,rn.	0
46	mdx 1106.ab,ti,kf,rn.	6
47	mdx1106.ab,ti,kf,rn.	1
48	ono 4538.ab,ti,kf,rn.	16
49	ono4538.ab,ti,kf,rn.	0
50	opdivo.ab,ti,kf,rn.	65
51	cmab 819.ab,ti,kf,rn.	0
52	cmab819.ab,ti,kf,rn.	0
53	946414-94-4.ab,ti,kf,rn.	1
54	31YO63LBSN.ab,ti,kf,rn.	2386
55	43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54	5058
56	42 or 55	5058
57	Ipilimumab/	1864
58	ipilimumab.ab,ti,kf,rn.	3584
59	yervoy.ab,ti,kf,rn.	57
60	strentarga.ab,ti,kf,rn.	0



Date	June 23, 2020	
61	"mdx 010".ab,ti,kf,rf.	24
62	mdx10.ab,ti,kf,rn.	0
63	mdx ctla 4.ab,ti,kf,rn.	3
64	bms 734016.ab,ti,kf,rn.	3
65	bms734016.ab,ti,kf,rn.	1
66	mdx 101.ab,ti,kf,rn.	3
67	mdx101.ab,ti,kf,rn.	0
68	477202-00-9.ab,ti,kf,rn.	1
69	6T8C155666.ab,ti,kf,rn.	1
70	58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69	3591
71	57 or 70	3591
72	Vemurafenib/	1305
73	plx 4032.ab,ti,kf,rn.	24
74	plx4032.ab,ti,kf,rn.	172
75	RO5185426.ab,ti,kf,rn.	2
76	RO 5185426.ab,ti,kf,rn.	1
77	rg 7204.ab,ti,kf,rn.	1
78	rg7204.ab,ti,kf,rn.	22
79	vemurafenib.ab,ti,kf,rn.	2335
80	zelboraf.ab,ti,kf,rn.	40
81	r 7204.ab,ti,kf,rn.	0
82	r7204.ab,ti,kf,rn.	0
83	918504-65-1.ab,ti,kf,rn.	1
84	207SMY3FQT.ab,ti,kf,rn.	1306
85	73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84	2384
86	72 or 85	2384
87	trametinib.ab,ti,kf,rn.	1226
88	1187431-43-1.ab,ti,kf,rn.	0
89	gsk 1120212.ab,ti,kf,rn.	6
90	gsk1120212.ab,ti,kf,rn.	52
91	gsk 1120212b.ab,ti,kf,rn.	0
92	gsk1120212b.ab,ti,kf,rn.	1
93	jtp 74057.ab,ti,kf,rn.	6



Date	June 23, 2020	
94	jtp74057.ab,ti,kf,rn.	0
95	mekinist.ab,ti,kf,rn.	11
96	33E86K87QN.ab,ti,kf,rn.	571
97	87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96	1241
98	dabrafenib.ab,ti,kf,rn.	1139
99	gsk 2118436.ab,ti,kf,rn.	3
100	gsk2118436.ab,ti,kf,rn.	33
101	gsk 2118436a.ab,ti,kf,rn.	1
102	gsk2118436a.ab,ti,kf,rn.	1
103	gsk 2118436b.ab,ti,kf,rn.	0
104	gsk2118436b.ab,ti,kf,rn.	0
105	tafinlar.ab,ti,kf,rn.	14
106	1195765-45-7.ab,ti,kf,rn.	1
107	1195768-06-9.ab,ti,kf,rn.	0
108	QGP4HA4G1B.ab,ti,kf,rn.	543
109	98 or 99 or 100 or 101 or 102 or 103 or 104 or 105 or 106 or 107 or 108	1147
110	41 or 56 or 71 or 86 or 97 or 109	12252
111	CTLA-4 Antigen/ai [Antagonists & Inhibitors]	1066
112	Programmed Cell Death 1 Receptor/ai [Antagonists & Inhibitors]	2579
113	Proto-Oncogene Proteins B-raf/ai [Antagonists & Inhibitors]	1734
114	"map kinase kinase kinases"/ai	882
115	exp Mitogen-Activated Protein Kinases/ai	12586
116	exp Mitogen-Activated Protein Kinase Kinases/ai	2850
117	111 or 112 or 113 or 114 or 115 or 116	19849
118	((CTLA-4 or CTLA4 or CD152) adj3 (inhibit* or antagonist? or target* or block* or against or anti or multi-targets or multi-target or multi-targeting or reduc*)).ab,ti,kf.	3593
119	((PD-1 or PD1 or CD279) adj3 (inhibit* or antagonist? or target* or block* or against or anti or multi-targets or multi-target or multi-targeting or reduc*)).ab,ti,kf.	8416
120	(programmed cell death adj3 (inhibit* or antagonist? or target* or block* or against or anti or multi-targets or multi-target or multi-targeting or reduc*)).ab,ti,kf.	2507
121	(MEK? adj3 (inhibit* or antagonist? or target* or block* or against or anti or multi-targets or multi-target or multi-targeting or reduc*)).ab,ti,kf.	10985
122	(Mitogen-activated adj5 (inhibit* or antagonist? or target* or block* or against or anti or multi-targets or multi-target or multi-targeting or reduc*)).ab,ti,kf.	7909



Date	June 23, 2020	
123	(BRAF adj3 (inhibit* or antagonist? or target* or block* or against or anti or multi-targets or multi-target or multi-targeting or reduc*)).ab,ti,kf.	3601
124	(B-RAF adj3 (inhibit* or antagonist? or target* or block* or against or anti or multi-targets or multi-target or multi-targeting or reduc*)).ab,ti,kf.	464
125	118 or 119 or 120 or 121 or 122 or 123 or 124	32668
126	117 or 125	44814
127	exp Antibodies, Monoclonal/	235325
128	Protein Kinase Inhibitors/	45263
129	Molecular Targeted Therapy/	27959
130	127 or 128 or 129	301366
131	((new class* or innovative or target*) adj3 (drug? or therapy or therapies or therapeutic* or treatment? or chemotherap*)).ab,ti,kf.	330433
132	(kinase? adj3 (inhibit* or antagonist? or target* or block* or against or anti or multi-targets or multi-target or multi-targeting or reduc*)).ab,ti,kf.	118162
133	(monoclonal adj3 antibod*).ab,ti,kf.	196475
134	Molecular Targeted Therapy.ab,ti,kf.	1691
135	131 or 132 or 133 or 134	618530
136	130 or 135	761344
137	31 and 110	4059
138	31 and 126	4663
139	31 and 136	19413
140	137 or 138 or 139	21261
141	((systematic review or systematic literature review or systematic scoping review or systematic narrative review or systematic qualitative review or systematic evidence review or systematic quantitative review or systematic meta-review or systematic critical review or systematic mixed studies review or systematic mapping review or systematic cochrane review or "systematic search and review" or systematic integrative review).ti. not comment.pt. not (protocol or protocols).ti. not medline.st.) or (Cochrane Database Syst Rev.ja. and review.pt.) or systematic review.pt.	159535
142	meta-analys*.ti.	109097
143	meta-analysis.pt.	116362
144	exp Technology Assessment, Biomedical/	11075
145	health technology assessment.ti,kf.	1925
146	HtA.ti,kf.	596
147	141 or 142 or 143 or 144 or 145 or 146	253258
148	140 and 147	267



Date	June 23, 2020	
149	limit 148 to yr="2017-Current"	124
Comments		

Appendix 5.4. Economic literature

Appendix 5.4.1. Search economic literature (HTA reports)

The search strategy in CRD's HTA database identified 131 references (Table 78). In a first round, 41 references were selected based on a review of title, keywords and abstract. The 90 remaining references were excluded for the following reasons: intervention (88), design (1), or population (1). In a second round, the full text of the 41 selected references was reviewed. 36 references were excluded (design (18), language (15), price (2) and duplicate (1). Five references were retained. These references are indicated in Table 79 with an asterix (*).

Furthermore, in March and April 2020, the website of the National Institute for Health Research (NIHR) was searched for relevant reports. The following search terms were used: ipilimumab melanoma (28 hits, 3 relevant hits, 1 not previously identified); pembrolizumab melanoma (42 hits, 3 relevant hits, 3 not previously identified); nivolumab melanoma (42 hits, 3 relevant hits, 2 not previously identified); dabrafenib melanoma (25 hits, 3 relevant hits, 2 not previously identified); vemurafenib melanoma (25 hits, 1 relevant hit, 1 not previously identified); trametinib melanoma (25 hits, 2 relevant hits, 0 not previously identified).

Finally, also in March and April 2020, the website of the National Institute for Health and Care Excellence (NICE) was searched. The following search terms were used: ipilimumab melanoma (16 hits, 3 relevant Technology Assessments (TAs), 3 not previously identified); pembrolizumab melanoma (10 hits, 3 relevant TAs, 3 not previously identified); nivolumab melanoma (10 hits, 3 relevant TAs, 2 not previously identified); dabrafenib melanoma (11 hits, 3 relevant TAs, 3 not previously identified); vemurafenib melanoma (13 hits, 1 relevant TA, 1 not previously identified); trametinib melanoma (8 hits, 2 relevant TAs, 2 not previously identified).

An overview of the identified references is provided in Table 79.

Table 78 – Search strategy and results for CRD: HTA

Date			
Date covered	All		
Search Strategy	1	MeSH DESCRIPTOR Melanoma EXPLODE ALL TREES	221
	2	MeSH DESCRIPTOR Skin Neoplasms EXPLODE ALL TREES	194
	3	#1 OR #2	300
	4	* IN HTA	17 351
	5	#3 AND #4	131 references
Note	/		

**Table 79 – Malignant melanoma of skin – Identified HTA reports for the selected drugs**

Selected reports	
•	Nivolumab, Pembrolizumab, Ipilimumab, Vemurafenib, Dabrafenib & Trametinib
•	Pike E, Torkilseng EB, Sæterdal I, Jimenez E, Odgaard-Jensen J, Harboe I, Klemp M. A health technology assessment of the new drugs for inoperable or metastatic malignant melanoma patients. Report from Kunnskapssenteret no. 22–2015. Oslo: Norwegian Knowledge Centre for the Health Services, 2015. ⁸⁸ *
•	Ipilimumab
•	Pan-Canadian Oncology Drug Review (pCODR). 2014. Ipilimumab (Yervoy) for first line advanced melanoma. ⁸⁹ *
•	NICE, TA400. July 2016. Nivolumab in combination with ipilimumab for treating advanced melanoma. ⁹⁰ β <ul style="list-style-type: none"> ○ See nivolumab references.
•	NICE, TA319. July 2014. Ipilimumab for previously untreated advanced (unresectable or metastatic) melanoma. ⁹¹ β <ul style="list-style-type: none"> ○ Wade R, Giannopoulou C, Sideris E, Moe-Byrne T, Harden M, McKenna C, Eastwood A. Ipilimumab for previously untreated unresectable malignant melanoma: A Single Technology Appraisal. CRD and CHE Technology Assessment Group, 2013.⁹² * α
•	NICE, TA268. December 2012. Ipilimumab for previously treated advanced (unresectable or metastatic) melanoma. ⁹³ β <ul style="list-style-type: none"> ○ Dickson R, Boland A, Bagust A, Blundell M, Massey G, Dundar Y, Davis H and Marshall E. Ipilimumab for previously treated unresectable malignant melanoma: A Single Technology Appraisal. LRIg, The University of Liverpool, 2011.⁹⁴ * α
•	Pembrolizumab
•	NICE, TA553. December 2018. Pembrolizumab for adjuvant treatment of resected melanoma with high risk of recurrence. ⁹⁵ β <ul style="list-style-type: none"> ○ Greenhalgh J, Mahon J, Nevitt S, Beale S, Boland A, Lambe T, Dundar Y, Kotas E, McEntee J and Marshall E. Pembrolizumab for adjuvant treatment of resected melanoma with high risk of recurrence [ID1266]: A Single Technology Appraisal. LRIg, University of Liverpool, 2018.⁹⁶ α
•	NICE, TA366. November 2015. Pembrolizumab for advanced melanoma not previously treated with ipilimumab. ⁹⁷ β <ul style="list-style-type: none"> ○ Greenhalgh J, Mahon J, Richardson M, Krishan A, Aslam RW, Beale S, Boland A, Stainthorpe A, Bagust A, Kotas E, Banks L, Payne E. Pembrolizumab for treating advanced melanoma previously untreated with ipilimumab: A Single Technology Appraisal. LRIg, University of Liverpool, 2015.⁹⁸ α
•	NICE, TA357. October 2015. Pembrolizumab for treating advanced melanoma after disease progression with ipilimumab. ⁹⁹ β <ul style="list-style-type: none"> ○ Fleeman N, Bagust A, Richardson M, Krishan A, Boland A, Beale S, Stainthorpe A, Dodd S, Kotas E, Banks L, Payne M. Pembrolizumab for treating unresectable, metastatic melanoma after progression with ipilimumab: A Single Technology Appraisal. LRIg, University of Liverpool, 2015.¹⁰⁰ α
•	Nivolumab
•	NICE, TA558. January 2019. Nivolumab for adjuvant treatment of completely resected melanoma with lymph node involvement or metastatic disease. ¹⁰¹ β <ul style="list-style-type: none"> ○ Edwards SJ, Wakefield V, Cain P, Barton S, Bacelar M. Nivolumab for adjuvant treatment of resected stage III and IV melanoma: A Single Technology Appraisal. BMJ Technology Assessment Group, 2018.¹⁰² α
•	NICE, TA400. July 2016. Nivolumab in combination with ipilimumab for treating advanced melanoma. ⁹⁰ β



- Nivolumab in combination with ipilimumab for untreated, advanced, unresectable melanoma [ID848]^α → no link to full report available. Only link to TA400.
- NICE, TA384. February 2016. Nivolumab for treating advanced (unresectable or metastatic) melanoma.^{103 β}
 - Cooper K, Kalita N, Streit E, Shepherd J, Chorooglou M, Frampton G. Nivolumab for treating advanced (unresectable or metastatic) melanoma: A Single Technology Appraisal. Southampton Health Technology Assessments Centre (SHTAC), 2015.^{104 α}
- Dabrafenib
- NICE, TA544. October 2018. Dabrafenib with trametinib for adjuvant treatment of resected BRAF V600 mutation-positive melanoma.^{105 β}
 - Connock M, Cummins E, Al-Khudairy L, Das A, Court R, Clarke A, Gallacher D, Senaratne S, Johnston R, Sutcliffe P. Dabrafenib in combination with trametinib for adjuvant treatment of resected BRAF V600 positive malignant melanoma (ID1226): A single Technology Appraisal. Warwick Evidence, 2018.^{106 α}
- NICE, TA396. June 2016. Trametinib in combination with dabrafenib for treating unresectable or metastatic melanoma.^{107 β}
 - See trametinib references.
- NICE, TA321. October 2014. Dabrafenib for treating unresectable or metastatic BRAF V600 mutation-positive melanoma.^{108 β}
 - Fleeman N, Bagust A, Beale S, Boland A, Dickson R, Dwan K, Richardson M, Dundar Y, Davis H, Banks L. Dabrafenib for the treatment of unresectable, advanced or metastatic BRAFv600 mutation-positive melanoma[ID605]: A Single Technology Appraisal. Liverpool Reviews and Implementation Group, 2014.^{109 * α}
- Vemurafenib
- NICE, TA269. December 2012. Vemurafenib for treating locally advanced or metastatic BRAF V600 mutation-positive malignant melanoma.^{110 β}
 - Dickson R, Bagust A, Beale S, Blundell M and Proudlove C. Vemurafenib for the treatment of locally advanced or metastatic BRAF V600 mutation positive malignant melanoma: A Single Technology Appraisal. Liverpool Reviews and Implementation Group, 2012.^{111 α}
- Trametinib
- NICE, TA544. October 2018. Dabrafenib with trametinib for adjuvant treatment of resected BRAF V600 mutation-positive melanoma.^{105 β}
 - See dabrafenib references.
- NICE, TA396. June 2016. Trametinib in combination with dabrafenib for treating unresectable or metastatic melanoma.^{107 β}
 - Trametinib and dabrafenib for the treatment of BRAF V600 mutation positive unresectable metastatic melanoma (ID661)^α → no link to full report available. Only link to TA396.

* These references were identified in CRD's HTA database. ^α References identified on NIHR's website. ^β References identified on NICE's website.



Appendix 5.4.2. Results economic literature (HTA reports)

Appendix 5.4.2.1. NOKC (2015): nivolumab, pembrolizumab, ipilimumab, vemurafenib, dabrafenib, trametinib (& cobimetinib)

- QoL:
 - “Ten of the 17 included trials reported health related quality of life.¹¹²⁻¹²¹ In all cases, except for Ribas 2015,¹¹² the health related quality of life were not reported in the mother publication, but in a separate publication reporting the HRQoL data. In all the ten trials the instrument use was the European Organization for Research and Treatment of cancer Quality of Life Questionnaire (EORCT-QLQ-C30), three of these trials also used the EuroQol (EQ-5D) Questionnaire.^{113, 116, 121} However, Long 2015 did not present any results from the EuroQol (EQ-5D).”⁸⁸
 - “The evidence available were mostly of poor quality, as six of the trials did not present the uncertainty (SD, SE, CI or p-value) associated with the results. Therefore, we cannot use the results from the trials in our network meta-analysis, and a cautious interpretation of the conclusions presented in the publications are needed.”⁸⁸
- Results:
 - Results when all interventions are included in the analysis: “Nivolumab has an incremental effect of 0.82 quality adjusted life years and an incremental cost-effectiveness ratio against dacarbazine of about 1.1 million NOK per quality adjusted life year gained. The combination vemurafenib in combination with cobimetinib has an incremental cost-effectiveness ratio against nivolumab of about 19.8 million NOK per quality adjusted life year gained.”⁸⁸
 - Results for the BRAF and MEK mono- and combination therapies: “Dabrafenib has an incremental effect of 0.36 quality adjusted life years and a cost-effectiveness ratio compared to dacarbazine of approximately NOK 2.2 million per quality adjusted life year gained The combination vemurafenib in combination with cobimetinib have an incremental effect of 0.53 quality adjusted life years and incremental cost-effectiveness ratio compared to dabrafenib of about NOK 2.9 million per quality adjusted life year gained.”⁸⁸
 - “The BRAF and MEK inhibitor monotherapies (dabrafenib, vemurafenib, trametinib) all had very similar costs and effectiveness. The same applied to the BRAF/MEK combinations (dabrafenib and trametinib or vemurafenib and cobimetinib), but at a higher level of costs and effectiveness.”⁸⁸
 - Results for the immunotherapies: “Nivolumab have an incremental effect of 0.82 quality adjusted life years and an incremental cost-effectiveness ratio of about 1.1 million NOK per quality adjusted life gained.”⁸⁸
 - “When the analysis was limited to the immunotherapies, nivolumab, pembrolizumab and the combination nivolumab and ipilimumab, all had similar levels of effectiveness and costs.”⁸⁸
- Uncertainty/sensitivity:
 - efficacy data used in the model was identified “as the dominating source of uncertainty, followed by the health related quality of life data, costs and serious adverse events.”⁸⁸
 - “Important differences between the interventions regarding patients health related quality of life may not have been captured in our analysis, due to very limited evidence on health related quality of life of the alternative interventions.”⁸⁸



- “There is uncertainty with regards to the correct treatment duration in the model, both for the new immunotherapies and the BRAF/MEK inhibitors.”⁸⁸
- Conclusions:
 - “Generally, all the interventions have very high incremental cost-effectiveness ratios.”⁸⁸
 - “None of the interventions are cost-effective at the maximum pharmacy retail prices. The budgetary impact of accepting some or all of the new interventions in clinical practice can be substantial, potentially diverting resources away from other interventions or treatment areas with better cost-effectiveness. The budgetary impact and incremental cost-effectiveness ratios can however be reduced through price reductions.
 - We believe that drug price reductions in the region of 63 to 84 percent,^a depending on drug, would be necessary for the interventions to represent cost-effective use of resources in the Norwegian setting.”⁸⁸
- (Confidential) prices:
 - The assessment is performed with list prices.

Reference	Population, Intervention & comparator	Remarks on use of generic utility instrument (e.g. EQ-5D) to measure impact on QoL in economic evaluations	Most uncertain variables or important variables in sensitivity analysis
Costs (list prices & remarks)	IC, IE and ICERs		
Nivolumab, Pembrolizumab, Ipilimumab, Vemurafenib, Dabrafenib, Trametinib (& Cobimetinib)			
NOKC (2015) ⁸⁸	Patients with metastatic and/or unresectable malignant melanoma. Seven drugs are compared (as monotherapy or in combinations). The drugs are: cobimetinib, dabrafenib, ipilimumab, nivolumab, pembrolizumab, trametinib and vemurafenib. Common comparator: Dacarbazine		
List prices, negotiated discounts are hidden. Drug costs per cycle (NOK, 2015): 1 st next	Results of the incremental analysis (with list prices), excluding dominated strategies: A) Results when all interventions are included in the analysis Costs (NOK) IC QALYs IE ICER Dac 161 107 0.88	EQ-5D: applied in 3/17 trials EORTC-QLQ-C30: applied in 10/17 trials (remark: available evidence of poor quality – e.g. 6/10 did not present uncertainty (SD, SE,	Efficacy data HRQoL Costs Serious adverse events Treatment duration

^a “The maximum pharmacy retail prices would have to be reduced by approximately 79 percent for dabrafenib, 83 percent for the combination dabrafenib and trametinib, 81 percent for vemurafenib, 84 percent for the combination vemurafenib and cobimetinib, 83 percent for trametinib, 75 percent for ipilimumab, 63 percent for nivolumab, 67 percent for the combination nivolumab and ipilimumab, and 64 percent for pembrolizumab in order to achieve incremental cost-effectiveness ratios of NOK 500.000 per quality adjusted life year gained against dacarbazine.”⁸⁸



	Month		Niv	1 063 549	902 442	1.70	0.82	1 098 111	CI or p-value) associated with
	months		Vem + cob	2 475 101	1 411 552	1.77	0.07	19 796 728	the results)
Dab:	80 962	idem							
Dab + tra:	169 949	idem							
Dac:	1259	idem							
Ipi*:	740 863	0	Dac	159 801		0.88			
Ipi* + dac:	740 863	0	Dab	940 235	780 434	1.24	0.36	2 191 383	
	1259	1259	Vem + cob	2 471 755	1 531 520	1.77	0.53	2 876 095	
Ipi* + niv:	677 360	0							
	28 817	28 817							
Niv:	86 452	idem							
Pem:	92 909	idem							
Tra:	88 987	idem							
Vem:	83 538	idem							
Vem + cob:	172 525	idem							
B) Results for the BRAF and MEK mono- and combination therapies									
Costs (NOK) IC QALYs IE ICER									
C) Results for the immunotherapies									
Costs (NOK) IC QALYs IE ICER									
Remark: results compared to dacarbazine (i.e. also including the (extendedly) dominated interventions) and results expressed in LYG are also presented in the report.									
Conclusion: None of the interventions are cost-effective at the maximum pharmacy retail prices.									

Cob: cobimetinib; dab: dabrafenib; dac: dacarbazine; IC: incremental cost; ICER: incremental cost-effectiveness ratio; IE: incremental effect; ipi: ipilimumab; LYG: life-years gained; NOK: Norwegian kroner; NOKC: Norwegian Knowledge Centre for the Health Services; niv: nivolumab; pem: pembrolizumab; QALY: quality-adjusted life year; tra: trametinib; vem: vemurafenib.

Exchange rate (31 July 2020): 1 Euro = 10.76 NOK.

* Ipi: Ipilimumab: Full cost in the first month of treatment in the model. Assumed 3,2 doses per patient on average in combination therapy with nivolumab and 3,5 doses per patient on average in monotherapy and in combination with dacarbazine. (source: NOKC⁸⁸)



Appendix 5.4.2.2. pCODR (2014): ipilimumab

- QoL:
 - “pERC [pCODR Expert Review Committee] noted that quality of life reporting was limited. pERC noted that quality of life is an important outcome and that trial investigators and manufacturers, should collect good data in clinical trials on this important outcome for patients.”⁸⁹
 - “Quality of life: Minimal reporting – pERC reviewed the health-related quality of life (HRQOL) data provided for ipilimumab ... and noted that results were only reported in abstract form. Patients in both groups reported a decline in the average Global Health Status (GHS) score from baseline (ipilimumab-dacarbazine, -6.5; dacarbazine-placebo, -10.0), indicating worsening health status; however, no p-value or 95% CI was reported for this comparison. pERC noted that quality of life is important to patients and while the trial investigators and manufacturers collected this data, the limited reporting on the quality of life results, the methods used to collect the data, and the lack of validated minimal clinically important differences made it difficult to interpret the results.”⁸⁹
- Results:
 - “the Economic Guidance Panel’s best estimate of the incremental cost-effectiveness ratio in untreated patients ... was between \$165,389 and \$197,382 per QALY for the comparison to DTIC [dacarbazine] and between \$9,231 and \$216,773 per QALY for the comparison to vemurafenib. pERC accepted the EGP’s [Economic Guidance Panel] reanalyses and concluded that ipilimumab is not cost-effective in comparison to DTIC and unknown in comparison to vemurafenib.”⁸⁹
- Uncertainty/sensitivity:
 - “pERC noted uncertainty in the clinical data inputs used to provide cost effectiveness estimates as the comparison between ipilimumab vs. DTIC and ipilimumab vs. vemurafenib were based upon a naive (side by side) comparison of a pooled analysis and two separate arms from different trials. pERC agreed that there was uncertainty in these clinical inputs which introduced a large amount of uncertainty in the cost-effectiveness estimates provided by the EGP.”⁸⁹
 - “A randomized clinical trial examining ipilimumab 3 mg/kg in the first line setting with standards of care, and that also collects utilities alongside the trial, would provide valuable information and reduce uncertainty in the results of an economic analysis.”⁸⁹
- Conclusions:
 - “the pCODR Expert Review Committee (pERC) recommends funding ipilimumab (Yervoy) for the treatment of adults with advanced (unresectable or metastatic) melanoma, conditional on cost effectiveness being improved to an acceptable level. ... at the submitted price and the Economic Guidance Panel’s best estimates of the incremental cost-effectiveness ratio, ipilimumab could not be considered cost-effective versus relevant comparators.”⁸⁹
- (Confidential) prices
 - The assessment is performed with list prices.



Reference Costs (list prices & remarks)	Population, Intervention & comparator IC, IE and ICERs	Remarks on use of generic utility instrument (e.g. EQ- 5D) to measure impact on QoL in economic evaluations	Most uncertain variables or important variables in sensitivity analysis
Ipilimumab			
pCOD (2014) ⁸⁹	Patients with previously untreated unresectable or metastatic melanoma. BRAV V600-negative patients: ipilimumab in comparison with dacarbazine. BRAV V600-positive patients: ipilimumab in comparison with vemurafenib.		
List prices.	Results of the incremental analysis (with list prices): A) BRAV V600 Mutation-Negative Disease: Ipilimumab vs Dacarbazine Incremental cost of ipilimumab: between \$108 880 and \$110 343. Incremental clinical effect of ipilimumab: between 0.525 and 0.667 QALYs. ICER: between \$165 389 and \$197 382 per QALY.	Limited QoL reporting. No information provided related to generic utility instrument.	Uncertainty in clinical data inputs.
Drug costs per cycle (28 days, CAD): Ipilimumab: \$32 480 Dacarbazine: \$567 – \$945 Vemurafenib: \$10 425	B) BRAV V600 Mutation-Positive Disease: Ipilimumab vs Vemurafenib Incremental cost of ipilimumab: between -\$2,051 and \$35,828. Incremental clinical effect of ipilimumab: between 0.165 and 0.222 QALYs. ICER: between \$9231 and \$216 773 per QALY.		

CAD: Canadian dollar.



Appendix 5.4.2.3. NICE, TA319 (2014): ipilimumab

- QoL:
 - “The ERG had concerns that no direct EQ-5D data were collected and that the Rowen algorithm may not be sufficiently generalisable to the current appraisal population. The ERG was also concerned about the progressively lower completion rates of EORTC QLQ-C30 among surviving patients at subsequent points in time, which could reflect selection bias.”⁹¹
- Results:
 - Including confidential discounts, “the Committee concluded that the most plausible ICER is £47,900 per QALY gained for ipilimumab compared with dacarbazine and £28,600 per QALY gained for ipilimumab compared with vemurafenib.”⁹¹
- Uncertainty/sensitivity:
 - “Cost effectiveness was most affected by shortening the time horizon”⁹¹
 - “The deterministic sensitivity analysis indicated that the model was most sensitive to the parameters used to model overall survival for ipilimumab and dacarbazine, the time spent on second-line treatment and the time spent on first-line treatment with ipilimumab compared with dacarbazine.”⁹¹
- Conclusions:
 - “Ipilimumab is recommended, within its marketing authorisation, as an option for treating adults with previously untreated advanced (unresectable or metastatic) melanoma, only if the manufacturer provides ipilimumab with the discount agreed in the patient access scheme. The Committee accepted that the updated ICER of £28,600 per QALY gained for ipilimumab compared with vemurafenib submitted by the manufacturer in response to consultation was plausible. It also accepted that the updated ICER, submitted in response to consultation, of £47,900 per QALY gained for ipilimumab compared with dacarbazine was plausible and in line with the previous appraisal (TA268), although it accepted that the ICER could be higher if other approaches are were used to model overall survival. The Committee was satisfied that ipilimumab met the criteria for being a life-extending, end-of-life treatment and that the trial evidence presented for this was robust.”⁹¹
- (Confidential) prices:
 - “The manufacturer of ipilimumab has agreed a patient access scheme with the Department of Health, in which a confidential discount on the list price of ipilimumab is offered.”⁹¹



Reference Costs (list prices & remarks)	Population, Intervention & comparator IC, IE and ICERs	Remarks on use of generic utility instrument (e.g. EQ- 5D) to measure impact on QoL in economic evaluations	Most uncertain variables or important variables in sensitivity analysis
Ipilimumab			
NICE, TA319 (2014) ⁹¹ Wade (2013) ⁹²	Patients with untreated advanced (unresectable or metastatic) melanoma. BRAF V600 mutation-negative melanoma: ipilimumab compared with dacarbazine. BRAF V600 mutation-positive melanoma: ipilimumab compared with dacarbazine and vemurafenib.		
List prices, negotiated discounts are hidden.	The details of the IC and IE of the most plausible ICERs (£47,900 per QALY gained for ipilimumab compared with dacarbazine and £28,600 per QALY gained for ipilimumab compared with vemurafenib) could not be retrieved in the underlying HTA report. Details for other scenarios are provided in the report of Wade et al. (2013).	The ERG was concerned at the lack of direct EQ-5D data.	Time horizon Overall survival Treatment duration
Drug costs per administration			
Ipilimumab: Confidential			
Vemurafenib: Confidential			
Dacarbazine: £53.88			



Appendix 5.4.2.4. NICE, TA268 (2012): ipilimumab

- QoL:
 - “Health related quality of life data were collected in the MDX010-20 trial¹²² using the EORTC QLQ-C30 and the short form 36 (SF-36); the manufacturer therefore had to map data using validated mapping algorithms in line with the NICE reference case.”⁹⁴
- Results:
 - The Committee “gave further consideration to the manufacturer’s ICER of £42,200 per QALY gained and the ERG’s updated preferred estimate of £58,600 per QALY gained. The Committee appreciated that the correct modelling approach was uncertain, but found no evidence to indicate that the ERG’s approach was based on more plausible assumptions than the manufacturer’s approach. The Committee concluded that the manufacturer’s ICER of £42,200 per QALY gained was a plausible estimate.”⁹³
- Uncertainty/sensitivity:
 - “The Committee noted that the approach to modelling overall survival was the key driver of cost effectiveness for ipilimumab.”⁹³
 - “the ICER was sensitive to the utility values assumed for the progressive disease health state.”⁹³
 - “The ERG reviewed the clinical-effectiveness evidence for ipilimumab and noted that none of the studies included in the manufacturer’s submission compared ipilimumab with any of the comparators listed in the decision problem (best supportive care, carboplatin-based chemotherapy and dacarbazine).”⁹³
- Conclusions:
 - “Having accepted that the supplementary advice for appraising a life-extending end-of-life treatment applies, and that the manufacturer’s ICER of £42,200 per QALY gained was plausible, but also recognising that it could be higher using other approaches to modelling overall survival, the Committee considered whether ipilimumab could be considered a cost-effective use of NHS resources.
 - On balance, the Committee considered that, given the robust clinical data available for a period of 50 to 70 months, the likelihood of long-term effectiveness in a small proportion of patients and the innovative nature of ipilimumab, it could be concluded that ipilimumab is a cost-effective use of NHS resources.”⁹³
- (Confidential) prices:
 - “The manufacturer of ipilimumab has agreed a patient access scheme with the Department of Health, in which a discount on the list price of ipilimumab is offered. The size of the discount is commercial in confidence.”⁹³



Reference Costs (list prices & remarks)	Population, Intervention & comparator IC, IE and ICERs	Remarks on use of generic utility instrument (e.g. EQ- 5D) to measure impact on QoL in economic evaluations	Most uncertain variables or important variables in sensitivity analysis
Ipilimumab			
NICE, TA268 (2012) ⁹³ Dickson (2011) ⁹⁴	Patients with previously treated (with interleukin-2, dacarbazine, temozolomide or other chemotherapies) advanced (unresectable or metastatic) melanoma. Ipilimumab plus gp100 compared with gp100 alone.		
List prices, negotiated discounts are hidden. Ipilimumab: - 50mg vial: £3750 - 200mg vial: £15,000	Results of the manufacturer's revised base-case analysis, including the patient access scheme, and using only the MDX010-20 trial data: The details of the manufacturer's ICER of £42,200 per QALY gained and the ERG's updated preferred estimate of £58,600 per QALY gained could not be retrieved in the underlying HTA report. Details for other scenarios are provided in the report of Dickson et al. (2011).	No generic utility information gathered in the underlying trial.	OS modelling approach Utility values

* "The manufacturer has recently confirmed the list price of ipilimumab as £3750 per 50mg vial and £15,000 per 200mg vial. The manufacturer estimates that the average number of vials used per patient dose is as follows: $1.24 \times 50\text{mg} + 0.99 \times 200\text{mg}$. In the base case economic evaluation, there is wastage and the model rounds the usage per patient to the nearest vial."⁹⁴



Appendix 5.4.2.5. NICE, TA553 (2018): pembrolizumab

- QoL:
 - “Utility estimates in the company model were derived from the EQ-5D-3L data collected during the KEYNOTE-054 trial and from an observational study in which the general public were asked to value the HRQoL of people living with different stages of melanoma.”⁹⁶
 - “The company used a linear mixed-effect model to estimate utility value for each health state”⁹⁶
- Results:
 - “The ERG also incorporated the commercial arrangements for the subsequent treatments for people who develop metastatic disease. The exact ICERs cannot be reported because the commercial arrangements are confidential. The results showed that in the company's base case and scenario analyses, the ICERs for pembrolizumab compared with routine surveillance did not exceed £10,000 per quality-adjusted life year (QALY) gained in any of the analyses.”⁹⁵
 - “The committee noted that the company's ICERs were within the range usually considered a cost-effective use of NHS resources. The ERG did not do any exploratory analyses because the data from KEYNOTE-054 were too immature and noted that only 1% of the total discounted QALYs came from the actual trial data.”⁹⁵
 - “The ERG considers that the company's estimated ICERs per QALY gained are unreliable. Furthermore, given the immaturity of the data, the ERG was unable to produce ICERs per QALY gained that were more reliable than those presented in the CS.”⁹⁶
- Uncertainty/sensitivity:
 - “The committee considered that the distant metastases-free survival estimates from the company's model for routine surveillance are unreliable given the data available. The committee concluded that more data on distant metastases-free survival from the ongoing KEYNOTE-054 trial should reduce uncertainty in the modelling.”⁹⁵
 - “The committee recognised the uncertainty in the assumption of lifetime treatment benefit with pembrolizumab as adjuvant treatment and concluded that more mature data on overall survival would help decision making.”⁹⁵
 - “Clinical evidence comes from KEYNOTE-054, an ongoing randomised trial. It is likely to improve recurrence-free survival but the size of the benefit is unclear in the long term, because the trial is ongoing. Also, data about overall survival and how long people might live without developing distant metastases are limited. This means that the estimates of cost effectiveness are also very uncertain. ...
 - Pembrolizumab has the potential to be cost effective, but more evidence is needed to address the clinical uncertainties.”⁹⁵
 - “The most influential parameter was the parametric function used to model transitions from the RF [recurrence-free] health state to the LR [locoregional recurrence] health state.”⁹⁶



- Conclusions:
 - “Considering the very limited data for distant metastases-free and overall survival, the committee agreed the ICER for pembrolizumab compared with routine surveillance was very uncertain. Therefore, the committee concluded the ICER for pembrolizumab compared with routine surveillance was very uncertain, and because this is a significant change to the existing treatment pathway for melanoma, it could not recommend pembrolizumab for routine use.”⁹⁵
 - “Pembrolizumab is recommended for use within the Cancer Drugs Fund as an option for the adjuvant treatment of stage III melanoma with lymph node involvement in adults who have had complete resection. It is recommended only if the conditions in the managed access agreement for pembrolizumab are followed.”⁹⁵
- (Confidential) prices:
 - “A Commercial Access Agreement (CAA) discount (***) is in place for pembrolizumab is applied to list price of pembrolizumab in the base case analyses.”⁹⁶

Reference Costs (list prices & remarks)	Population, Intervention & comparator IC, IE and ICERs	Remarks on use of generic utility instrument (e.g. EQ- 5D) to measure impact on QoL in economic evaluations	Most uncertain variables or important variables in sensitivity analysis
Pembrolizumab			
NICE, TA553 (2018) ⁹⁵ Greenhalgh (2018) ⁹⁶	Patients with completely resected stage III melanoma at high risk of recurrence. Pembrolizumab compared with routine surveillance.		
List prices, negotiated discounts are hidden. Total costs per administration: Pembrolizumab: £5260	Results from the company's base case comparison showed that treatment with pembrolizumab dominated routine surveillance, being both cheaper (-£3,988) and more effective (+3.18 life years, +2.73 QALYs). The ERG, however, considers that the KEYNOTE-054 trial data are too immature to produce a reliable ICER per QALY gained and, therefore, has not undertaken any additional or exploratory analyses. The ERG considers that this approach avoids generating spurious ICERs per QALY gained.	EQ-5D-3L data collected during the KEYNOTE-054 trial.	Parametric function to model transitions. Immaturity of KEYNOTE-054 trial.



Appendix 5.4.2.6. NICE, TA366 (2015): pembrolizumab

- QoL:
 - “Utility values were estimated using EuroQol EQ-5D data from KEYNOTE 006, by assuming that quality of life decreases as people approach the last months of life. The utility scores decreased from 0.82, for people who were more than 360 days before death, to 0.33 for people in the 30 days before death. The ERG considered that there were important limitations in the estimation of utility, because of the use of EQ-5D data based on patients from all regions and the assumption that utility did not change when disease progressed.”⁹⁷
 - “The company carried out a systematic review to identify studies reporting HRQoL for patients with advanced melanoma. As no studies assessing patients who were naïve to treatment with ipilimumab before entering the study were identified, the search was widened to include patients with advanced melanoma. Eleven studies¹²³⁻¹³³ were identified. However, only one paper¹³³ collected data using the EQ-5D tool from a UK population with advanced melanoma.”⁹⁸
- Results:
 - “The Committee concluded that the most plausible ICERs for pembrolizumab (compared with ipilimumab, dabrafenib and vemurafenib) were less than £50,000 per QALY gained. The exact ICERs are confidential and cannot be reported here.”⁹⁷
 - “The company's base-case results ... were based on the discount in the patient access scheme for pembrolizumab and the list prices for all other drugs, and therefore were not used for decision-making ... Results from the company's model including the patient access schemes for pembrolizumab and all 3 comparators were presented by the ERG; these results are commercial in confidence and cannot be reported here.”⁹⁷
- Uncertainty/sensitivity:
 - “The ERG considered that the network meta-analysis did not provide valid treatment effect estimates, particularly for pembrolizumab compared with dabrafenib and vemurafenib.”⁹⁷
 - “the ERG expressed concerns about the modelling of overall survival, progression-free survival, treatment costs and quality of life. It considered that there were limitations in the methods of extrapolation for both progression-free survival and overall survival.”⁹⁷
 - “The ERG considered that the key factors affecting results of the model were drug costs, duration of treatment and overall survival.”⁹⁷
 - “The Committee identified 4 key uncertainties: the optimum duration of treatment with pembrolizumab, the long-term benefits of pembrolizumab compared with ipilimumab, the effectiveness of pembrolizumab compared with dabrafenib and vemurafenib, the extension to life offered by pembrolizumab.”⁹⁷
- Conclusions:
 - “Pembrolizumab is recommended as an option for treating advanced (unresectable or metastatic) melanoma that has not been previously treated with ipilimumab, in adults, when the company provides pembrolizumab with the discount agreed in the patient access scheme.
 - - Pembrolizumab is likely to provide improved short-term clinical effectiveness and a better tolerability profile compared with ipilimumab. The long-term benefits compared with ipilimumab and the effectiveness compared with dabrafenib and vemurafenib are highly uncertain.



- - The most plausible incremental cost-effectiveness ratios (ICERs) were less than £50,000 per quality-adjusted life year (QALY) gained.
- - The Committee concluded that pembrolizumab meets all the criteria to be considered a life-extending, end-of-life treatment.”⁹⁷
- (Confidential) prices:
 - “The company has agreed a patient access scheme, in which pembrolizumab is provided with a simple discount to its list price.”⁹⁷ “After guidance publication in November 2015, the company agreed a commercial access agreement with NHS England that replaces the patient access scheme on equivalent terms. The financial terms of the agreement are commercial in confidence.”⁹⁷

Reference	Population, Intervention & comparator	Remarks on use of generic utility instrument (e.g. EQ-5D) to measure impact on QoL in economic evaluations	Most uncertain variables or important variables in sensitivity analysis
Costs (list prices & remarks)	IC, IE and ICERs		
Pembrolizumab			
NICE, TA366 (2015) ⁹⁷	Patients with advanced (unresectable or metastatic) melanoma that had not been previously treated with ipilimumab.		
Greenhalgh (2015) ⁹⁸	Pembrolizumab compared with ipilimumab, dabrafenib and vemurafenib.		
List prices, negotiated discounts are hidden.	In the underlying HTA report, the company and the ERG’s main cost effectiveness results use the PAS price for pembrolizumab and list prices for the comparator drugs. These analyses do not correctly reflect the real incremental costs.	EQ-5D data from KEYNOTE-006.	Modelling of overall survival (long-term benefits), progression-free survival, treatment costs and quality of life.
Drug costs per vial	The ERG presented analyses incorporating the confidential patient access schemes for pembrolizumab, ipilimumab, dabrafenib and vemurafenib. The Committee took into account all 4 patient access schemes. The results of these analyses are not reported since these are confidential.		Optimum duration of treatment.
Pembrolizumab:			
£1315 per 50mg vial			
Ipilimumab:			
£3750 per 50mg vial			
£15 000 per 200mg vial			
Vemurafenib:£1,750 per 240mg 56-tab pack			
Dabrafenib:£933.33 per 50 mg, 28-cap pack, £1,400 per 75 mg, 28-cap pack			



Appendix 5.4.2.7. NICE, TA357 (2015): pembrolizumab

- QoL:
 - “The company got the utility values from EQ-5D questionnaire data from KEYNOTE-002. The utility values were incorporated into the model based on time to death.”⁹⁹
 - “HRQoL data are only presented from the KEYNOTE-002 trial. Assessments were made using both the condition specific European Organisation for Research and Treatment Cancer Quality of Life Questionnaire (EORTC QLQ-C30) questionnaire and the generic EuroQoL EQ-5D questionnaire. Patient reported outcomes were assessed at the following time points: baseline-cycle 1 (week 0), cycle 2 (week 3), cycle 3 (week 6), cycle 5 (week 12), cycle 9 (week 24); cycle 13 (week 36), end of chemotherapy/pre-crossover, discontinuation/end of treatment and once post-progression at the safety follow up (approximately 30 days after the last dose of study drug or before the initiation of a new antineoplastic treatment, whichever occurred first). EQ-5D data were used to inform the cost effectiveness analyses and thus not reported by the company in the clinical section of the CS.”¹⁰⁰
- Results:
 - “The Committee concluded that the most plausible incremental cost-effectiveness ratio (ICER) for pembrolizumab compared with best supportive care was likely to be less than £50,000 per quality-adjusted life year (QALY) gained.”⁹⁹
- Uncertainty/sensitivity:
 - “The variables with the biggest impact on the results were the parameters used to extrapolate progression-free survival and the hazard ratio for overall survival ... used to extrapolate the overall survival results.”⁹⁹
 - “An analysis of the company’s base case results show that 72% of the estimated health gain (in terms of additional survival) attributed to treatment with pembrolizumab occurs after disease progression (and after treatment with pembrolizumab has ceased), mainly in the extended projection period (years 2 to 30). This means that the method used to predict survival is extremely influential.”¹⁰⁰
- Conclusions:
 - “In summary, for the comparison of pembrolizumab 2mg/kg Q3W vs chemotherapy/BSC, the company and the ERG have estimated ICERs that are less than £50,000 per QALY gained. However, the ERG cautions that these estimates are reliant on the use of immature survival data that have been compromised by crossover.”¹⁰⁰
 - “Having accepted that the supplementary advice for appraising a life-extending, end-of-life treatment applies, the Committee discussed whether pembrolizumab could be considered a cost-effective use of NHS resources. ... it was likely that the most plausible ICER for pembrolizumab compared with best supportive care was less than £50,000 per QALY gained. Therefore, the Committee concluded that, on balance, pembrolizumab could be considered a cost-effective use of NHS resources for people with advanced (unresectable or metastatic melanoma) after progression with ipilimumab and, for BRAF V600 mutation-positive disease, a BRAF or MEK inhibitor.”⁹⁹



- (Confidential) prices:
 - “The company has agreed a patient access scheme with the Department of Health. This scheme provides a simple discount to the list price of pembrolizumab, with the discount applied at the point of purchase or invoice. The level of the discount is commercial in confidence.”⁹⁹

Reference Costs (list prices & remarks)	Population, Intervention & comparator IC, IE and ICERs	Remarks on use of generic utility instrument (e.g. EQ- 5D) to measure impact on QoL in economic evaluations	Most uncertain variables or important variables in sensitivity analysis																		
Pembrolizumab																					
NICE, TA357 (2015) ⁹⁹ Fleeman (2015) ¹⁰⁰	Patients with unresectable or metastatic melanoma previously treated with ipilimumab and whose disease had progressed within 24 weeks of the last dose. Pembrolizumab compared with best supportive care (Best supportive care included systemic therapies such as dacarbazine, paclitaxel, paclitaxel plus carboplatin, carboplatin or temozolomide.).																				
List prices, negotiated discounts are hidden.	Results of the incremental analysis (including PAS) – the company’s base case result:	EQ-5D data from KEYNOTE-002.	Extrapolation PFS and OS.																		
Drug costs per vial Pembrolizumab: £1315 per 50mg vial	<table><thead><tr><th></th><th>Costs</th><th>IC</th><th>QALYs</th><th>IE</th><th>ICER</th></tr></thead><tbody><tr><td>BSC</td><td>£15,960</td><td></td><td>1.07</td><td></td><td></td></tr><tr><td>Pembrolizumab</td><td>£66,955</td><td>£50,995</td><td>2.26</td><td>1.188</td><td>£42,923</td></tr></tbody></table> <p>The Committee noted that the company's economic analysis resulted in a deterministic incremental cost-effectiveness ratio (ICER) for pembrolizumab compared with best supportive care of about £43,000 per quality-adjusted life year (QALY) gained, and a probabilistic ICER of about £68,000 per QALY gained.</p> <p>The ICER for pembrolizumab compared with best supportive care including all of the ERG's preferred amendments was £46,662 per QALY gained.</p>		Costs	IC	QALYs	IE	ICER	BSC	£15,960		1.07			Pembrolizumab	£66,955	£50,995	2.26	1.188	£42,923		
	Costs	IC	QALYs	IE	ICER																
BSC	£15,960		1.07																		
Pembrolizumab	£66,955	£50,995	2.26	1.188	£42,923																



Appendix 5.4.2.8. NICE, TA400 (2016): nivolumab & ipilimumab

- QoL
 - In this technology appraisal guidance, no details related to the QoL impact is provided.
- Results
 - “The committee considered the ERG’s preferred base-case scenario comparing nivolumab plus ipilimumab with ipilimumab alone. This included both BRAF mutation-negative and mutation-positive disease in the same ratio as that in CheckMate-067, with a number of changes. The committee noted that, using the list prices, this increased the company’s base case incremental cost-effectiveness ratio (ICER) for nivolumab plus ipilimumab compared with ipilimumab alone from £10,400 per quality-adjusted life year (QALY) gained (in the BRAF mutation-negative population) to £19,300 per QALY gained (for the mixed population). The committee further considered the cost effectiveness when the patient access scheme discounts were applied and noted that the ICER remained below £30,000 per QALY gained.”⁹⁰
 - “The committee considered the cost effectiveness of nivolumab plus ipilimumab compared with pembrolizumab alone, which they considered to be the most clinically relevant comparator in the scope based on the testimony of clinical experts.
 - ... In the BRAF mutation-negative population, ipilimumab alone was dominated by pembrolizumab. In the BRAF mutation-positive population, dabrafenib, vemurafenib and ipilimumab were dominated by pembrolizumab and nivolumab plus ipilimumab and therefore excluded from the analysis. The committee noted that, compared with pembrolizumab, nivolumab plus ipilimumab resulted in an increase of 1.63 and 1.64 QALYs and an ICER of £29,900 and £27,900 per QALY gained for the BRAF mutation-negative and mutation-positive populations respectively when list prices were used. The committee was aware that the ERG considered this comparison to be unreliable due to the assumptions made by the company”⁹⁰
- Uncertainty
 - “The modelling of post-progression survival was the biggest driver of cost effectiveness.”⁹⁰
- Conclusions:
 - “The committee concluded that, on balance, the ICER for nivolumab plus ipilimumab compared to pembrolizumab is likely to be less than £30,000 per QALY gained in the mixed population of BRAF mutation-positive and mutation-negative advanced melanoma when the patient access scheme prices were used in the model. It therefore considered that nivolumab plus ipilimumab could be considered a cost-effective use of NHS resources.”
 - “Nivolumab in combination with ipilimumab is recommended, within its marketing authorisation, as an option for treating advanced (unresectable or metastatic) melanoma in adults only when the company provides ipilimumab with the discount agreed in the patient access scheme. The committee concluded that the incremental cost-effectiveness ratio (ICER) for nivolumab plus ipilimumab compared with pembrolizumab (the most clinically relevant comparator) was likely to be less than £30,000 per quality adjusted life year (QALY) gained.”⁹⁰



- (Confidential) prices:
 - The company has agreed a patient access scheme for ipilimumab with the Department of Health. ... The level of the discount is commercial in confidence.⁹⁰

Reference Costs (list prices & remarks)	Population, Intervention & comparator IC, IE and ICERs	Remarks on use of generic utility instrument (e.g. EQ- 5D) to measure impact on QoL in economic evaluations	Most uncertain variables or important variables in sensitivity analysis
Nivolumab & ipilimumab			
NICE, TA400 (2016) ⁹⁰	Nivolumab in combination with ipilimumab for treating advanced melanoma (mixed population of BRAF mutation-positive and mutation-negative advanced melanoma). Nivolumab + ipilimumab versus ipilimumab alone. In a second analysis, pembrolizumab was also included as a comparator.		
List prices, commercial in confidence discount	Nivolumab plus ipilimumab compared with ipilimumab alone (with list prices): no information on incremental costs and effects is provided.	No QoL information is presented.	Post-progression survival
Nivolumab:	- company's base case ICER in the BRAF mutation-negative population: £10 400/QALY gained		
- 4-ml vial (40mg): £439	- ERG's preferred base-case ICER in the mixed population: £19 300/QALY gained		
Ipilimumab	The committee further considered the cost effectiveness when the patient access scheme discounts were applied and noted that the ICER remained below £30 000 per QALY gained.		
- 10-ml vial (50mg): £3750			
- 40-ml vial (200mg): £15 000			
	Nivolumab plus ipilimumab compared with pembrolizumab alone:		
	- In the BRAF mutation-negative population: £29 900/QALY gained		
	- In the BRAF mutation-positive population: £27 900/QALY gained		
	Remark: the ERG considered this comparison to be unreliable (and did not perform calculations to compare nivolumab plus ipilimumab against pembrolizumab).		



Appendix 5.4.2.9. NICE, TA558 (2019): nivolumab

- QoL
 - “The economic model was based mostly on the CheckMate 238 trial, comparing nivolumab with ipilimumab, and CA184-029 trial, comparing ipilimumab with placebo.”¹⁰²
 - “Health-related quality-of-life (HRQoL) was measured in the CheckMate 238 trial using the EQ-5D-3L generic health questionnaire. The CA184-029 trial did not obtain EQ-5D data but did use the EORTC QLQ-C30 cancer specific HRQoL measure, as did the CheckMate 238 trial.”¹⁰²
 - For the CheckMate 238 trial, “the company did not report any numerical data for HRQL in the clinical effectiveness review section of the CS although they reported that *“HRQL scores were maintained after treatment in both groups with respect to the score on the EORTC QLQ-C30 Global Health Status or on any of the individual scales, as well as to scores on the EQ-5D utility index and the EQ-5D visual analogue scale (VAS)”*.”¹⁰²
 - Health-state utility values (HSUVs) were derived from EQ-5D-3L data collected in the CheckMate 238 trial. These HSUVs were derived from a regression analysis that included covariates for treatment, disease recurrence, disease stage and an interaction term for recurrence after ipilimumab treatment.”¹⁰²
 - “The company also used EORTC-QLQ-C30 from the two trials to map to the EQ-5D using a published mapping algorithm.”¹⁰²
 - In both the NICE technology appraisal guidance¹⁰¹ and the underlying HTA report,¹⁰² none of the original utility values are transparently reported. The reported information (mean (SD), median (IQR) and range) are made confidentials in the tables (tables ‘Utility summaries by health state and treatment’, ‘Pre-recurrence utility summaries by time to event’, and ‘Utility summaries by patient characteristics’). Also the estimated utilities from the final regression model for the pre- and post-recurrence health state are made confidential in the report.¹⁰²
- Results
 - “The company ICERs [about £18 000 per QALY gained] included a commercial access agreement for nivolumab and a patient access scheme for ipilimumab, but did not take account of commercial arrangements for other agents that may be used subsequently in the metastatic setting because the discounts are commercial in confidence. Exploratory analyses done by the ERG showed that when these discounts were included, the ICERs were slightly higher in both cases, but still within the range that may be considered cost effective.”¹⁰¹
- Uncertainty
 - “An ERG exploratory worst-case scenario (where adjuvant nivolumab was assumed to have no overall survival benefit over routine surveillance) produced an ICER of £80,401 per QALY gained (excluding confidential discounts for subsequent treatments other than nivolumab and ipilimumab). This was considerably higher than the company’s equivalent base-case ICER, which was £18,423 per QALY gained The committee considered that this showed how sensitive the ICER is to the projected overall survival benefit. The committee noted that there were very limited overall survival data currently available from CheckMate 238 and concluded that it is not possible to resolve the uncertainty in the model predictions until more mature data are available.”¹⁰¹
 - The ERG noticed that “a key underlying problem throughout the company’s analyses is the lack of OS data” and that “the company’s use of a surrogate relationship between RFS and OS is uncertain”¹⁰²



- “The committee noted that the company assumed the treatment benefit for recurrence-free survival continued after stopping treatment up to year 10. The committee noted the uncertainty in this assumption and considered that more mature data on both recurrence-free survival and overall survival would be crucial in determining the benefit of changing the current patient pathway of care to include adjuvant therapy.”¹⁰¹
- “The committee noted that when all commercial arrangements are taken into account, the company's base-case ICERs are within the range usually considered a cost-effective use of NHS resources. However, the committee recognised that the clinical effectiveness of adjuvant nivolumab is very uncertain, because of the lack of mature overall survival data and the need for an indirect comparison. As a consequence, the cost-effectiveness estimates are also very uncertain.”¹⁰¹
- Conclusions:
 - “Adjuvant nivolumab is not recommended for routine use in the NHS
 - The committee noted that when all commercial arrangements are taken into account, the company's base-case ICERs are within the range usually considered a cost-effective use of NHS resources However, the committee recognised that the clinical effectiveness of adjuvant nivolumab is very uncertain, because of the lack of mature overall survival data and the need for an indirect comparison. As a consequence, the cost-effectiveness estimates are also very uncertain. Also, the benefit of changing the strategy for managing completely resected stage III and IV melanoma from routine surveillance to adjuvant nivolumab is not known. Because of these uncertainties, the committee concluded that nivolumab for the adjuvant treatment of completely resected melanoma with lymph node involvement or metastatic disease cannot be recommended for routine commissioning in the NHS.”¹⁰¹
 - “Adjuvant nivolumab is recommended for use in the Cancer Drugs Fund
 - ... The committee accepted that the early trial results are promising. It noted that despite the current uncertainty about the clinical and cost effectiveness of adjuvant nivolumab, there is the plausible potential for nivolumab to be cost effective if further data confirm the current efficacy predictions for recurrence-free and overall survival. The committee also took the view that further data collection could help reduce the current uncertainty.”¹⁰¹
- (Confidential) prices:
 - “The company has a commercial arrangement. This makes nivolumab available to the NHS with a discount. The size of the discount is commercial in confidence.”¹⁰¹



Reference Costs (list prices & remarks)	Population, Intervention & comparator IC, IE and ICERs	Remarks on use of generic utility instrument (e.g. EQ- 5D) to measure impact on QoL in economic evaluations	Most uncertain variables or important variables in sensitivity analysis
Nivolumab			
NICE, TA558 (2019) ¹⁰¹	Adjuvant treatment of completely resected melanoma in adults with lymph node involvement or metastatic disease.		
Edwards (2018) ¹⁰²	Nivolumab compared to routine surveillance.		
List prices, commercial in confidence discount	Company ICERs including discounts for nivolumab and ipilimumab, but did not for other agents that may be used subsequently in the metastatic setting.	No transparent reporting of QoL outcomes	Overall survival Recurrence-free survival
Nivolumab: - 4-ml vial (40mg): £439 - 10-ml vial (100mg): £1097	The company submitted 2 models comparing adjuvant nivolumab with routine surveillance. The ICERs were similar in both models: - £18 423/QALY gained - £18 018/QALY gained ERG exploratory worst-case scenario (where adjuvant nivolumab was assumed to have no overall survival benefit over routine surveillance) produced an ICER of £80 401 per QALY gained.		



Appendix 5.4.2.10. NICE, TA384 (2016): nivolumab

- QoL
 - “The company included health-related quality of life results only from CheckMate-066. EQ-5D utility index scores and EORTC QLQ-C30 global health status scores were higher at baseline and for the entire period of observation for nivolumab compared with dacarbazine. However, there was no improvement in quality of life from baseline in the nivolumab arm, or a consistent difference in quality of life between nivolumab and dacarbazine.”¹⁰³
 - “The company used EQ-5D values from CheckMate-066, using regression analysis to estimate utility values for health states in the model.”¹⁰³
- Results
 - “The company presented base-case results using the list prices for all drugs In the company’s base-case analyses, nivolumab provided a total of 4.31 and 4.27 quality-adjusted life years (QALYs) in the BRAF mutation-negative melanoma and BRAF mutation-positive melanoma groups respectively. When compared with ipilimumab the absolute increment in QALY gained with nivolumab was 1.67 and 1.82 for BRAF mutation-negative melanoma and BRAF mutation-positive melanoma respectively. The fully incremental comparisons with all comparators demonstrated that for BRAF mutation-negative melanoma, ipilimumab was extendedly dominated (that is, it had an incremental cost effective ratio [ICER] relative to dacarbazine, higher than that of the next most effective strategy, nivolumab). Nivolumab had an ICER of £23,583 per QALY gained compared with dacarbazine (see table [...]). Similarly, in BRAF mutation-positive melanoma nivolumab dominated (that is, provided more QALYs at lower cost than) both dabrafenib and vemurafenib. Nivolumab was more costly and more effective than ipilimumab, with an ICER of £7346 per QALY gained (see table [...]).”¹⁰³
 - “Because ipilimumab, vemurafenib and dabrafenib are recommended by NICE only with patient access schemes, these results were not used for decision-making and are included here for illustration only. The ERG re-ran these analyses incorporating the confidential discounted prices agreed in the patient access schemes for all 3 comparators; these results are commercial in confidence and cannot be reported here.”¹⁰³
- Uncertainty/sensitivity
 - “The Committee noted that in the company’s deterministic sensitivity analyses, the results were most sensitive to the choice of the fitted parametric curves. The Committee noted that time spent on treatment was a key factor influencing the cost-effectiveness results.”¹⁰³
 - The ERG “noted that there is considerable uncertainty in the cost-effectiveness results because of the assumptions made, particularly for long-term overall survival and time on treatment for nivolumab.”¹⁰³
 - “The Committee concluded that the long-term benefit of nivolumab remains highly uncertain until further follow-up data are available. The Committee appreciated that there is considerable uncertainty about the optimum duration of treatment with nivolumab.”¹⁰³
 - “The Committee concluded that lack of evidence on the optimal duration of treatment made the cost-effectiveness results uncertain.”¹⁰³
- Conclusion
 - The Committee concluded that “the ICER for nivolumab is likely to be less than £30,000 per QALY gained in both BRAF mutation-positive and BRAF mutation-negative advanced melanoma. It therefore considered nivolumab to be a cost effective use of NHS resources.”¹⁰³
- (Confidential) prices



- “Ipilimumab, vemurafenib and dabrafenib are recommended by NICE only with patient access schemes.”¹⁰³

Reference	Population, Intervention & comparator						Remarks on use of generic utility instrument (e.g. EQ-5D) to measure impact on QoL in economic evaluations	Most uncertain variables or important variables in sensitivity analysis																																																				
Costs (list prices & remarks)	IC, IE and ICERs																																																											
Nivolumab																																																												
NICE, TA384 (2016) ¹⁰³	Previously untreated advanced (unresectable, metastatic) melanoma.																																																											
Cooper (2015) ¹⁰⁴	Nivolumab versus dacarbazine, ipilimumab, dabrafenib and vemurafenib																																																											
List prices, commercial in confidence discount	Company's base case cost effectiveness results – drug prices based on list price.						The company used EQ-5D values from CheckMate-066, using regression analysis to estimate utility values for health states in the model.	Long-term benefit (fitted parametric curves) Treatment duration																																																				
Niv:* £2809.47 per IV Ipi: £19 574.00 per IV Dac: £48.21 per IV Dab: £200.00 per day Vem: £250.00 per day	<div>A) BRAF mutation-negative disease (nivolumab compared with dacarbazine and ipilimumab)</div> <table> <tr> <th></th> <th>Costs (£)</th> <th>IC</th> <th>QALYs</th> <th>IE</th> <th>ICER</th> </tr> <tr> <td>Dacarbazine</td> <td>Conf.</td> <td></td> <td>1.23</td> <td></td> <td></td> </tr> <tr> <td>Ipilimumab</td> <td>Conf.</td> <td>48 429</td> <td>2.64</td> <td>1.41</td> <td>Ext. dom.</td> </tr> <tr> <td>Nivolumab</td> <td>Conf.</td> <td>72 578</td> <td>4.31</td> <td>3.08</td> <td>23 583</td> </tr> </table> <div>B) BRAF mutation-positive disease (nivolumab compared with dabrafenib, ipilimumab and vemurafenib).</div> <table> <tr> <th></th> <th>Costs (NOK)</th> <th>IC</th> <th>QALYs</th> <th>IE</th> <th>ICER</th> </tr> <tr> <td>Ipilimumab</td> <td>Conf.</td> <td></td> <td>2.44</td> <td></td> <td></td> </tr> <tr> <td>Nivolumab</td> <td>Conf.</td> <td>13 374</td> <td>4.27</td> <td>1.82</td> <td>7346</td> </tr> <tr> <td>Dabrafenib</td> <td>Conf.</td> <td>6228</td> <td>1.69</td> <td>-2.57</td> <td>Dominated</td> </tr> <tr> <td>Vemurafenib</td> <td>Conf.</td> <td>24 659</td> <td>1.70</td> <td>-2.56</td> <td>Dominated</td> </tr> </table>									Costs (£)	IC	QALYs	IE	ICER	Dacarbazine	Conf.		1.23			Ipilimumab	Conf.	48 429	2.64	1.41	Ext. dom.	Nivolumab	Conf.	72 578	4.31	3.08	23 583		Costs (NOK)	IC	QALYs	IE	ICER	Ipilimumab	Conf.		2.44			Nivolumab	Conf.	13 374	4.27	1.82	7346	Dabrafenib	Conf.	6228	1.69	-2.57	Dominated	Vemurafenib	Conf.	24 659	1.70
	Costs (£)	IC	QALYs	IE	ICER																																																							
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Vemurafenib	Conf.	24 659	1.70	-2.56	Dominated																																																							
<p>Remark: in ERG's preferred scenario, nivolumab was dominated by ipilimumab.</p> <p>Re-analyses with confidential discounted prices for ipilimumab, vemurafenib and dabrafenib: The Committee concluded that the ICER for nivolumab is likely to be less than £30 000 per quality-adjusted life year (QALY) gained in both BRAF mutation-positive and BRAF mutation-</p>						<p>Remark: extra information provided by company → no evidence that nivolumab leads to consistent and sustained improvement in HRQoL in comparison with dacarbazine.</p>																																																						



negative advanced melanoma. The exact ICERs are confidential and cannot be reported here.

* Nivolumab: £439 per 4 ml (40 mg) vial and £1097 per 10 ml (100 mg) vial (excluding VAT; company's submission).

Conf.: confidential; ERG: Evidence Review Group; Ext. dom.: Excluded due to extended dominance

Appendix 5.4.2.11. NICE, TA544 (2018): dabrafenib & trametinib

- QoL:
 - Mean EQ-5D QoL values and reporting rates are kept confidential in the underlying HTA report. The following is stated: “As the company notes, EQ-5D reporting rates while high initially tend to decline to month 24 which is the point at which the number of patients remaining in the trial starts to decline. During this period the mean reported quality of life values show some tendency to increase. Whether this reflects reporting bias or genuine improvements in quality of life cannot be determined. But it is notable that the mean EQ-5D evolves in a similar manner in both arms, despite reporting rates in the placebo arm declining more precipitously than in the dabrafenib+trametinib arm.”¹⁰⁶
- Results:
 - “Using the ERG's base-case assumptions ... , the incremental cost-effectiveness ratios (ICERs) ranged from £20,701 per quality-adjusted life year (QALY) gained for the log-logistic unrestricted mixture model and £20,167 per QALY gained for the ERG's flexible parametric fit model. The committee noted that these were almost identical to the company's base-case ICER of £20,039 per QALY gained.”¹⁰⁵ Details of the incremental costs and QALYs gained are kept confidential in the underlying HTA report.
- Uncertainty/sensitivity:
 - “The main driver of the cost-effectiveness modelling is the projection of long-term relapse-free survival.”¹⁰⁵
- Conclusions:
 - “The committee further noted that the results were consistent across the ERG's scenario analyses and were in the range normally considered cost effective. It therefore concluded that dabrafenib with trametinib is a potentially innovative treatment for stage III melanoma and represents a cost-effective use of NHS resources. Therefore, it can be recommended for routine commissioning.”¹⁰⁵
 - “Dabrafenib with trametinib is recommended, within its marketing authorisation, as an option for the adjuvant treatment of resected stage III BRAF V600 mutation-positive melanoma in adults. It is recommended only if the company provides dabrafenib and trametinib with the discounts agreed in the commercial arrangements.”¹⁰⁵
- (Confidential) prices:
 - “The company has a commercial arrangement for each drug. This makes dabrafenib with trametinib available to the NHS with a discount. The size of the discount is commercial in confidence.”¹⁰⁵



Reference Costs (list prices & remarks)	Population, Intervention & comparator IC, IE and ICERs	Remarks on use of generic utility instrument (e.g. EQ- 5D) to measure impact on QoL in economic evaluations	Most uncertain variables or important variables in sensitivity analysis
Dabrafenib			
NICE, TA544 (2018) ¹⁰⁵	BRAF V600 mutation-positive patients who when at stage III had their disease resected.		
Connock (2018) ¹⁰⁶	Dabrafenib with trametinib compared with routine surveillance.		
List prices, negotiated discounts are hidden. Information on the number of packs of dabrafenib and trametinib, or the mean treatment duration, is confidential.	Including the dabrafenib PAS and the trametinib PAS, the company base case deterministic estimates result in an ICER of £20,039 per QALY. The probabilistic modelling results are in line with those of the deterministic analysis, with a central ICER of £20,037 per QALY. Details on IC and IE are kept confidential.	The EQ-5D-3L questionnaire was applied in the COMBI-AD trial.	The choice of curve for modelling relapse-free survival.



Appendix 5.4.2.12. NICE, TA321 (2014): dabrafenib

- QoL:
 - “Treatment-specific EQ-5D utility data for pre-progression and post-progression, derived directly from BREAK-3, were used in the model for dabrafenib and dacarbazine. In the absence of comparable EQ-5D utility data for vemurafenib, the company assumed that the vemurafenib utility values would be the same as those for dabrafenib.”¹⁰⁸
 - “Health-related quality of life (HRQoL) was assessed in BREAK-3 using the EuroQoL (EQ-5D) utility index. EQ-5D data were collected for all the participants in the trial at screening, week 6, week 12, week 15, at disease progression, and approximately 30 days after disease progression. The mean change in EQ-5D utility index score from baseline to week 15 was lower in the dabrafenib group (+0.053) than in the dacarbazine group (+0.128).”¹⁰⁸
- Results:
 - “The Committee noted that the company's base case ICER was £11,000 per QALY gained for dabrafenib compared with vemurafenib, but was much lower than this if a class effect was assumed for dabrafenib and vemurafenib. In the absence of any further numerical analysis by the ERG, the Committee could not give an estimate of the most plausible ICER for the comparison of dabrafenib with vemurafenib.”¹⁰⁸
 - “To estimate the effectiveness of dabrafenib compared with vemurafenib, in the absence of head-to-head trials comparing dabrafenib and vemurafenib, the company conducted an indirect treatment comparison using data from the BREAK-3 and BRIM-3 trials.”¹⁰⁸ “The ERG did not conduct exploratory analyses because of its concerns that any estimated ICERs generated from the results of the company's indirect comparison would be unreliable. In the absence of any further numerical analysis by the ERG, the Committee could not give an estimate of the most plausible ICER for the comparison of dabrafenib with vemurafenib.”¹⁰⁸
- Uncertainty/sensitivity:
 - “The key driver of the cost-effectiveness result for the comparison of dabrafenib with vemurafenib was the progression-free survival assumption.”¹⁰⁸
- Conclusions:
 - “The ERG concluded that any estimated ICERs generated by this indirect comparison would be unreliable and likely to be misleading.”¹⁰⁸ “The manufacturer has employed a simple indirect treatment comparison based on two clinical trials (BREAK-32 and BRIM-31) to facilitate a cost-effectiveness comparison between dabrafenib and vemurafenib. This relies on strong assumptions about constant proportional hazards both within and between the two trials, and on examination of the evidence the ERG concludes that such an indirect comparison is not valid, and the results should not be considered meaningful or reliable.”¹⁰⁹
 - “Having considered the lack of evidence of difference in clinical effectiveness between dabrafenib and vemurafenib, and that the overall costs were not different in the economic analysis, the Committee concluded that any difference in the cost effectiveness would be small and, would fall within the range considered to be a cost effective use of NHS resources.”¹⁰⁸
 - “Dabrafenib is recommended, within its marketing authorisation, as an option for treating unresectable or metastatic BRAF V600 mutation-positive melanoma only if the company provides dabrafenib with the discount agreed in the patient access scheme.”¹⁰⁸



- (Confidential) prices:
 - “Novartis has agreed a patient access scheme with the Department of Health that makes dabrafenib available with a discount applied at the point of purchase or invoice. The size of the discount is commercial in confidence.”¹⁰⁸

Reference Costs (list prices & remarks)	Population, Intervention & comparator IC, IE and ICERs	Remarks on use of generic utility instrument (e.g. EQ- 5D) to measure impact on QoL in economic evaluations	Most uncertain variables or important variables in sensitivity analysis
Dabrafenib			
NICE, TA321 (2014) ¹⁰⁸ Fleeman (2014) ¹⁰⁹	Previously untreated patients with unresectable or metastatic BRAF V600 mutation-positive melanoma. Dabrafenib compared with vemurafenib (The Committee did not consider the cost effectiveness of dabrafenib compared with dacarbazine, having noted that dacarbazine was not an appropriate comparator as it was no longer used in clinical practice. It restricted its cost-effectiveness discussion to the comparison with vemurafenib)		
List prices, negotiated discounts are hidden. Drug costs per cycle of 28 days: Dabrafenib: £5600 Vemurafenib: £7000	The results included in the manufacturer's submission have been generated using PAS costs for dabrafenib and vemurafenib. The ICERs for dabrafenib vs vemurafenib are £11,028 per QALY gained and £7,523 per life-year gained. The ERG did not conduct exploratory analyses because of its concerns that any estimated ICERs generated from the results of the company's indirect comparison would be unreliable.	For dabrafenib, EQ-5D utility data for pre-progression and post-progression were derived directly from the BREAK-3 trial. There was an absence of comparable EQ-5D utility data for vemurafenib.	Progression-free survival assumption.



Appendix 5.4.2.13. NICE, TA269 (2012): vemurafenib

- QoL:
 - “The manufacturer collected health-related quality-of-life data in the BRIM3 study using the functional assessment of cancer therapy-melanoma (FACT-M) questionnaire; however, results were not presented because completion rates were low. Instead, utility values from a study by Beusterien et al. (2009) were used.”¹¹⁰
 - “It is recognised that quality of life data, although collected, are not available from the BRIM 3 trial.”¹¹¹
- Results:
 - “The manufacturer's revised cost-effectiveness estimate was £51,800 per QALY gained when using the RPSFT adjusted February 2012 data cut-off and £44,400 when using the Bedikian trial data to represent the dacarbazine arm. These estimates take into account the evidence review group's (ERG) suggested amendments to discounting and costs.”¹¹⁰
- Uncertainty/sensitivity:
 - “The Committee acknowledged that the existence or magnitude of continued benefit from vemurafenib after treatment is stopped is uncertain, but recognised there is no evidence currently available to suggest that people who stop vemurafenib treatment will experience accelerated disease progression compared with those who have been treated with dacarbazine.”¹¹⁰
 - “The main area that gave cause for concern was the modelling of OS.”¹¹¹
- Conclusions:
 - The Committee “accepted vemurafenib represents an effective new therapy in an area of unmet need, has a novel mechanism of action, is life-extending, and meets the criteria for an end-of-life treatment. The Committee concluded that the most plausible ICER was in the range of £44,000 to £51,800 per QALY gained, and the combined value of these factors meant that vemurafenib could be considered a cost-effective use of NHS resources.”¹¹⁰
 - “Vemurafenib is recommended as an option for treating BRAF V600 mutation-positive unresectable or metastatic melanoma only if the manufacturer makes vemurafenib available with the discount agreed as part of the patient access scheme.”¹¹⁰
- (Confidential) prices:
 - “The manufacturer of vemurafenib has agreed a patient access scheme with the Department of Health, in which a confidential discount on the list price of vemurafenib is offered.”¹¹⁰



Reference Costs (list prices & remarks)	Population, Intervention & comparator IC, IE and ICERs	Remarks on use of generic utility instrument (e.g. EQ- 5D) to measure impact on QoL in economic evaluations	Most uncertain variables or important variables in sensitivity analysis
Vemurafenib			
NICE, TA269 (2012) ¹¹⁰	Patients with locally advanced or metastatic BRAF V600 mutation-positive malignant melanoma.		
Dickson (2012) ¹¹¹	Vemurafenib compared with dacarbazine.		
List prices, negotiated discounts are hidden. Drug costs: Vemurafenib: £1750 for 1 pack of 56 x 240mg tablets (1 week's supply) Dacarbazine: £63.60 per dose (given every 3 weeks)	<p>The results included in the manufacturer's submission have been generated including the patient access scheme for vemurafenib. Incremental costs and benefits are considered as commercial-in-confidence.</p> <p>The manufacturer's revised cost-effectiveness estimate was £51,800 per QALY gained when using the RPSFT adjusted February 2012 data cut-off and £44,400 when using the Bedikian trial data to represent the dacarbazine arm.</p> <p>The ERG disagreed with the manufacturer's comments, and reported a cost-effectiveness estimate of £121,000 per QALY gained using the February 2012 data cut-off.</p> <p>The Committee was not satisfied that the alternative ICER (based on the Committee's requested scenario) of £121,000 per QALY gained represented the true benefit of vemurafenib because it accepted that it was implausible that post-progression survival after vemurafenib was shorter than after dacarbazine. The Committee therefore concluded that the most plausible ICER was in the range of £44,000 to £51,800 per QALY gained.</p>	No generic utility instrument was used in the underlying trial.	Modelling overall survival Continued benefit from vemurafenib after treatment is stopped.



Appendix 5.4.2.14. NICE, TA396 (2016): trametinib

- QoL:
 - “The committee examined the data presented on health-related quality of life in the company's submission. It noted with approval that the company had collected quality of life data in the trials, and that rates of completion were high. Data had been gathered using EQ-5D and other instruments.”¹⁰⁷
 - “The company presented health-related quality of life results from both trials using 2 measures; the EuroQol-5 dimension questionnaire (EQ-5D) and the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC-QLQ-30). The rates of completion of EORTC-QLQ-30 among patients in both studies, and of EQ-5D in COMBI-v (the company did not present EQ-5D completion rates for COMBI-d) were over 90% at baseline, and over 70% at disease progression. For COMBI-d, EQ-5D scores at baseline were similar between treatment groups with a statistically significant difference in results favouring the combination group at week 16 only. Results from COMBI-v showed similar baseline EQ-5D scores between treatment groups and, for all assessments, the differences between scores were significantly better for the combination group compared with the monotherapy group.”¹⁰⁷
 - “Adverse events were indirectly incorporated in the model because utility data were taken directly from the trials.”¹⁰⁷
- Results:
 - “Applying the ERG's preferred method of extrapolating OS reduced the number of QALYs gained for trametinib plus dabrafenib from 1.297 QALYs to 0.878 QALYs compared with dabrafenib alone, and from 1.345 QALYs to 0.925 QALYs compared with vemurafenib alone.”¹⁰⁷
 - “The committee considered that while the most plausible ICER was uncertain, it would be no higher than the ERG's estimate using its preferred method of modelling overall survival. The committee agreed that the estimates presented by the ERG and the company were within the range normally considered a cost effective use of NHS resources.”¹⁰⁷
 - “Because trametinib, dabrafenib and vemurafenib have confidential patient access schemes, the incremental cost-effectiveness ratios (ICERs) presented are not reflective of the actual cost to the NHS.”¹⁰⁷
- Uncertainty/sensitivity:
 - “The committee concluded that there were uncertainties in modelling of overall survival which required long-term extrapolation of data beyond the end of the trial.”¹⁰⁷
- Conclusions:
 - “the estimates presented by the ERG and the company were within the range normally considered a cost effective use of NHS resources. It concluded that trametinib plus dabrafenib could therefore be recommended as a treatment option for people with unresectable or metastatic BRAF V600 mutation-positive melanoma.”¹⁰⁷
 - “Trametinib in combination with dabrafenib is recommended, within its marketing authorisation, as an option for treating unresectable or metastatic melanoma in adults with a BRAF V600 mutation, only when the company provides trametinib and dabrafenib with the discounts agreed in the patient access schemes.”¹⁰⁷



- (Confidential) prices:
 - “The company has agreed patient access schemes with the Department of Health. These schemes provide simple discounts to the list prices of trametinib and dabrafenib with the discounts applied at the point of purchase or invoice. The levels of the discounts are commercial in confidence.”¹⁰⁷

Reference Costs (list prices & remarks)	Population, Intervention & comparator IC, IE and ICERs	Remarks on use of generic utility instrument (e.g. EQ- 5D) to measure impact on QoL in economic evaluations	Most uncertain variables or important variables in sensitivity analysis
Trametinib			
NICE, TA396 (2016) ¹⁰⁷	Patients with unresectable or metastatic BRAF V600 mutation-positive melanoma. Trametinib plus dabrafenib versus dabrafenib or vemurafenib alone.		
List prices, negotiated discounts are hidden. Drug costs: Trametinib: £1,120 per pack of 2-mg tablets (7 tablets per pack) Dabrafenib: £1,400 per pack of 75-mg tablets (28 tablets per pack)	No information on incremental costs and ICERs is presented in the report. Only information on the incremental benefit was identified. Results from the company showed that trametinib plus dabrafenib was associated with a greater number of quality-adjusted life years (QALYs) compared with the monotherapies (1.345 more QALYs than vemurafenib and 1.298 more QALYs than dabrafenib). Applying the ERG's preferred method of extrapolating OS reduced the number of QALYs gained for trametinib plus dabrafenib from 1.298 QALYs to 0.878 QALYs compared with dabrafenib alone, and from 1.345 QALYs to 0.925 QALYs compared with vemurafenib alone.	EQ-5D is used in the trial but no details are provided in the NICE report.	Modelling of overall survival.



APPENDIX 6. MESOTHELIOMA

Appendix 6.1. BCR data

Appendix 6.1.1. Descriptive statistics

Appendix 6.1.1.1. Malignant epithelioid mesothelioma of pleura, exploration

Table 80 – Mesothelioma (2004-2017): Frequency table of patient and tumour characteristics

Characteristic	Total	Incidence period		
		2004-2008	2009-2013	2014-2017
Overall	1,962	538	719	705
Gender				
Male	1,615 (82.3)	442 (82.2)	593 (82.5)	580 (82.3)
Female	347 (17.7)	96 (17.8)	126 (17.5)	125 (17.7)
Age at diagnosis (year)				
<50 years	52 (2.7)	19 (3.5)	21 (2.9)	12 (1.7)
50-59 years	233 (11.9)	83 (15.4)	84 (11.7)	66 (9.4)
60-69 years	538 (27.4)	162 (30.1)	194 (27.0)	182 (25.8)
70-79 years	764 (38.9)	210 (39.0)	287 (39.9)	267 (37.9)
80+ years	375 (19.1)	64 (11.9)	133 (18.5)	178 (25.2)
WHO - Performance Status				
0 – Asymptomatic	156 (8.0)	39 (7.2)	50 (7.0)	67 (9.5)
1 – Symptomatic but completely ambulatory	1,163 (59.3)	274 (50.9)	433 (60.2)	456 (64.7)
2 – Symptomatic, <50% in bed during the day	181 (9.2)	55 (10.2)	62 (8.6)	64 (9.1)
3 – Symptomatic, >50% in bed, but not bedbound	36 (1.8)	11 (2.0)	12 (1.7)	13 (1.8)
4 – Bedbound	11 (0.6)	3 (0.6)	4 (0.6)	4 (0.6)
Not reported	415 (21.2)	156 (29.0)	158 (22.0)	101 (14.3)
Combined stage				
I	277 (14.1)	57 (10.6)	72 (10.0)	148 (21.0)
II	230 (11.7)	74 (13.8)	83 (11.5)	73 (10.4)
III	359 (18.3)	77 (14.3)	140 (19.5)	142 (20.1)



IV	348 (17.7)	88 (16.4)	127 (17.7)	133 (18.9)
X	748 (38.1)	242 (45.0)	297 (41.3)	209 (29.6)

Note: the values between parentheses are column percentages.

Table 81 – Mesothelioma (2004-2017), Combined stage I, Frequency table of patient and tumour characteristics

Characteristic	Total	Incidence period		
		2004-2008	2009-2013	2014-2017
Overall	277	57	72	148
Gender				
Male	231 (83.4)	50 (87.7)	61 (84.7)	120 (81.1)
Female	46 (16.6)	7 (12.3)	11 (15.3)	28 (18.9)
Age at diagnosis (year)				
<50 years	8 (2.9)	4 (7.0)	2 (2.8)	2 (1.4)
50-59 years	28 (10.1)	8 (14.0)	8 (11.1)	12 (8.1)
60-69 years	66 (23.8)	18 (31.6)	18 (25.0)	30 (20.3)
70-79 years	116 (41.9)	21 (36.8)	36 (50.0)	59 (39.9)
80+ years	59 (21.3)	6 (10.5)	8 (11.1)	45 (30.4)
WHO - Performance Status				
0 – Asymptomatic	33 (11.9)	5 (8.8)	8 (11.1)	20 (13.5)
1 – Symptomatic but completely ambulatory	176 (63.5)	37 (64.9)	47 (65.3)	92 (62.2)
2 – Symptomatic, <50% in bed during the day	32 (11.6)	8 (14.0)	7 (9.7)	17 (11.5)
3 – Symptomatic, >50% in bed, but not bedbound	4 (1.4)	0 (0.0)	1 (1.4)	3 (2.0)
Not reported	32 (11.6)	7 (12.3)	9 (12.5)	16 (10.8)

Note: the values between parentheses are column percentages.


Table 82 – Mesothelioma (2004-2017), Combined stage II, Frequency table of patient and tumour characteristics

Characteristic	Total	Incidence period		
		2004-2008	2009-2013	2014-2017
Overall	230	74	83	73
Gender				
Male	195 (84.8)	62 (83.8)	70 (84.3)	63 (86.3)
Female	35 (15.2)	12 (16.2)	13 (15.7)	10 (13.7)
Age at diagnosis (year)				
<50 years	7 (3.0)	3 (4.1)	3 (3.6)	1 (1.4)
50-59 years	36 (15.7)	16 (21.6)	13 (15.7)	7 (9.6)
60-69 years	71 (30.9)	26 (35.1)	27 (32.5)	18 (24.7)
70-79 years	75 (32.6)	19 (25.7)	29 (34.9)	27 (37.0)
80+ years	41 (17.8)	10 (13.5)	11 (13.3)	20 (27.4)
WHO - Performance Status				
0 – Asymptomatic	24 (10.4)	8 (10.8)	5 (6.0)	11 (15.1)
1 – Symptomatic but completely ambulatory	160 (69.6)	46 (62.2)	61 (73.5)	53 (72.6)
2 – Symptomatic, <50% in bed during the day	21 (9.1)	9 (12.2)	7 (8.4)	5 (6.8)
3 – Symptomatic, >50% in bed, but not bedbound	1 (0.4)	0 (0.0)	0 (0.0)	1 (1.4)
Not reported	24 (10.4)	11 (14.9)	10 (12.0)	3 (4.1)

Note: the values between parentheses are column percentages.



Table 83 – Mesothelioma (2004-2017), Combined stage III/IV/X, Frequency table of patient and tumour characteristics

Characteristic	Total	Incidence period		
		2004-2008	2009-2013	2014-2017
Overall	1,455	407	564	484
Gender				
Male	1,189 (81.7)	330 (81.1)	462 (81.9)	397 (82.0)
Female	266 (18.3)	77 (18.9)	102 (18.1)	87 (18.0)
Age at diagnosis (year)				
<50 years	37 (2.5)	12 (2.9)	16 (2.8)	9 (1.9)
50-59 years	169 (11.6)	59 (14.5)	63 (11.2)	47 (9.7)
60-69 years	401 (27.6)	118 (29.0)	149 (26.4)	134 (27.7)
70-79 years	573 (39.4)	170 (41.8)	222 (39.4)	181 (37.4)
80+ years	275 (18.9)	48 (11.8)	114 (20.2)	113 (23.3)
WHO - Performance Status				
0 – Asymptomatic	99 (6.8)	26 (6.4)	37 (6.6)	36 (7.4)
1 – Symptomatic but completely ambulatory	827 (56.8)	191 (46.9)	325 (57.6)	311 (64.3)
2 – Symptomatic, <50% in bed during the day	128 (8.8)	38 (9.3)	48 (8.5)	42 (8.7)
3 – Symptomatic, >50% in bed, but not bedbound	31 (2.1)	11 (2.7)	11 (2.0)	9 (1.9)
4 – Bedbound	11 (0.8)	3 (0.7)	4 (0.7)	4 (0.8)
Not reported	359 (24.7)	138 (33.9)	139 (24.6)	82 (16.9)

Note: the values between parentheses are column percentages.



Appendix 6.1.1.2. *Mesothelioma (2004-2017), Observed and Relative Survival graphs*

Malignant epithelioid mesothelioma of pleura (2004-2017)

Figure 145 – Mesothelioma (2004-2017), Kaplan-Meier graphs observed survival by incidence period

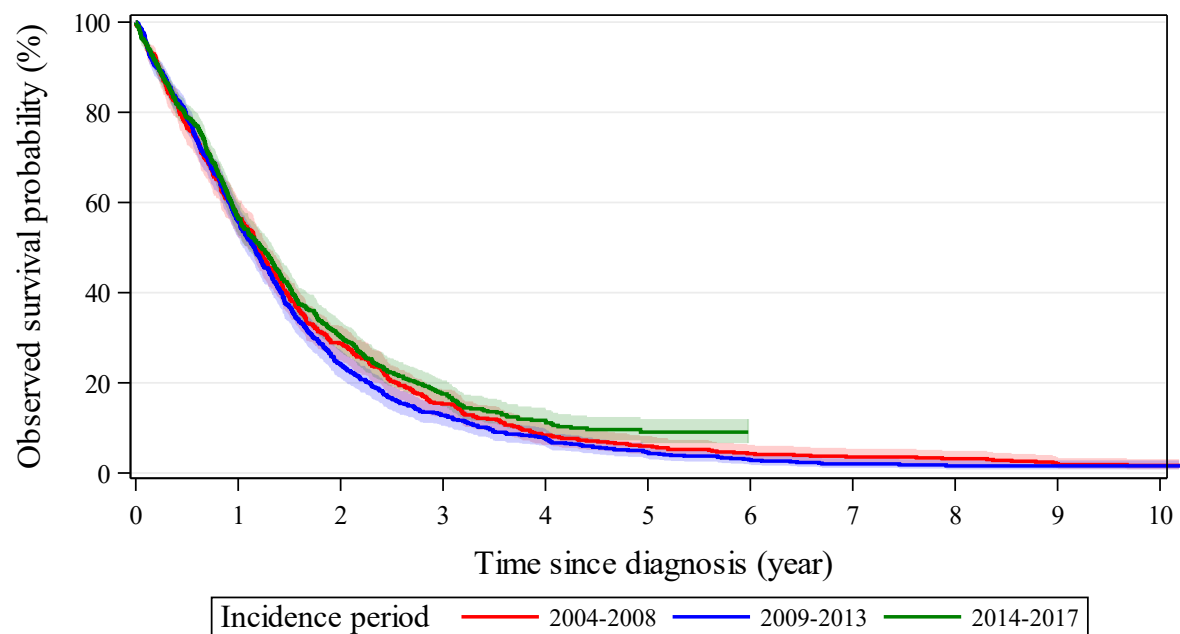
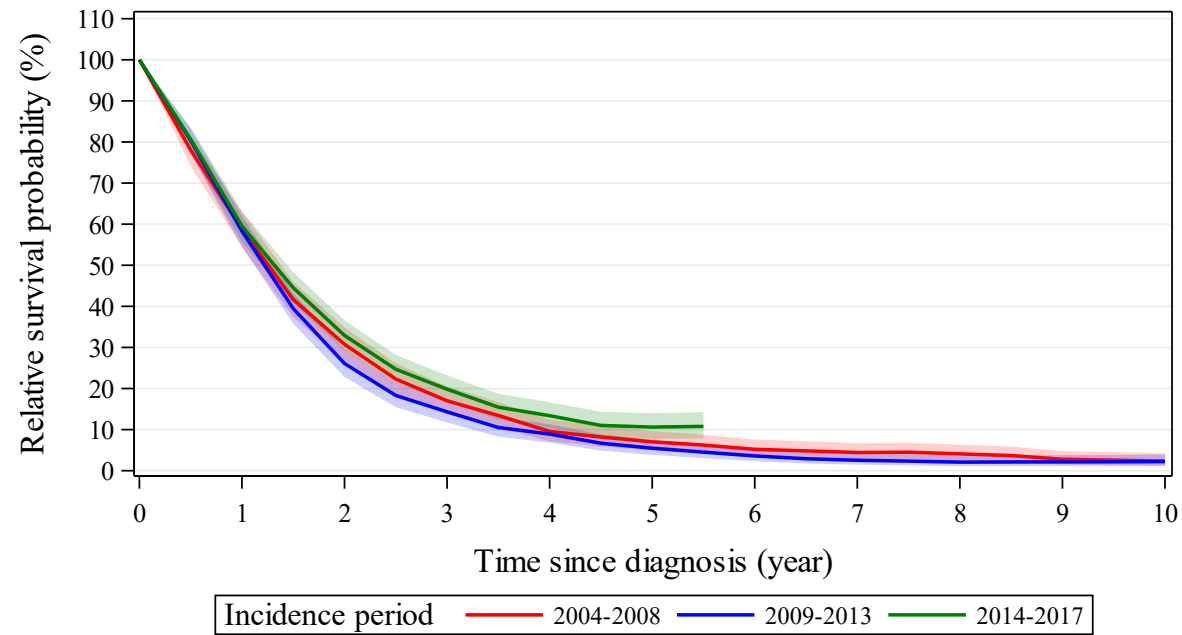




Figure 146 – Mesothelioma (2004-2017), relative survival graphs by incidence period



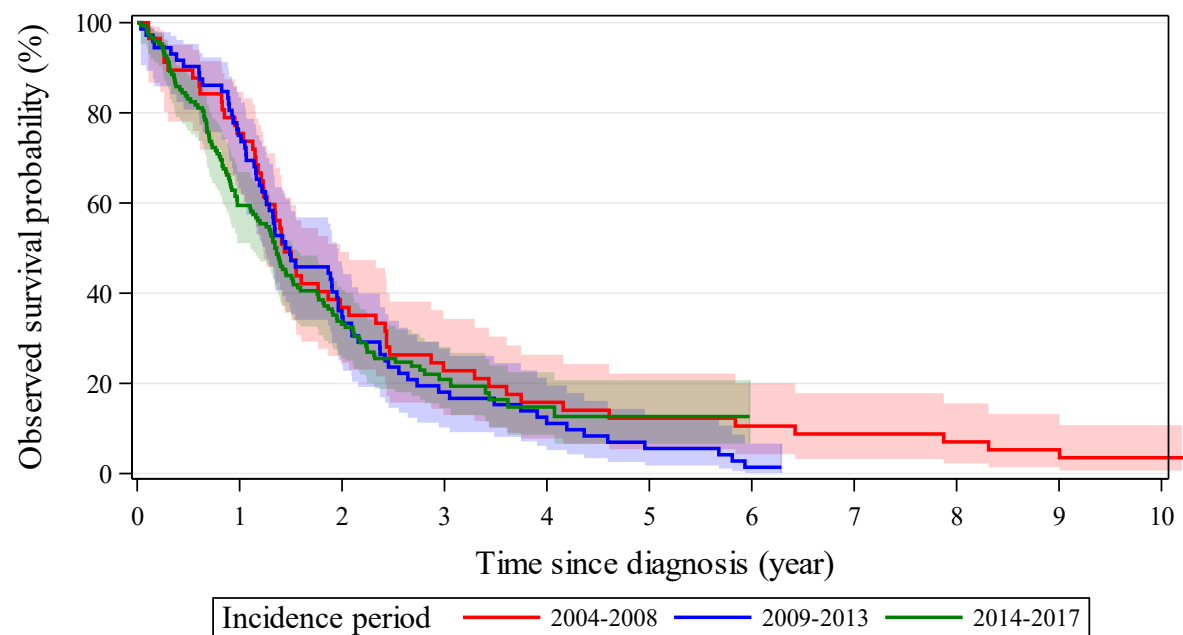
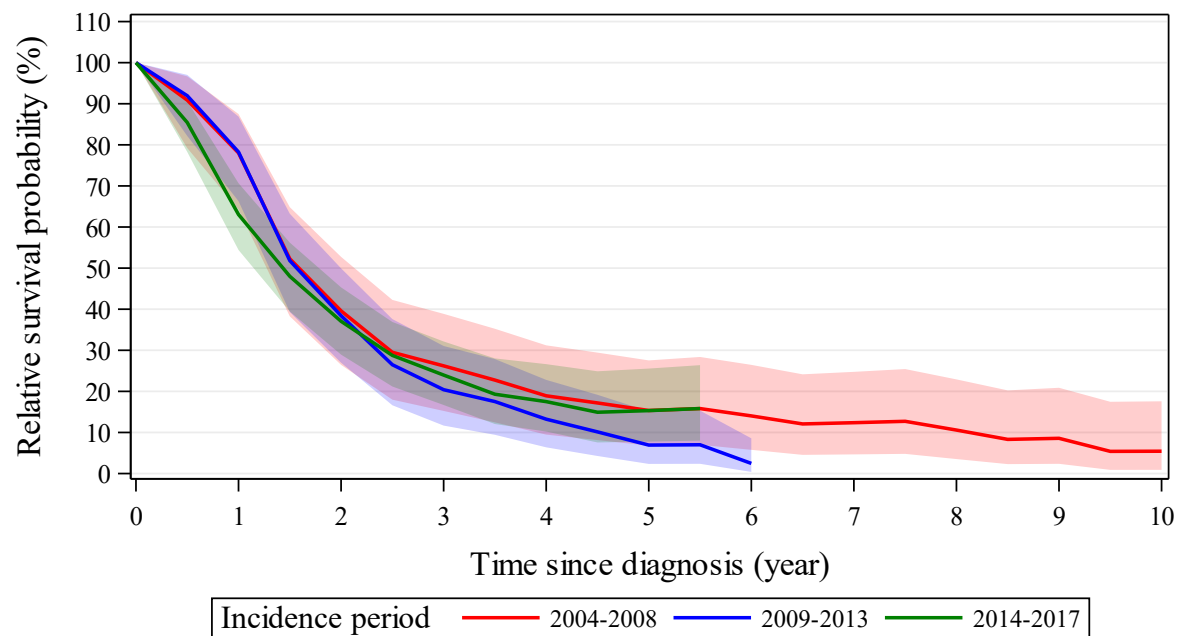
**Malignant epithelioid mesothelioma of pleura, combined stage I (2004-2017)****Figure 147 – Mesothelioma (2004-2017), combined stage I, Kaplan-Meier graphs observed survival by incidence period**



Figure 148 – Mesothelioma (2004-2017), combined stage I, relative survival graphs by incidence period



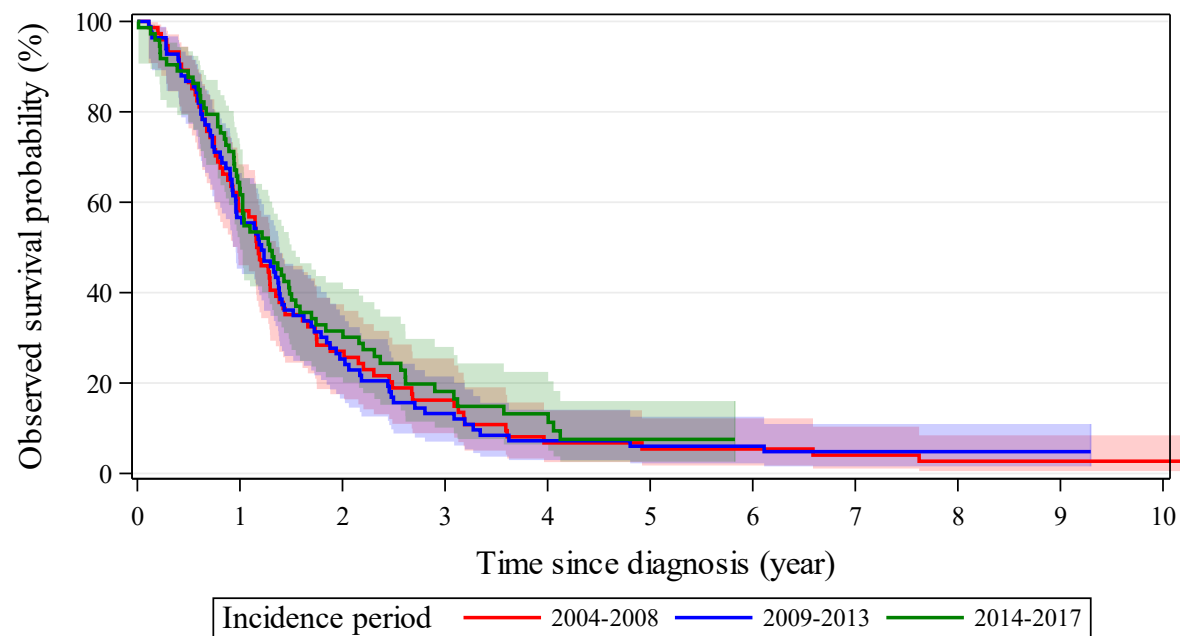
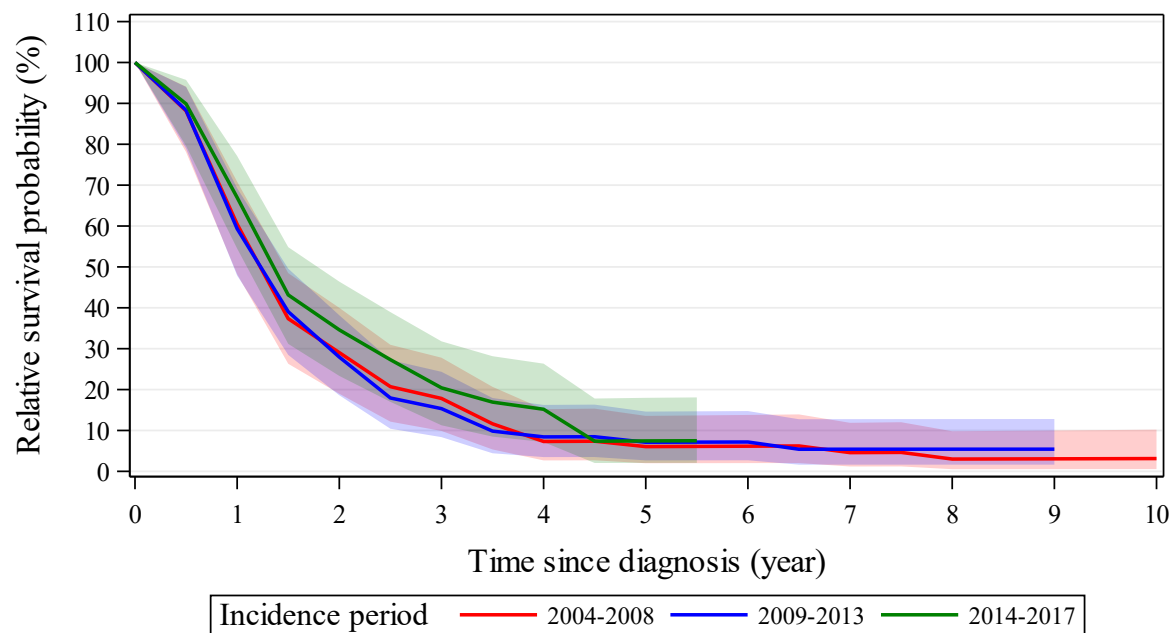
**Malignant epithelioid mesothelioma of pleura, combined stage II (2004-2017)****Figure 149 – Mesothelioma (2004-2017), combined stage II, Kaplan-Meier graphs observed survival by incidence period**



Figure 150 – Mesothelioma (2004-2017), combined stage II, relative survival graphs by incidence period



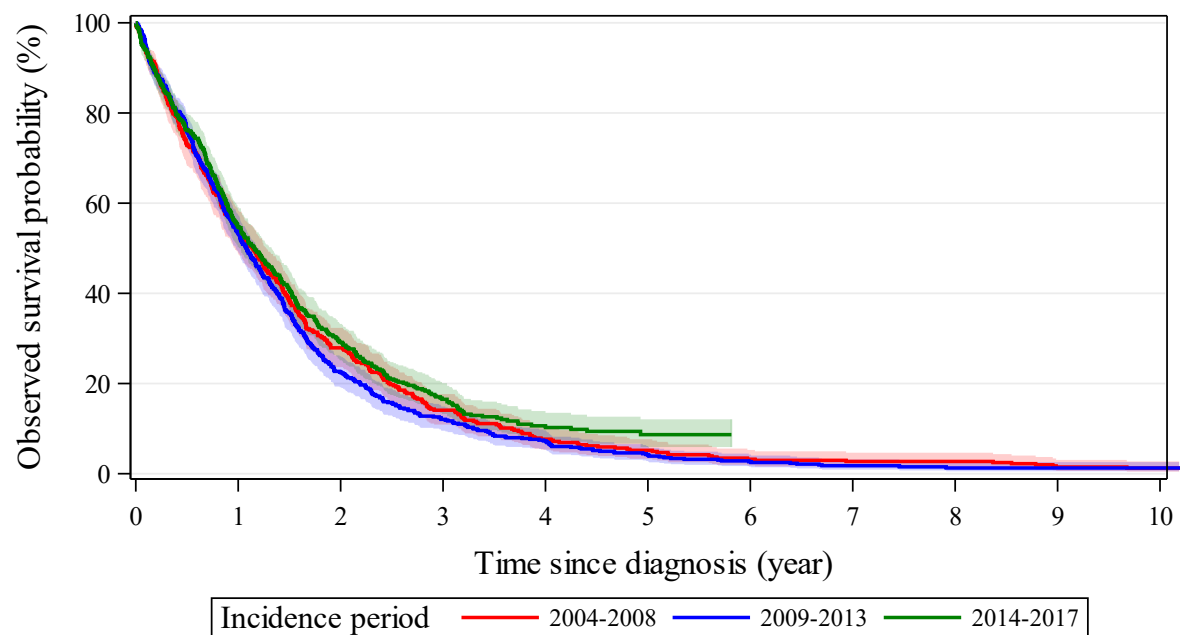
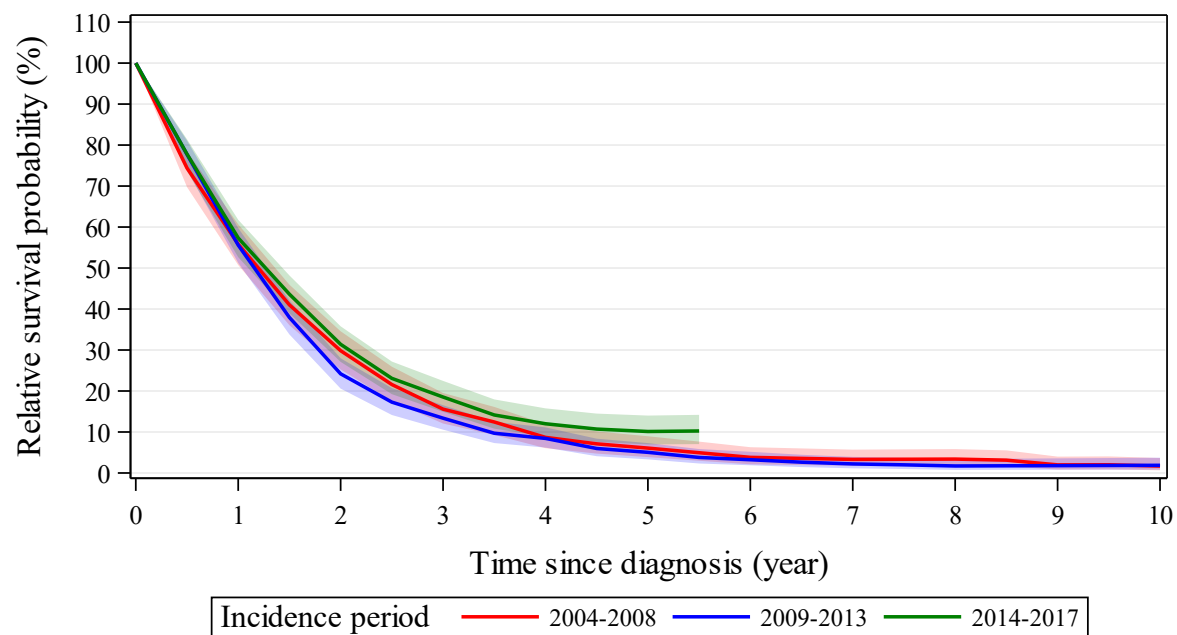
**Malignant epithelioid mesothelioma of pleura, combined stage III/IV/X (2004-2017)****Figure 151 – Mesothelioma (2004-2017), combined stage III/IV/X, Kaplan-Meier graphs observed survival by incidence period**



Figure 152 – Mesothelioma (2004-2017), combined stage III/IV/X, relative survival graphs by incidence period

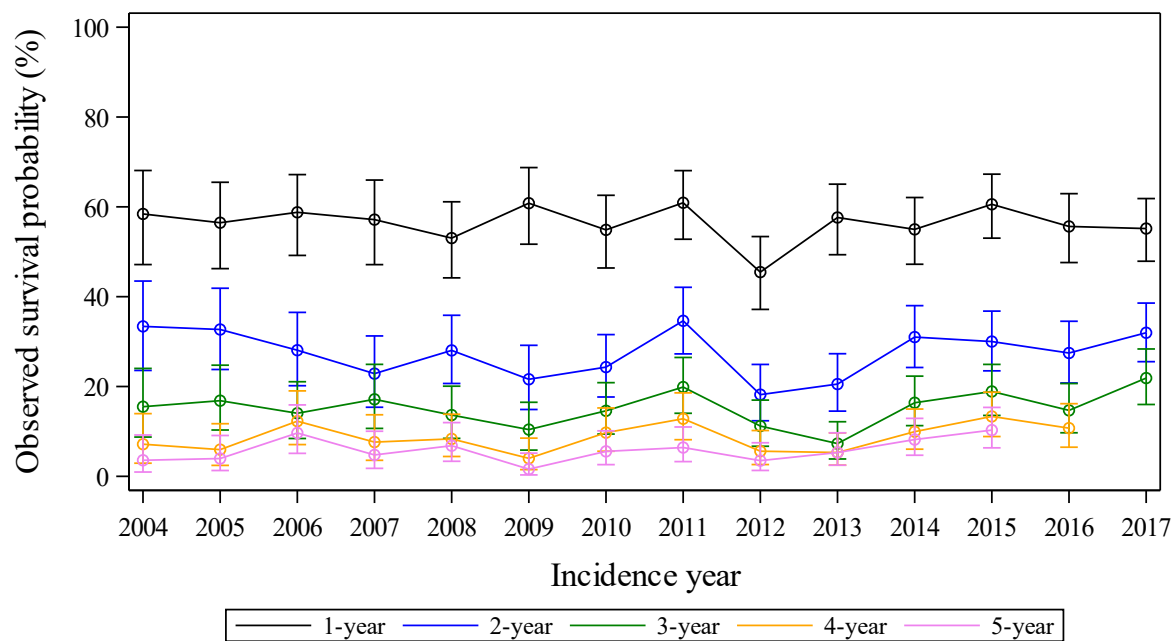




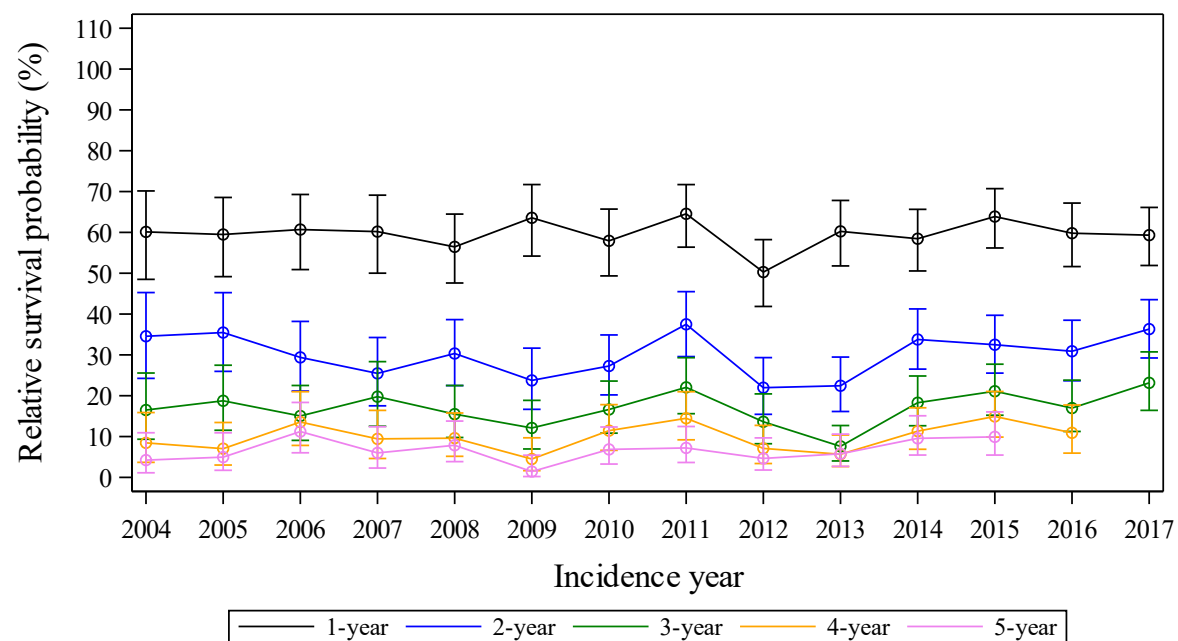
Appendix 6.1.1.3. Malignant epithelioid mesothelioma of pleura, time trend Observed and Relative Survival

Malignant epithelioid mesothelioma of pleura (2004-2017)

Figure 153 – Mesothelioma (2004-2017), time trend observed survival with incidence year

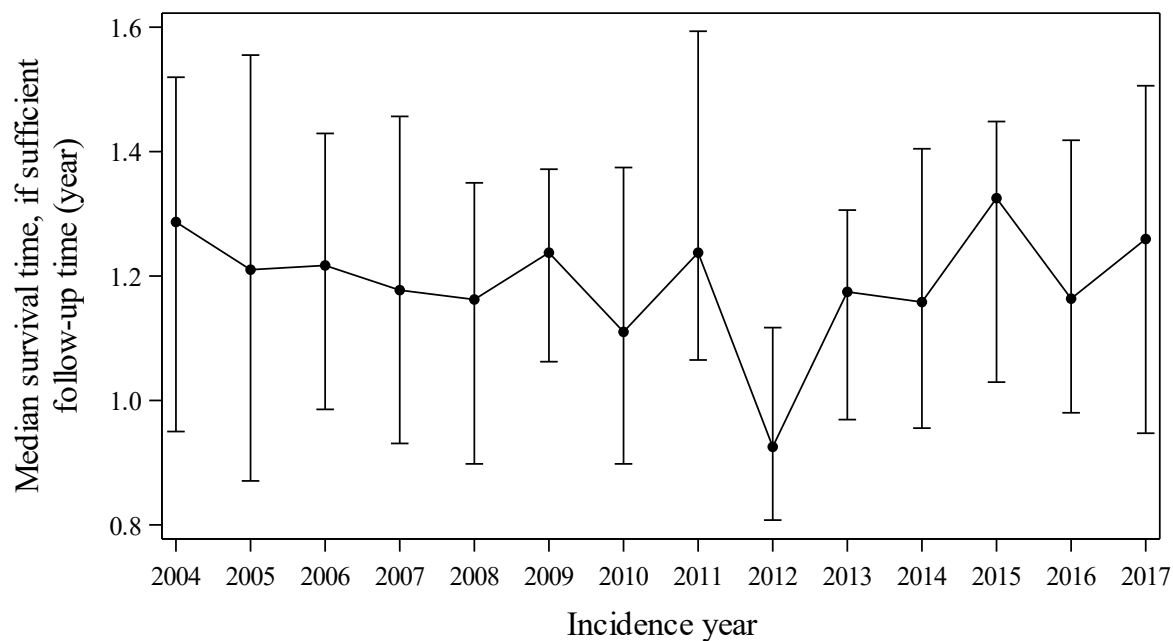


Note: the error bars represent the 95% CI.

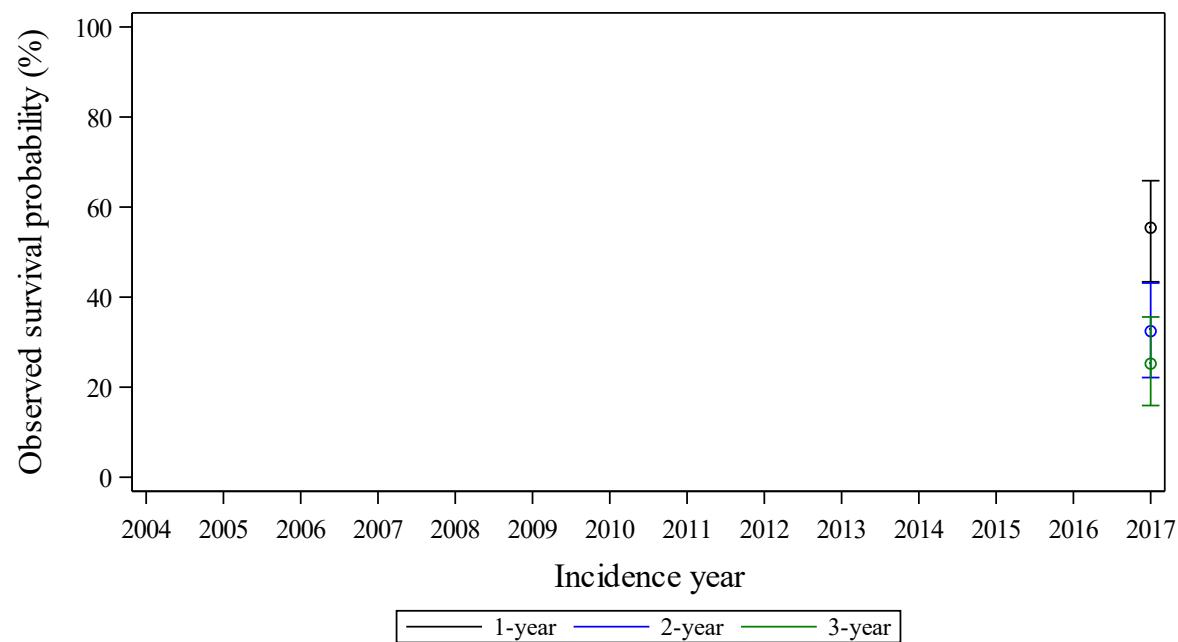
**Figure 154 – Mesothelioma (2004-2017), time trend relative survival with incidence year**

Note: the error bars represent the 95% CI.

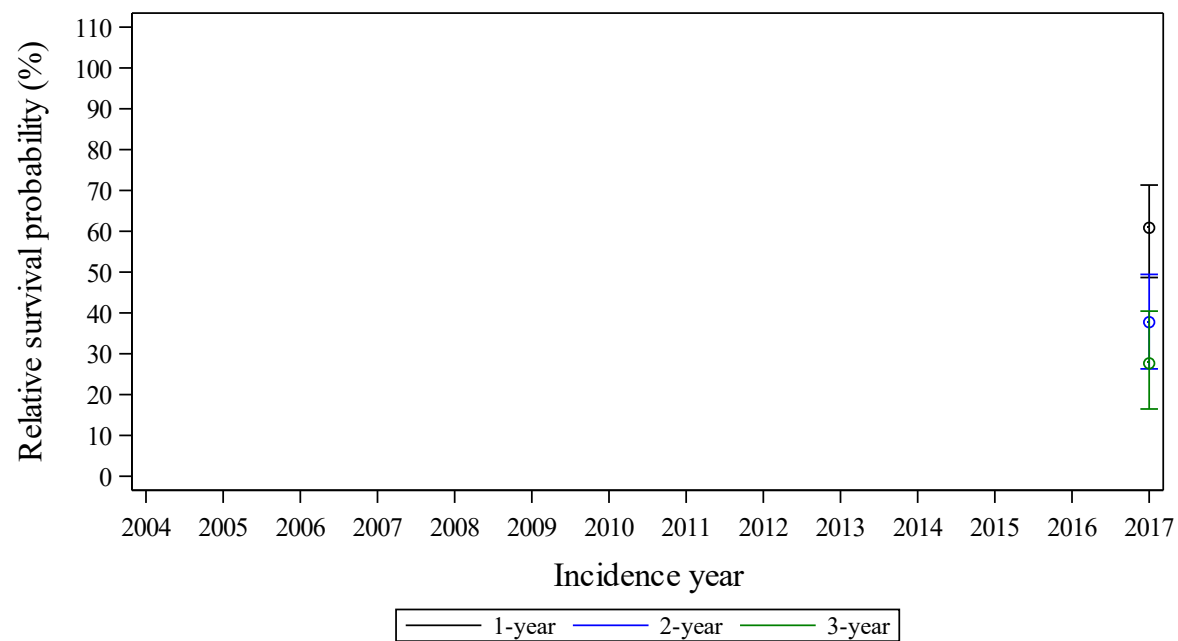
Figure 155 – Mesothelioma (2004-2017), Median time observed survival



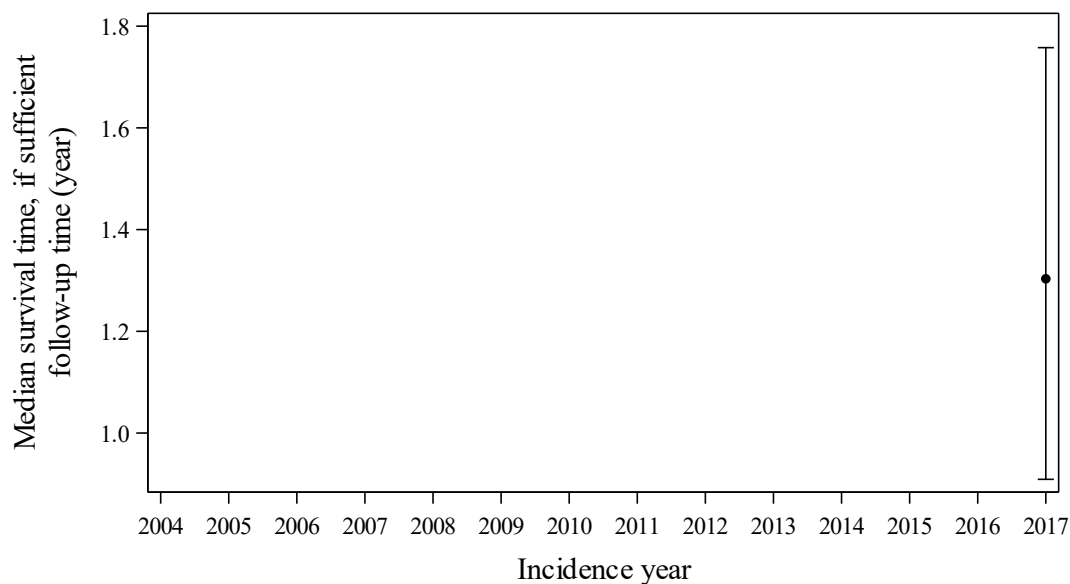
Note: the error bars represent the 95% CI. When the upper error is not plotted, the upper limit could not be determined with the follow-up available.

**Malignant epithelioid mesothelioma of pleura, combined stage I (2004-2017)****Figure 156 – Mesothelioma (2004-2017), combined stage I, time trend observed survival with incidence year**

Note: the error bars represent the 95% CI.

**Figure 157 – Mesothelioma (2004-2017), combined stage I, time trend relative survival with incidence year**

Note: the error bars represent the 95% CI.

**Figure 158 – Mesothelioma (2004-2017), combined stage I, median time observed survival**

Survival results based on small number of persons initially at risk ($N < 35$) can be too variable to be practically meaningful and are therefore not reported.

Malignant epithelioid mesothelioma of pleura, combined stage II (2004-2017)**Figure 159 – Mesothelioma (2004-2017), combined stage II, time trend observed survival with incidence year**

No data points to plot.

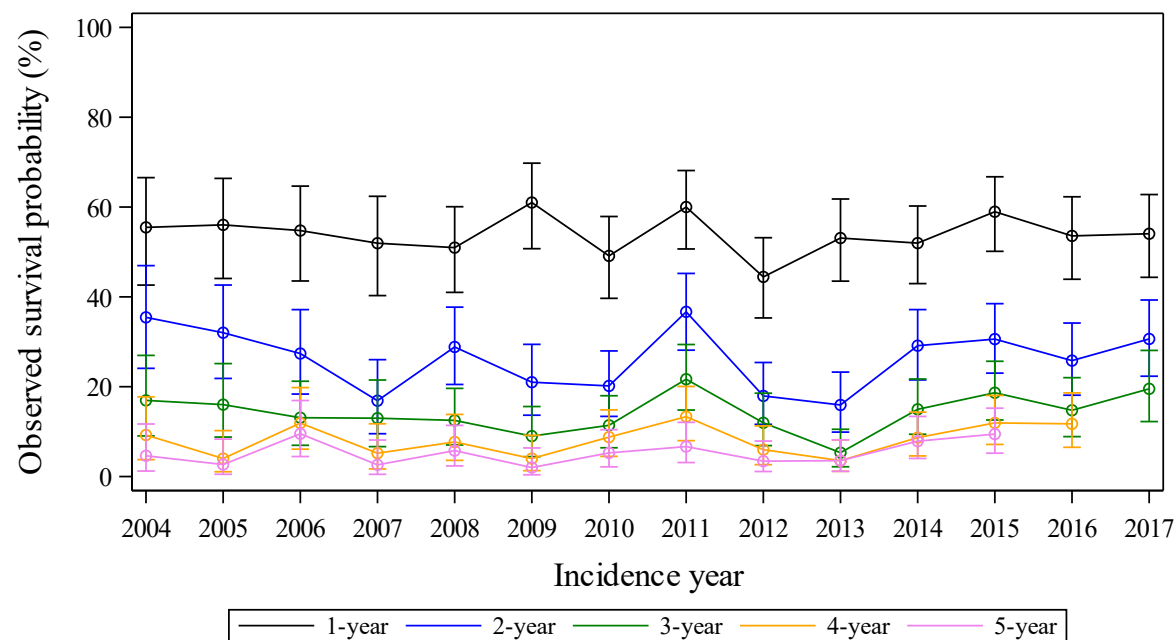
Figure 160 – Mesothelioma (2004-2017), combined stage II, time trend relative survival with incidence year

No data points to plot.

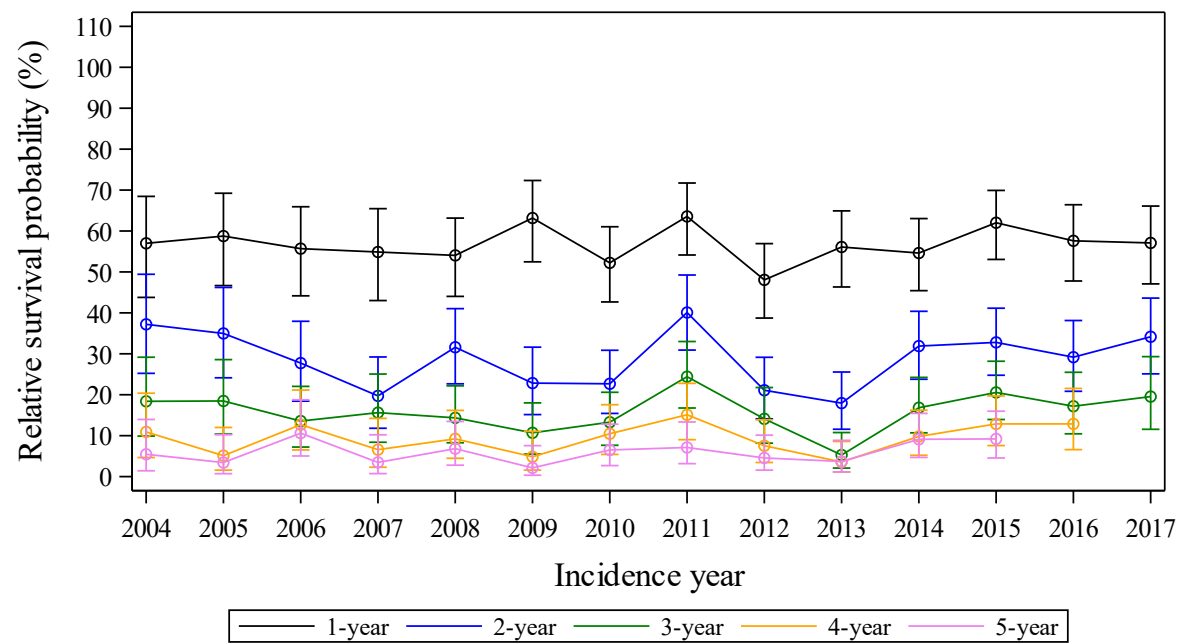
Figure 161 – Mesothelioma (2004-2017), combined stage II, median time observed survival

No data points to plot.

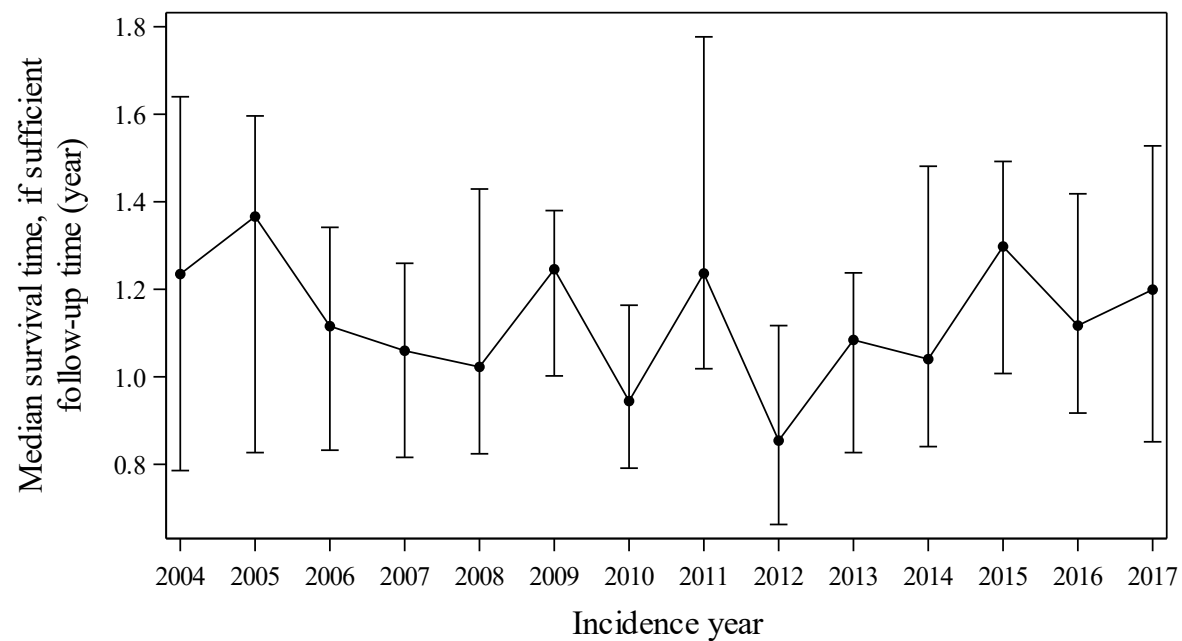
Survival results based on small number of persons initially at risk ($N < 35$) can be too variable to be practically meaningful and are therefore not reported.

**Malignant epithelioid mesothelioma of pleura, combined stage III/IV/X (2004-2017)****Figure 162 – Mesothelioma (2004-2017), combined stage III/IV/X, time trend observed survival with incidence year**

Note: the error bars represent the 95% CI.

**Figure 163 – Mesothelioma (2004-2017), combined stage III/IV/X, time trend relative survival with incidence year**

Note: the error bars represent the 95% CI.

**Figure 164 – Mesothelioma (2004-2017), combined stage III/IV/X, median time observed survival**

Note: the error bars represent the 95% CI. When the upper error is not plotted, the upper limit could not be determined with the follow-up available.



2009	8	N<35	–	N<35	–	N<35	–	N<35	–	N<35	–	N<35	–
2010	14	N<35	–	N<35	–	N<35	–	N<35	–	N<35	–	N<35	–
2011	16	N<35	–	N<35	–	N<35	–	N<35	–	N<35	–	N<35	–
2012	14	N<35	–	N<35	–	N<35	–	N<35	–	N<35	–	N<35	–
2013	20	N<35	–	N<35	–	N<35	–	N<35	–	N<35	–	N<35	–
2014	23	N<35	–	N<35	–	N<35	–	N<35	–	N<35	–	N<35	–
2015	22	N<35	–	N<35	–	N<35	–	N<35	–	N<35	–	N<35	–
2016	29	N<35	–	N<35	–	N<35	–	N<35	–	N<35	–	N<35	–
2017	74	55.4	[43.4, 65.9]	32.4	[22.1, 43.1]	25.2	[15.9, 35.6]	no FU	–	no FU	–	1.3	[0.9, 1.8]
Combined Stage II													
2004	7	N<35	–	N<35	–	N<35	–	N<35	–	N<35	–	N<35	–
2005	14	N<35	–	N<35	–	N<35	–	N<35	–	N<35	–	N<35	–
2006	16	N<35	–	N<35	–	N<35	–	N<35	–	N<35	–	N<35	–
2007	19	N<35	–	N<35	–	N<35	–	N<35	–	N<35	–	N<35	–
2008	18	N<35	–	N<35	–	N<35	–	N<35	–	N<35	–	N<35	–
2009	17	N<35	–	N<35	–	N<35	–	N<35	–	N<35	–	N<35	–
2010	16	N<35	–	N<35	–	N<35	–	N<35	–	N<35	–	N<35	–
2011	20	N<35	–	N<35	–	N<35	–	N<35	–	N<35	–	N<35	–
2012	12	N<35	–	N<35	–	N<35	–	N<35	–	N<35	–	N<35	–
2013	18	N<35	–	N<35	–	N<35	–	N<35	–	N<35	–	N<35	–
2014	21	N<35	–	N<35	–	N<35	–	N<35	–	N<35	–	N<35	–
2015	24	N<35	–	N<35	–	N<35	–	N<35	–	N<35	–	N<35	–
2016	19	N<35	–	N<35	–	N<35	–	N<35	–	N<35	–	N<35	–
2017	9	N<35	–	N<35	–	N<35	–	N<35	–	N<35	–	N<35	–
Combined Stage III/IV/X													
2004	66	55.5	[42.6, 66.5]	35.4	[24.1, 47.0]	16.9	[9.0, 27.0]	9.2	[3.8, 17.7]	4.6	[1.2, 11.7]	1.2	[0.8, 1.6]
2005	76	56.0	[44.1, 66.4]	32.0	[21.8, 42.6]	16.0	[8.8, 25.1]	4.0	[1.1, 10.2]	2.7	[0.5, 8.3]	1.4	[0.8, 1.6]
2006	84	54.8	[43.5, 64.7]	27.4	[18.4, 37.2]	13.1	[7.0, 21.2]	11.9	[6.1, 19.8]	9.5	[4.5, 16.9]	1.1	[0.8, 1.3]



2007	77	51.9	[40.3, 62.4]	16.9	[9.5, 26.0]	13.0	[6.7, 21.5]	5.2	[1.7, 11.7]	2.6	[0.5, 8.1]	1.1	[0.8, 1.3]
2008	104	51.0	[41.0, 60.1]	28.8	[20.5, 37.7]	12.5	[7.0, 19.6]	7.7	[3.6, 13.8]	5.8	[2.4, 11.4]	1.0	[0.8, 1.4]
2009	100	61.0	[50.7, 69.8]	21.0	[13.7, 29.4]	9.0	[4.4, 15.6]	4.0	[1.3, 9.2]	2.0	[0.4, 6.4]	1.2	[1.0, 1.4]
2010	114	49.1	[39.7, 57.9]	20.2	[13.4, 28.0]	11.4	[6.4, 18.0]	8.8	[4.5, 14.8]	5.3	[2.2, 10.4]	0.9	[0.8, 1.2]
2011	120	60.0	[50.7, 68.1]	36.7	[28.1, 45.2]	21.7	[14.8, 29.4]	13.3	[8.0, 20.1]	6.7	[3.1, 12.1]	1.2	[1.0, 1.8]
2012	117	44.4	[35.3, 53.2]	17.9	[11.6, 25.4]	12.0	[6.9, 18.6]	6.0	[2.6, 11.3]	3.4	[1.1, 7.9]	0.9	[0.7, 1.1]
2013	113	53.1	[43.5, 61.8]	15.9	[9.9, 23.3]	5.3	[2.2, 10.5]	3.5	[1.2, 8.2]	3.5	[1.2, 8.2]	1.1	[0.8, 1.2]
2014	127	52.0	[43.0, 60.2]	29.1	[21.5, 37.2]	15.0	[9.4, 21.7]	8.7	[4.6, 14.3]	7.9	[4.0, 13.4]	1.0	[0.8, 1.5]
2015	134	59.0	[50.1, 66.7]	30.6	[23.0, 38.5]	18.7	[12.6, 25.7]	11.9	[7.1, 18.1]	9.4	[5.2, 15.2]	1.3	[1.0, 1.5]
2016	112	53.6	[43.9, 62.3]	25.8	[18.1, 34.2]	14.7	[8.9, 22.0]	11.7	[6.5, 18.6]	no FU	—	1.1	[0.9, 1.4]
2017	111	54.1	[44.4, 62.8]	30.6	[22.3, 39.3]	19.5	[12.2, 28.1]	no FU	—	no FU	—	1.2	[0.9, 1.5]

Survival results based on small number of persons initially at risk (N<35) can be too variable to be practically meaningful and are therefore not reported.


Table 85 – Mesothelioma (2004-2017), time trend relative survival with incidence year

Unadjusted relative survival, %											
Characteristic	N at risk	1 year		2 year		3 year		4 year		5 year	
		%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI
<i>All</i>											
2004	85	60.1	[48.5, 70.2]	34.6	[24.2, 45.3]	16.5	[9.3, 25.6]	8.5	[3.7, 15.9]	4.2	[1.1, 10.9]
2005	102	59.5	[49.2, 68.6]	35.5	[26.0, 45.2]	18.8	[11.5, 27.5]	7.0	[3.0, 13.4]	5.0	[1.7, 10.9]
2006	114	60.7	[50.9, 69.3]	29.4	[21.1, 38.2]	15.0	[9.1, 22.5]	13.6	[7.8, 21.0]	11.2	[6.0, 18.4]
2007	105	60.2	[50.0, 69.1]	25.5	[17.5, 34.3]	19.8	[12.5, 28.3]	9.4	[4.6, 16.4]	6.0	[2.3, 12.4]
2008	132	56.5	[47.6, 64.5]	30.3	[22.5, 38.6]	15.5	[9.8, 22.5]	9.6	[5.2, 15.8]	7.9	[3.9, 13.8]
2009	125	63.6	[54.2, 71.7]	23.7	[16.7, 31.7]	12.1	[7.0, 18.9]	4.5	[1.6, 9.7]	1.4	[0.2, 5.4]
2010	144	57.9	[49.3, 65.7]	27.3	[20.2, 34.9]	16.6	[10.8, 23.6]	11.4	[6.6, 17.8]	6.9	[3.3, 12.3]
2011	156	64.5	[56.4, 71.7]	37.5	[29.6, 45.5]	22.0	[15.6, 29.3]	14.5	[9.2, 21.0]	7.2	[3.6, 12.5]
2012	143	50.3	[41.9, 58.2]	22.0	[15.4, 29.3]	13.6	[8.2, 20.4]	7.1	[3.4, 12.7]	4.6	[1.8, 9.7]
2013	151	60.2	[51.8, 67.8]	22.4	[16.1, 29.5]	7.6	[4.0, 12.7]	5.7	[2.6, 10.4]	5.8	[2.7, 10.6]
2014	171	58.4	[50.6, 65.6]	33.8	[26.5, 41.3]	18.3	[12.6, 24.8]	11.3	[6.9, 17.0]	9.6	[5.5, 15.1]
2015	180	63.9	[56.2, 70.7]	32.5	[25.5, 39.7]	21.1	[15.2, 27.7]	14.9	[9.9, 21.0]	9.9	[5.5, 16.0]
2016	160	59.8	[51.6, 67.2]	30.9	[23.7, 38.5]	17.0	[11.2, 23.8]	10.9	[5.9, 17.7]	no FU	—
2017	194	59.3	[51.9, 66.1]	36.3	[29.2, 43.5]	23.2	[16.4, 30.7]	no FU	—	no FU	—
<i>Combined Stage I</i>											
2004	12	N<35	—	N<35	—	N<35	—	N<35	—	N<35	—
2005	12	N<35	—	N<35	—	N<35	—	N<35	—	N<35	—
2006	14	N<35	—	N<35	—	N<35	—	N<35	—	N<35	—
2007	9	N<35	—	N<35	—	N<35	—	N<35	—	N<35	—
2008	10	N<35	—	N<35	—	N<35	—	N<35	—	N<35	—
2009	8	N<35	—	N<35	—	N<35	—	N<35	—	N<35	—
2010	14	N<35	—	N<35	—	N<35	—	N<35	—	N<35	—
2011	16	N<35	—	N<35	—	N<35	—	N<35	—	N<35	—



2012	14	N<35	—	N<35	—	N<35	—	N<35	—	N<35	—
2013	20	N<35	—	N<35	—	N<35	—	N<35	—	N<35	—
2014	23	N<35	—	N<35	—	N<35	—	N<35	—	N<35	—
2015	22	N<35	—	N<35	—	N<35	—	N<35	—	N<35	—
2016	29	N<35	—	N<35	—	N<35	—	N<35	—	N<35	—
2017	74	60.8	[48.7, 71.3]	37.7	[26.3, 49.4]	27.6	[16.5, 40.4]	no FU	—	no FU	—
Combined Stage II											
2004	7	N<35	—	N<35	—	N<35	—	N<35	—	N<35	—
2005	14	N<35	—	N<35	—	N<35	—	N<35	—	N<35	—
2006	16	N<35	—	N<35	—	N<35	—	N<35	—	N<35	—
2007	19	N<35	—	N<35	—	N<35	—	N<35	—	N<35	—
2008	18	N<35	—	N<35	—	N<35	—	N<35	—	N<35	—
2009	17	N<35	—	N<35	—	N<35	—	N<35	—	N<35	—
2010	16	N<35	—	N<35	—	N<35	—	N<35	—	N<35	—
2011	20	N<35	—	N<35	—	N<35	—	N<35	—	N<35	—
2012	12	N<35	—	N<35	—	N<35	—	N<35	—	N<35	—
2013	18	N<35	—	N<35	—	N<35	—	N<35	—	N<35	—
2014	21	N<35	—	N<35	—	N<35	—	N<35	—	N<35	—
2015	24	N<35	—	N<35	—	N<35	—	N<35	—	N<35	—
2016	19	N<35	—	N<35	—	N<35	—	N<35	—	N<35	—
2017	9	N<35	—	N<35	—	N<35	—	N<35	—	N<35	—
Combined Stage III/IV/X											
2004	66	57.0	[43.8, 68.4]	37.2	[25.2, 49.4]	18.4	[9.9, 29.2]	10.9	[4.7, 20.4]	5.5	[1.4, 14.0]
2005	76	58.7	[46.7, 69.2]	35.0	[24.1, 46.2]	18.5	[10.4, 28.6]	5.1	[1.6, 12.0]	3.4	[0.7, 10.2]
2006	84	55.7	[44.1, 65.9]	27.7	[18.4, 37.9]	13.6	[7.2, 22.0]	12.7	[6.5, 21.1]	10.6	[5.0, 18.8]
2007	77	54.9	[43.0, 65.4]	19.7	[11.8, 29.2]	15.6	[8.4, 25.0]	6.6	[2.3, 14.2]	3.5	[0.7, 10.2]
2008	104	54.0	[44.0, 63.1]	31.6	[22.7, 41.0]	14.3	[8.3, 22.2]	9.2	[4.5, 16.2]	6.8	[2.8, 13.5]
2009	100	63.2	[52.5, 72.3]	22.8	[15.1, 31.6]	10.7	[5.5, 18.0]	4.8	[1.6, 11.1]	2.1	[0.3, 7.6]



2010	114	52.2	[42.7, 61.0]	22.7	[15.4, 30.9]	13.3	[7.6, 20.6]	10.5	[5.4, 17.6]	6.5	[2.7, 12.8]
2011	120	63.5	[54.1, 71.7]	40.1	[30.9, 49.2]	24.4	[16.7, 33.0]	15.1	[9.0, 22.8]	7.1	[3.2, 13.3]
2012	117	48.0	[38.7, 56.9]	21.1	[14.1, 29.1]	14.1	[8.2, 21.8]	7.5	[3.4, 13.9]	4.5	[1.6, 10.1]
2013	113	56.1	[46.3, 64.9]	17.9	[11.6, 25.5]	5.3	[2.1, 10.8]	3.6	[1.1, 8.6]	3.7	[1.1, 8.9]
2014	127	54.6	[45.4, 63.0]	31.9	[23.8, 40.4]	16.8	[10.7, 24.2]	9.8	[5.2, 16.2]	9.1	[4.7, 15.4]
2015	134	62.0	[53.0, 69.9]	32.8	[24.8, 41.1]	20.6	[13.9, 28.2]	12.9	[7.6, 19.7]	9.2	[4.5, 16.0]
2016	112	57.6	[47.8, 66.4]	29.2	[20.8, 38.1]	17.2	[10.4, 25.5]	12.9	[6.6, 21.5]	no FU	—
2017	111	57.1	[47.1, 66.1]	34.2	[25.1, 43.6]	19.5	[11.5, 29.3]	no FU	—	no FU	—

Survival results based on small number of persons initially at risk (N<35) can be too variable to be practically meaningful and are therefore not reported.



Appendix 6.1.2. Descriptive statistics

Appendix 6.1.2.1. Malignant epithelioid mesothelioma of pleura - Flanders, exploration

Table 86 – Mesothelioma Flanders (2000-2017): Frequency table of patient and tumour characteristics

Characteristic	Total	Incidence period		
		2000-2005	2006-2011	2012-2017
Overall	1,436	210	544	682
Gender				
Male	1,203 (83.8)	183 (87.1)	454 (83.5)	566 (83.0)
Female	233 (16.2)	27 (12.9)	90 (16.5)	116 (17.0)
Age at diagnosis (year)				
<50 years	43 (3.0)	12 (5.7)	18 (3.3)	13 (1.9)
50-59 years	167 (11.6)	25 (11.9)	78 (14.3)	64 (9.4)
60-69 years	408 (28.4)	70 (33.3)	160 (29.4)	178 (26.1)
70-79 years	552 (38.4)	79 (37.6)	220 (40.4)	253 (37.1)
80+ years	266 (18.5)	24 (11.4)	68 (12.5)	174 (25.5)
WHO - Performance Status				
0 – Asymptomatic	112 (7.8)	12 (5.7)	41 (7.5)	59 (8.7)
1 – Symptomatic but completely ambulatory	873 (60.8)	109 (51.9)	303 (55.7)	461 (67.6)
2 – Symptomatic, <50% in bed during the day	133 (9.3)	11 (5.2)	72 (13.2)	50 (7.3)
3 – Symptomatic, >50% in bed, but not bedbound	24 (1.7)	5 (2.4)	7 (1.3)	12 (1.8)
4 – Bedbound	8 (0.6)	2 (1.0)	4 (0.7)	2 (0.3)
Not reported	286 (19.9)	71 (33.8)	117 (21.5)	98 (14.4)
Combined stage				
I	245 (17.1)	49 (23.3)	56 (10.3)	140 (20.5)
II	170 (11.8)	24 (11.4)	82 (15.1)	64 (9.4)
III	258 (18.0)	31 (14.8)	96 (17.6)	131 (19.2)
IV	234 (16.3)	31 (14.8)	78 (14.3)	125 (18.3)
X	529 (36.8)	75 (35.7)	232 (42.6)	222 (32.6)

Note: the values between parentheses are column percentages.


Table 87 – Mesothelioma Flanders (2000-2017), Combined stage I, Frequency table of patient and tumour characteristics

Characteristic	Total	Incidence period		
		2000-2005	2006-2011	2012-2017
Overall	245	49	56	140
Gender				
Male	209 (85.3)	43 (87.8)	49 (87.5)	117 (83.6)
Female	36 (14.7)	6 (12.2)	7 (12.5)	23 (16.4)
Age at diagnosis (year)				
<50 years	5 (2.0)	2 (4.1)	2 (3.6)	1 (0.7)
50-59 years	28 (11.4)	8 (16.3)	8 (14.3)	12 (8.6)
60-69 years	56 (22.9)	12 (24.5)	15 (26.8)	29 (20.7)
70-79 years	105 (42.9)	22 (44.9)	25 (44.6)	58 (41.4)
80+ years	51 (20.8)	5 (10.2)	6 (10.7)	40 (28.6)
WHO - Performance Status				
0 – Asymptomatic	26 (10.6)	1 (2.0)	5 (8.9)	20 (14.3)
1 – Symptomatic but completely ambulatory	155 (63.3)	30 (61.2)	32 (57.1)	93 (66.4)
2 – Symptomatic, <50% in bed during the day	20 (8.2)	1 (2.0)	9 (16.1)	10 (7.1)
3 – Symptomatic, >50% in bed, but not bedbound	5 (2.0)	2 (4.1)	0 (0.0)	3 (2.1)
Not reported	39 (15.9)	15 (30.6)	10 (17.9)	14 (10.0)

Note: the values between parentheses are column percentages.



Table 88 – Mesothelioma Flanders (2000-2017), Combined stage II, Frequency table of patient and tumour characteristics

Characteristic	Total	Incidence period		
		2000-2005	2006-2011	2012-2017
Overall	170	24	82	64
Gender				
Male	152 (89.4)	23 (95.8)	72 (87.8)	57 (89.1)
Female	18 (10.6)	1 (4.2)	10 (12.2)	7 (10.9)
Age at diagnosis (year)				
<50 years	8 (4.7)	3 (12.5)	4 (4.9)	1 (1.6)
50-59 years	28 (16.5)	6 (25.0)	12 (14.6)	10 (15.6)
60-69 years	53 (31.2)	8 (33.3)	27 (32.9)	18 (28.1)
70-79 years	59 (34.7)	4 (16.7)	34 (41.5)	21 (32.8)
80+ years	22 (12.9)	3 (12.5)	5 (6.1)	14 (21.9)
WHO - Performance Status				
0 – Asymptomatic	17 (10.0)	4 (16.7)	8 (9.8)	5 (7.8)
1 – Symptomatic but completely ambulatory	114 (67.1)	14 (58.3)	51 (62.2)	49 (76.6)
2 – Symptomatic, <50% in bed during the day	18 (10.6)	1 (4.2)	12 (14.6)	5 (7.8)
3 – Symptomatic, >50% in bed, but not bedbound	1 (0.6)	0 (0.0)	0 (0.0)	1 (1.6)
Not reported	20 (11.8)	5 (20.8)	11 (13.4)	4 (6.3)

Note: the values between parentheses are column percentages.


Table 89 – Mesothelioma Flanders (2000-2017), Combined stage III/IV/X, Frequency table of patient and tumour characteristics

Characteristic	Total	Incidence period		
		2000-2005	2006-2011	2012-2017
Overall	1,021	137	406	478
Gender				
Male	842 (82.5)	117 (85.4)	333 (82.0)	392 (82.0)
Female	179 (17.5)	20 (14.6)	73 (18.0)	86 (18.0)
Age at diagnosis (year)				
<50 years	30 (2.9)	7 (5.1)	12 (3.0)	11 (2.3)
50-59 years	111 (10.9)	11 (8.0)	58 (14.3)	42 (8.8)
60-69 years	299 (29.3)	50 (36.5)	118 (29.1)	131 (27.4)
70-79 years	388 (38.0)	53 (38.7)	161 (39.7)	174 (36.4)
80+ years	193 (18.9)	16 (11.7)	57 (14.0)	120 (25.1)
WHO - Performance Status				
0 – Asymptomatic	69 (6.8)	7 (5.1)	28 (6.9)	34 (7.1)
1 – Symptomatic but completely ambulatory	604 (59.2)	65 (47.4)	220 (54.2)	319 (66.7)
2 – Symptomatic, <50% in bed during the day	95 (9.3)	9 (6.6)	51 (12.6)	35 (7.3)
3 – Symptomatic, >50% in bed, but not bedbound	18 (1.8)	3 (2.2)	7 (1.7)	8 (1.7)
4 – Bedbound	8 (0.8)	2 (1.5)	4 (1.0)	2 (0.4)
Not reported	227 (22.2)	51 (37.2)	96 (23.6)	80 (16.7)

Note: the values between parentheses are column percentages.



Appendix 6.1.2.2. Mesothelioma Flanders (2000-2017), Observed and Relative Survival graphs

Malignant epithelioid mesothelioma of pleura - Flanders (2000-2017)

Figure 165 – Mesothelioma Flanders (2000-2017), Kaplan-Meier graphs observed survival by incidence period

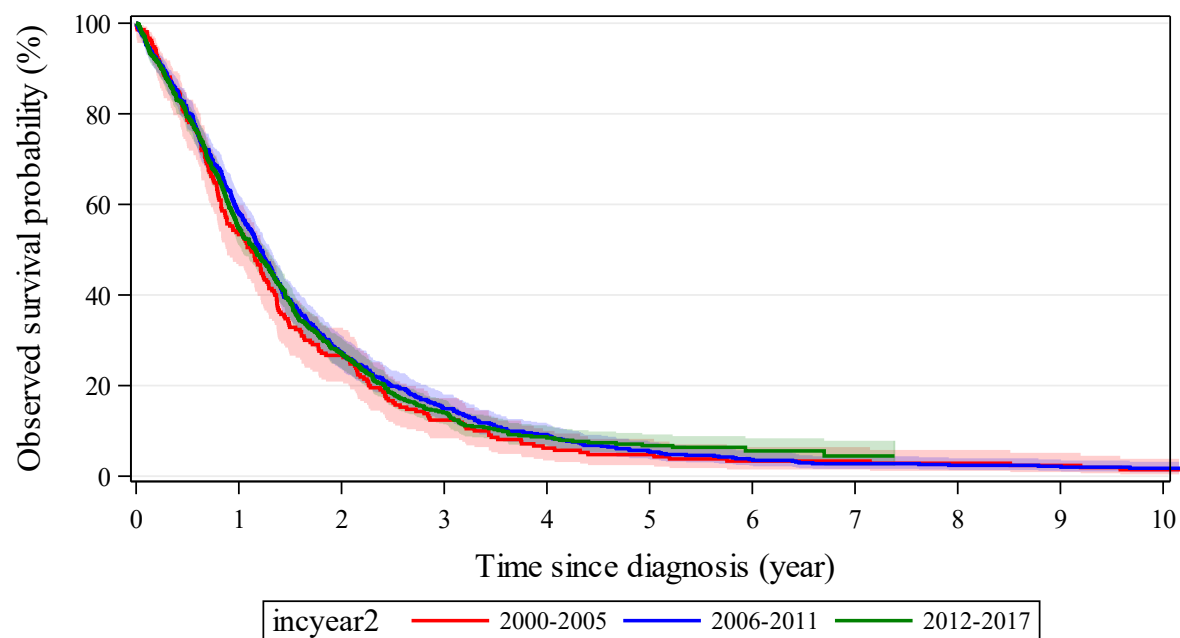
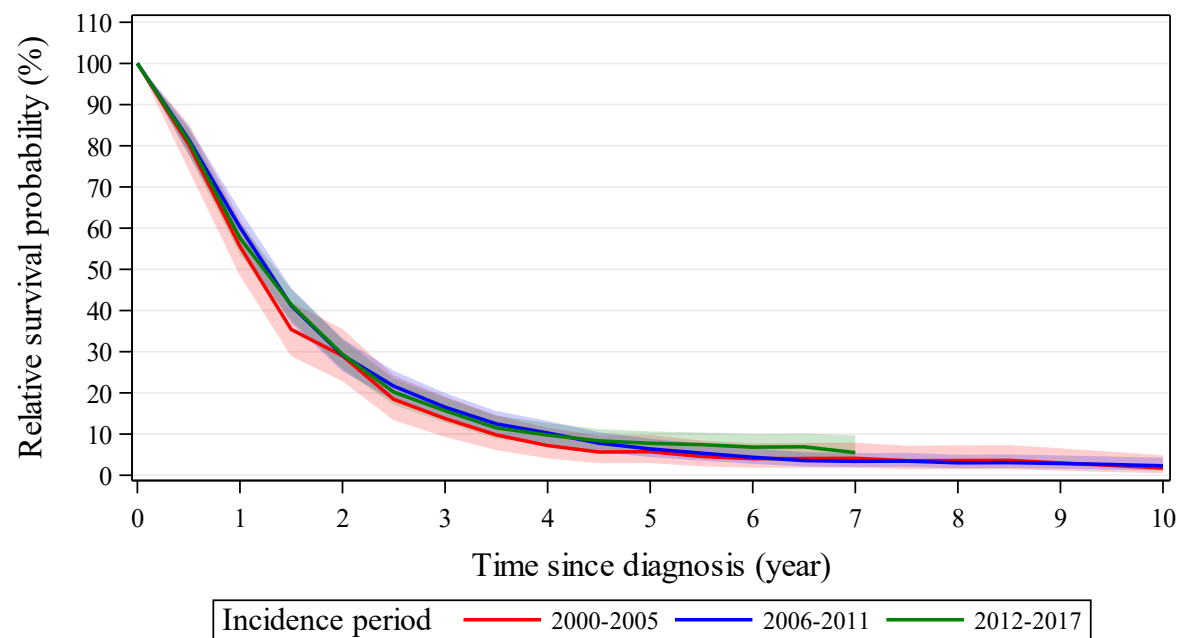


**Figure 166 – Mesothelioma Flanders (2000-2017), relative survival graphs by incidence period**

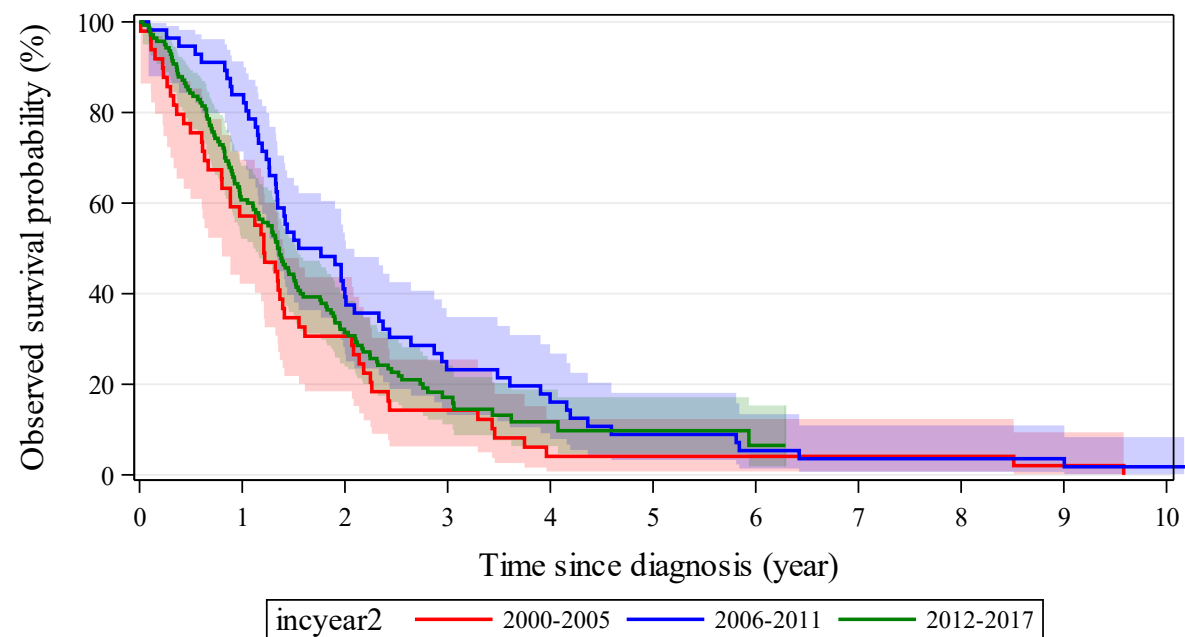
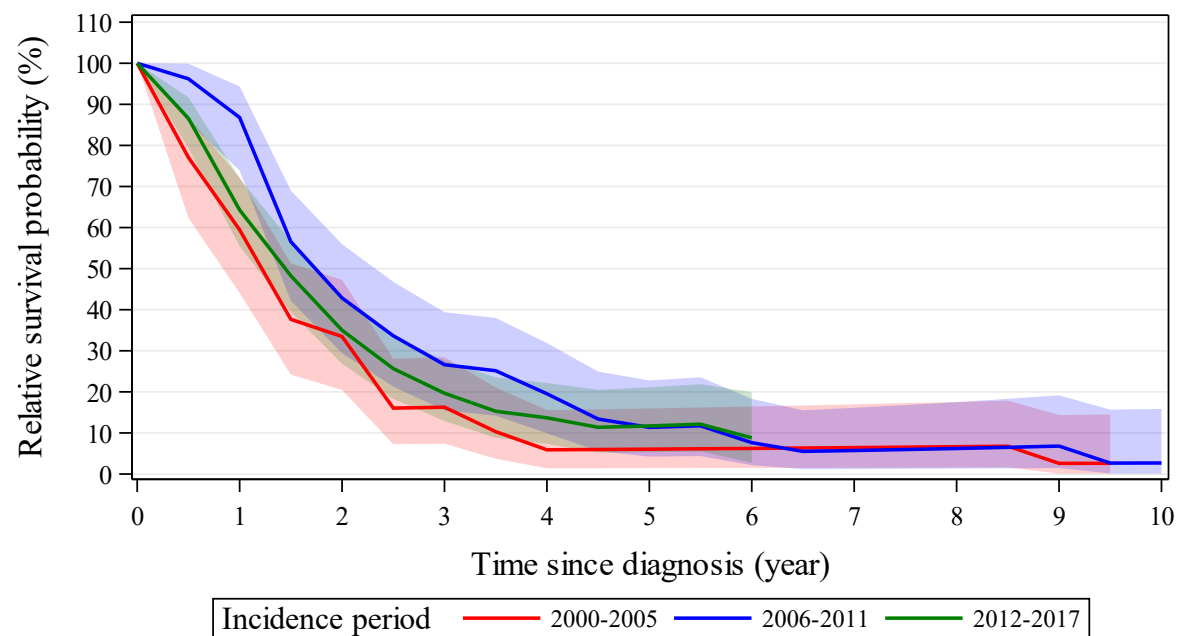
**Malignant epithelioid mesothelioma of pleura - Flanders, combined stage I (2000-2017)****Figure 167 – Mesothelioma Flanders (2000-2017), combined stage I, Kaplan-Meier graphs observed survival by incidence period**



Figure 168 – Mesothelioma Flanders (2000-2017), combined stage I, relative survival graphs by incidence period



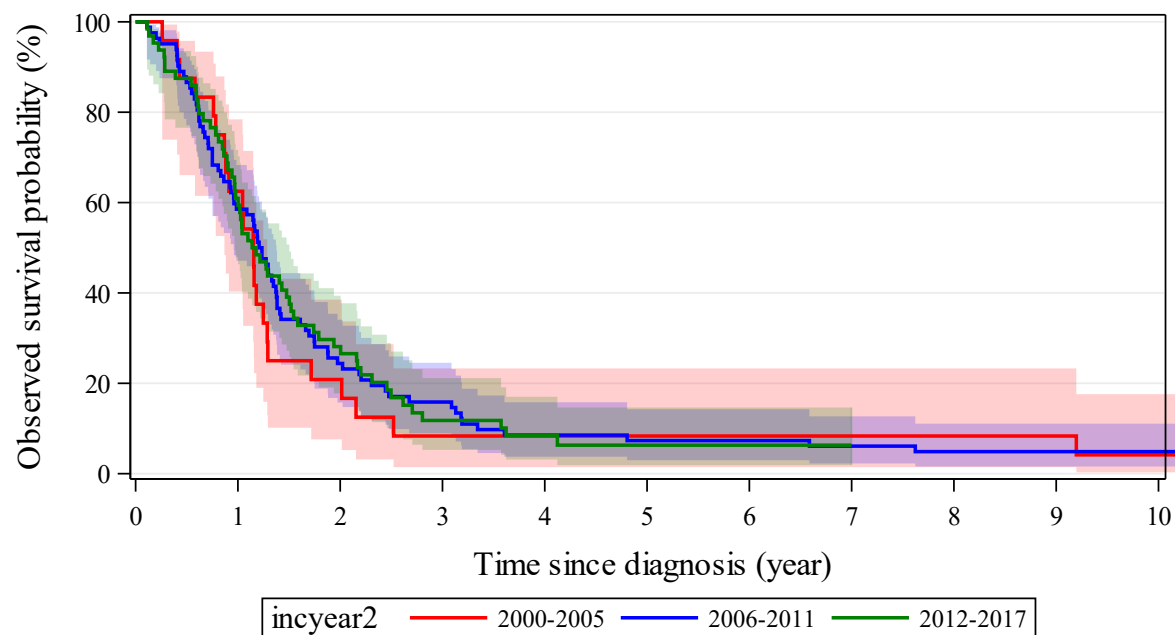
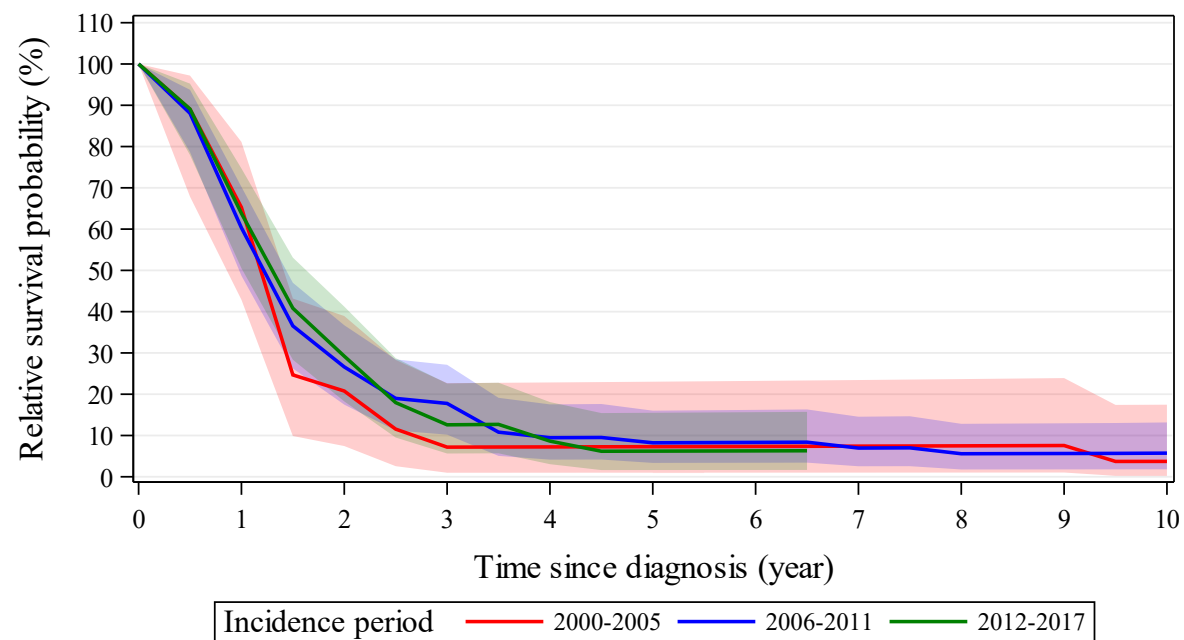
**Malignant epithelioid mesothelioma of pleura - Flanders, combined stage II (2000-2017)****Figure 169 – Mesothelioma Flanders (2000-2017), combined stage II, Kaplan-Meier graphs observed survival by incidence period**



Figure 170 – Mesothelioma Flanders (2000-2017), combined stage II, relative survival graphs by incidence period



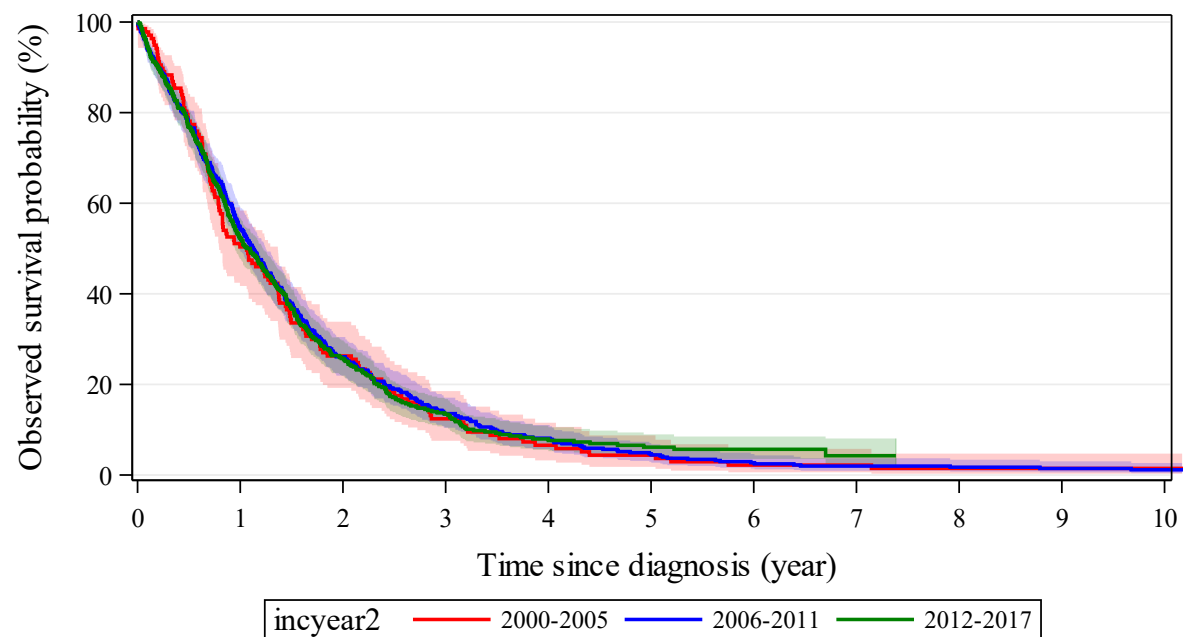
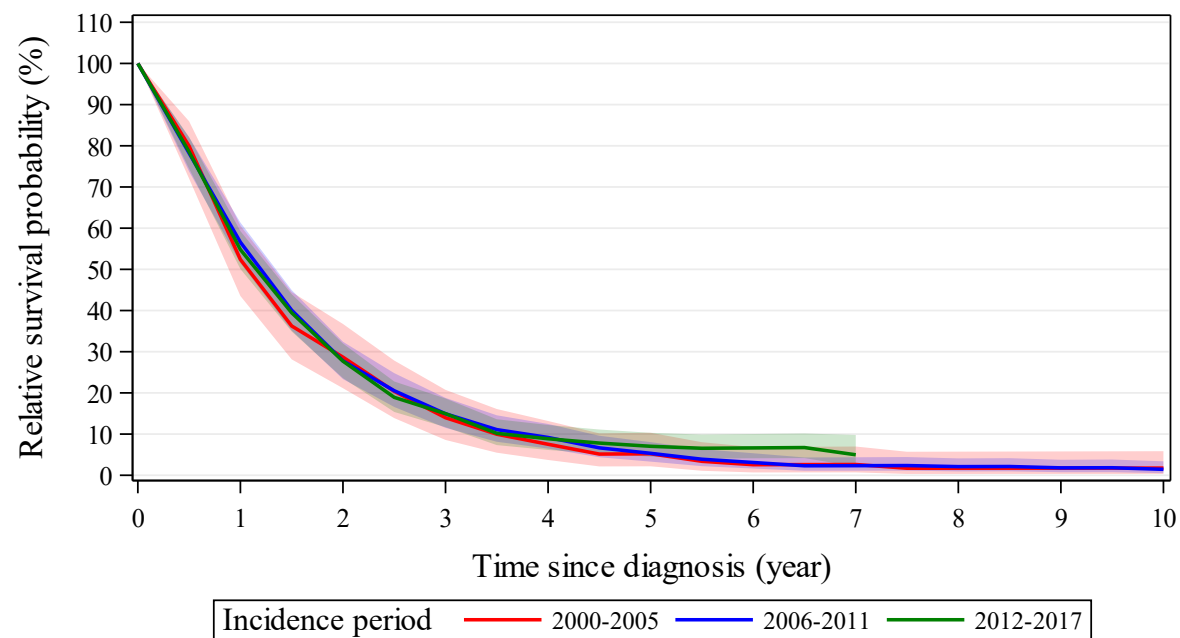
**Malignant epithelioid mesothelioma of pleura - Flanders, combined stage III/IV/X (2000-2017)****Figure 171 – Mesothelioma Flanders (2000-2017), combined stage III/IV/X, Kaplan-Meier graphs observed survival by incidence period**



Figure 172 – Mesothelioma Flanders (2000-2017), combined stage III/IV/X, relative survival graphs by incidence period

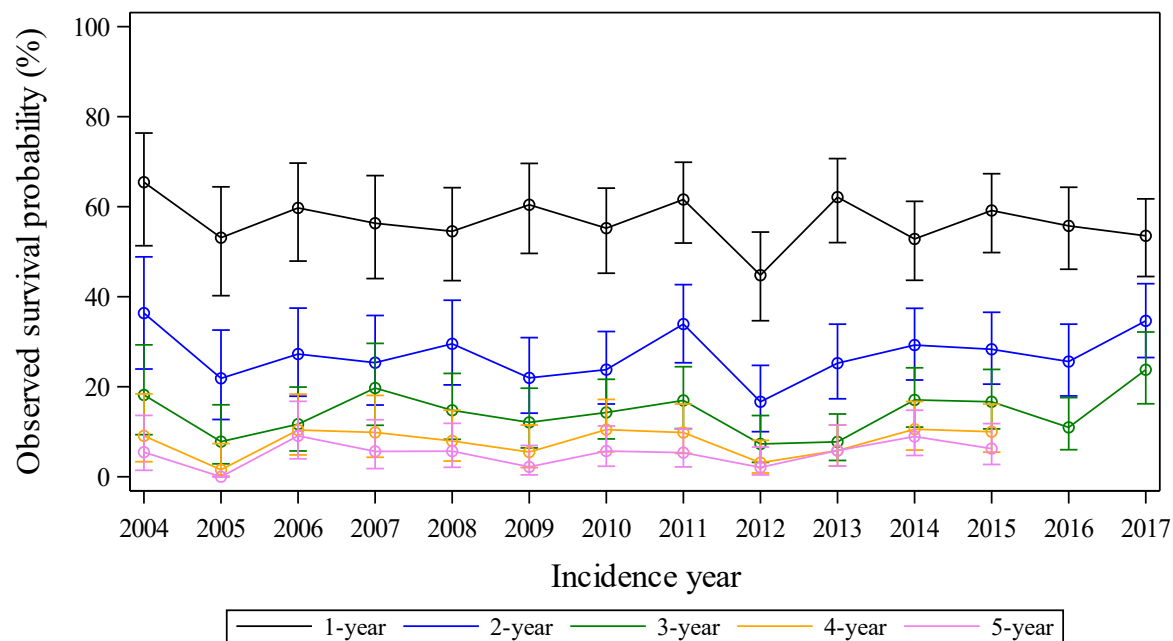




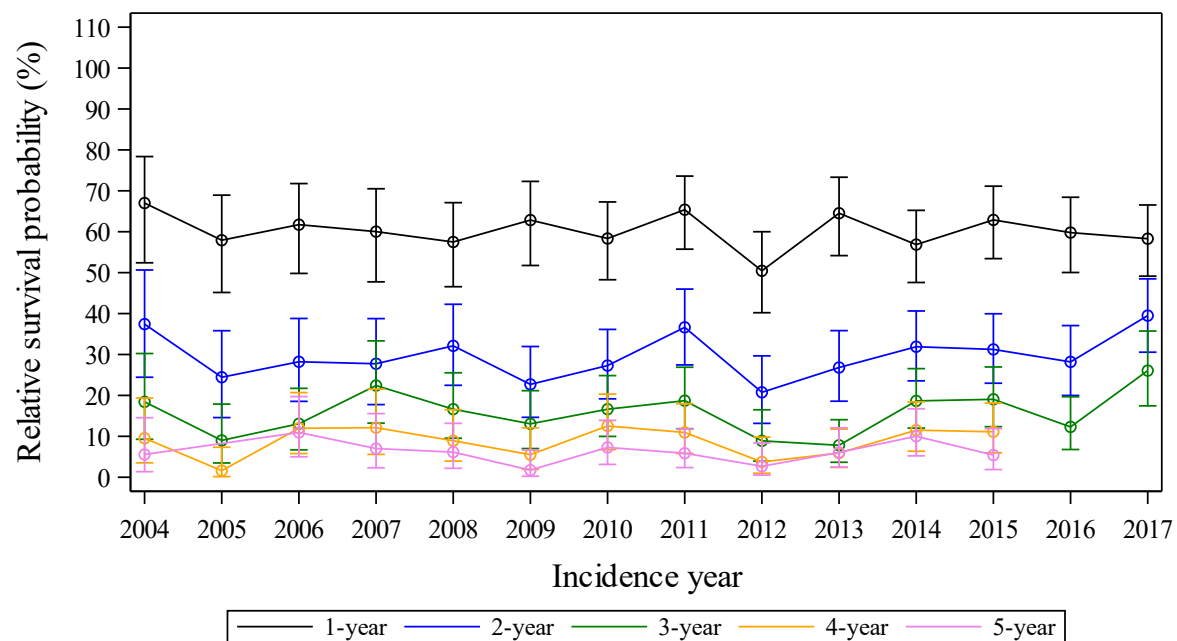
Appendix 6.1.2.3. Malignant epithelioid mesothelioma of pleura - Flanders, time trend Observed and Relative Survival

Malignant epithelioid mesothelioma of pleura - Flanders (2000-2017)

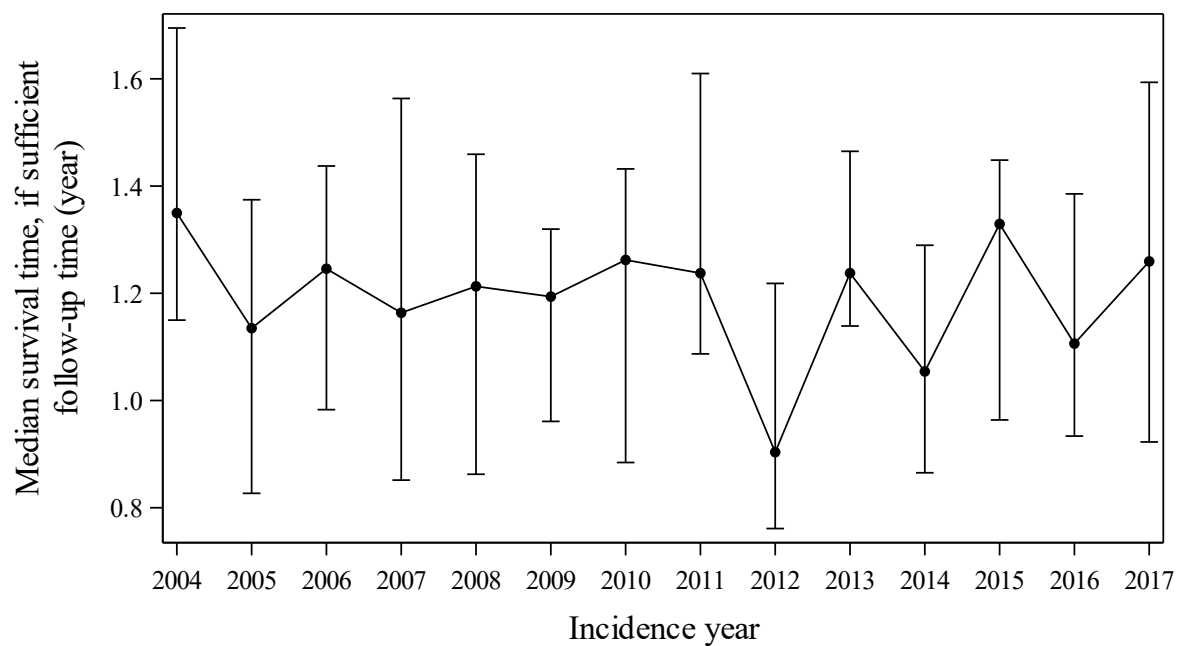
Figure 173 – Mesothelioma Flanders (2000-2017), time trend observed survival with incidence year



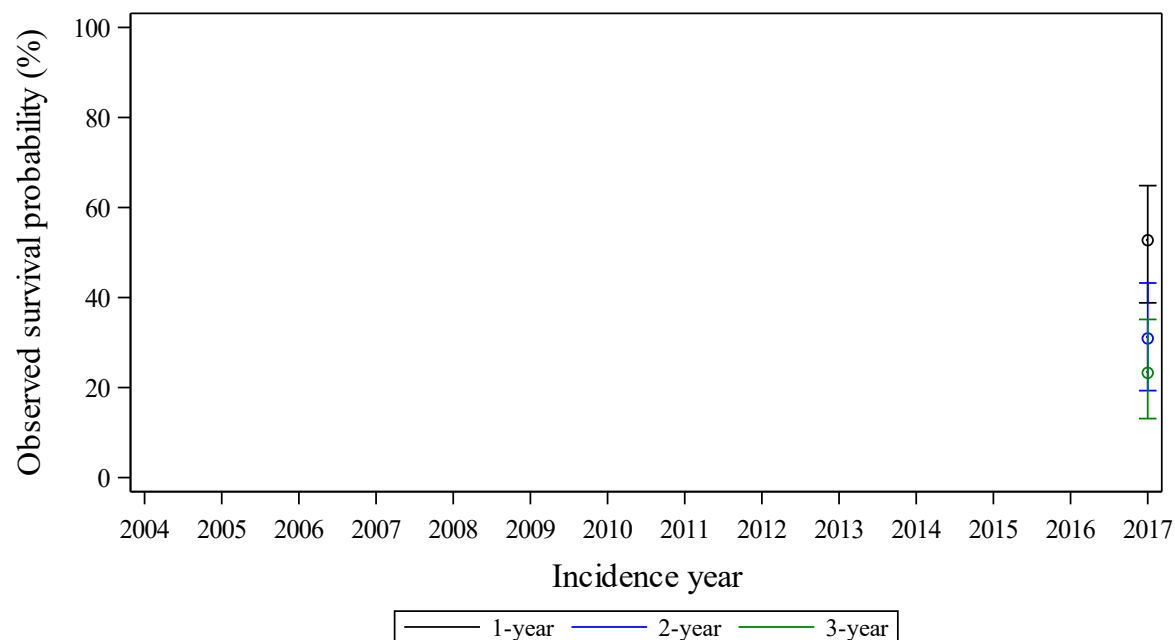
Note: the error bars represent the 95% CI.

**Figure 174 – Mesothelioma Flanders (2000-2017), time trend relative survival with incidence year**

Note: the error bars represent the 95% CI.

**Figure 175 – Mesothelioma Flanders (2000-2017), Median time observed survival**

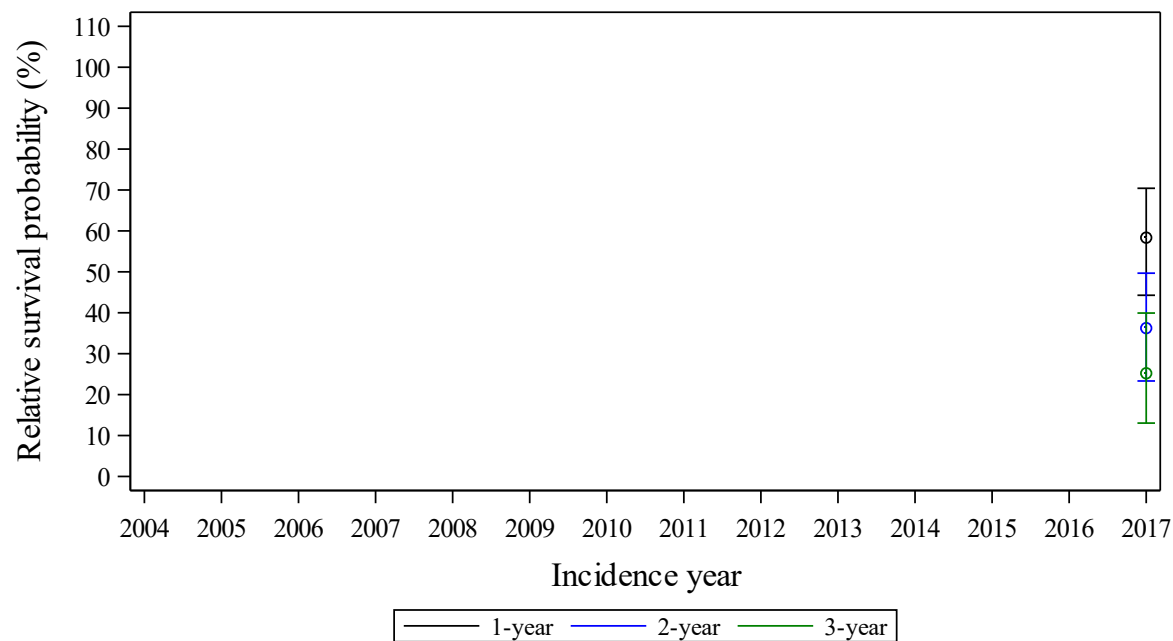
Note: the error bars represent the 95% CI. When the upper error is not plotted, the upper limit could not be determined with the follow-up available.

**Malignant epithelioid mesothelioma of pleura - Flanders, combined stage I (2000-2017)****Figure 176 – Mesothelioma Flanders (2000-2017), combined stage I, time trend observed survival with incidence year**

Survival results based on small number of persons initially at risk ($N < 35$) can be too variable to be practically meaningful and are therefore not reported. The error bars represent the 95% CI.

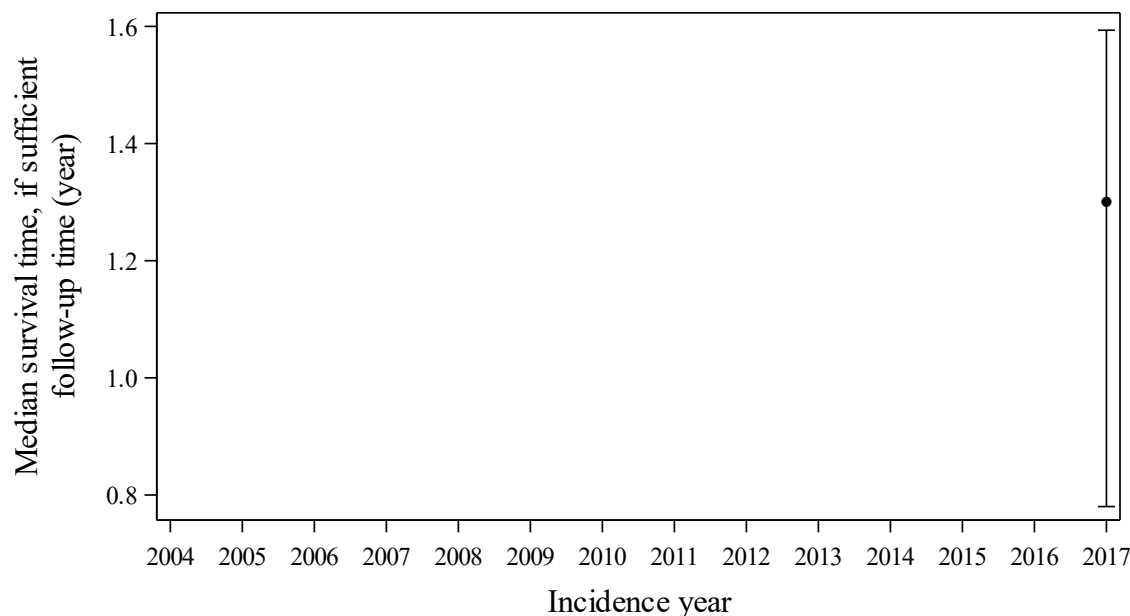


Figure 177 – Mesothelioma Flanders (2000-2017), combined stage I, time trend relative survival with incidence year



Survival results based on small number of persons initially at risk (N<35) can be too variable to be practically meaningful and are therefore not reported. The error bars represent the 95% CI.

Figure 178 – Mesothelioma Flanders (2000-2017), combined stage I, median time observed survival



Survival results based on small number of persons initially at risk ($N < 35$) can be too variable to be practically meaningful and are therefore not reported. The error bars represent the 95% CI. When the upper error is not plotted, the upper limit could not be determined with the follow-up available.

Malignant epithelioid mesothelioma of pleura - Flanders, combined stage II (2000-2017)

Figure 179 – Mesothelioma Flanders (2000-2017), combined stage II, time trend observed survival with incidence year

No data points to plot.

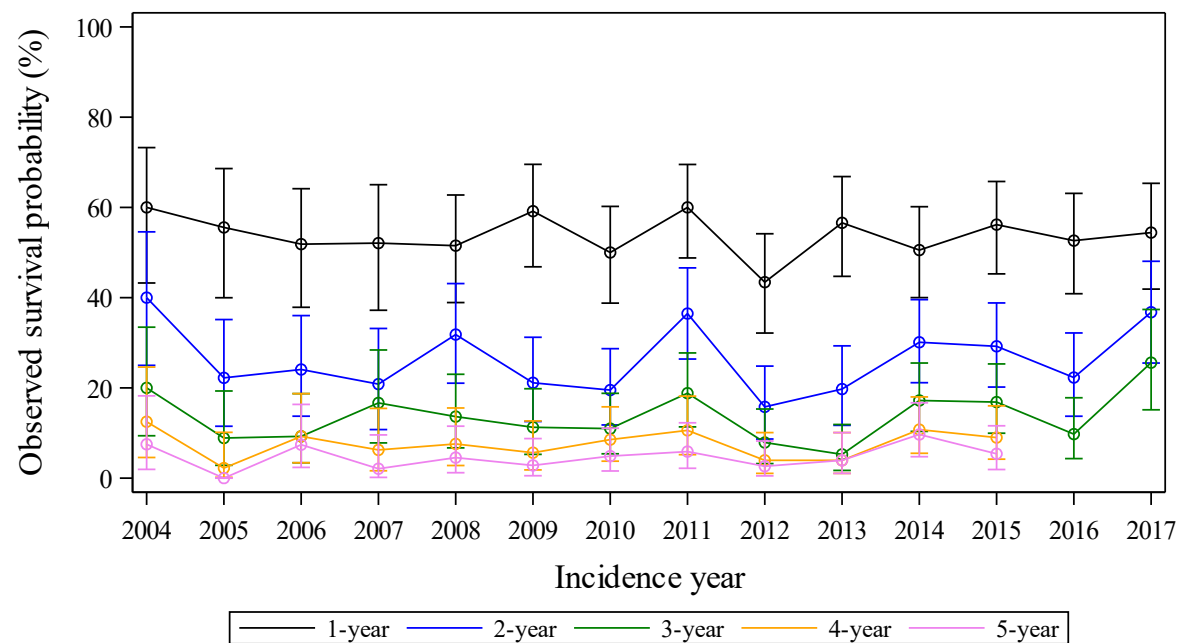
Figure 180 – Mesothelioma Flanders (2000-2017), combined stage II, time trend relative survival with incidence year

No data points to plot.

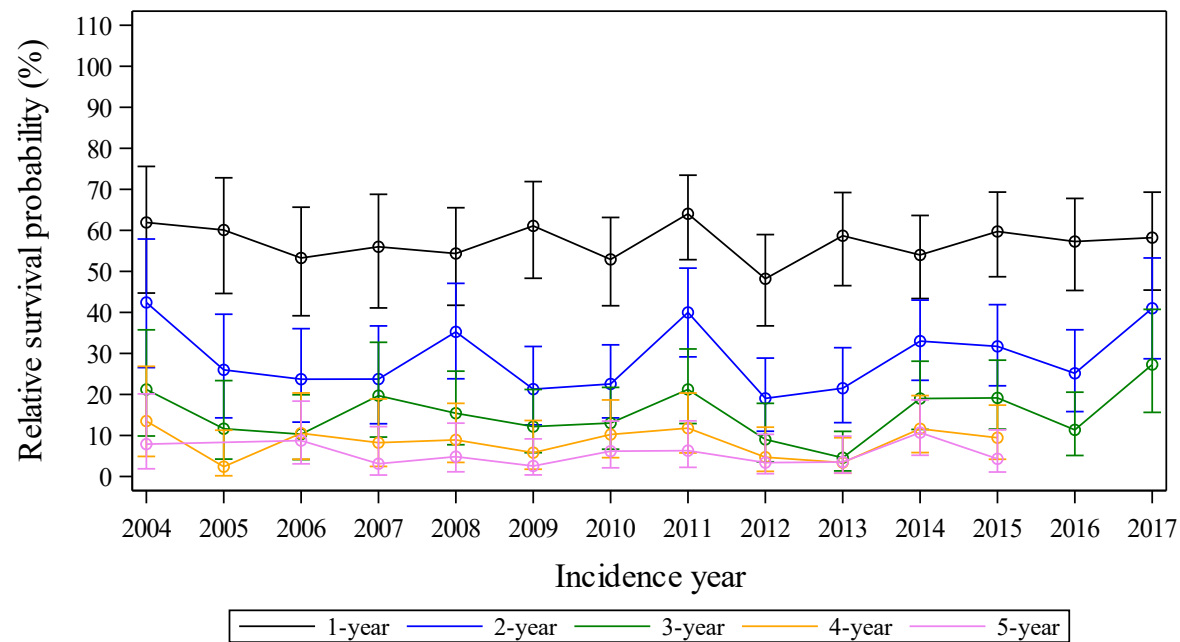
Figure 181 – Mesothelioma Flanders (2000-2017), combined stage II, median time observed survival

No data points to plot.

Survival results based on small number of persons initially at risk ($N < 35$) can be too variable to be practically meaningful and are therefore not reported.

**Malignant epithelioid mesothelioma of pleura - Flanders, combined stage III/IV/X (2000-2017)****Figure 182 – Mesothelioma Flanders (2000-2017), combined stage III/IV/X, time trend observed survival with incidence year**

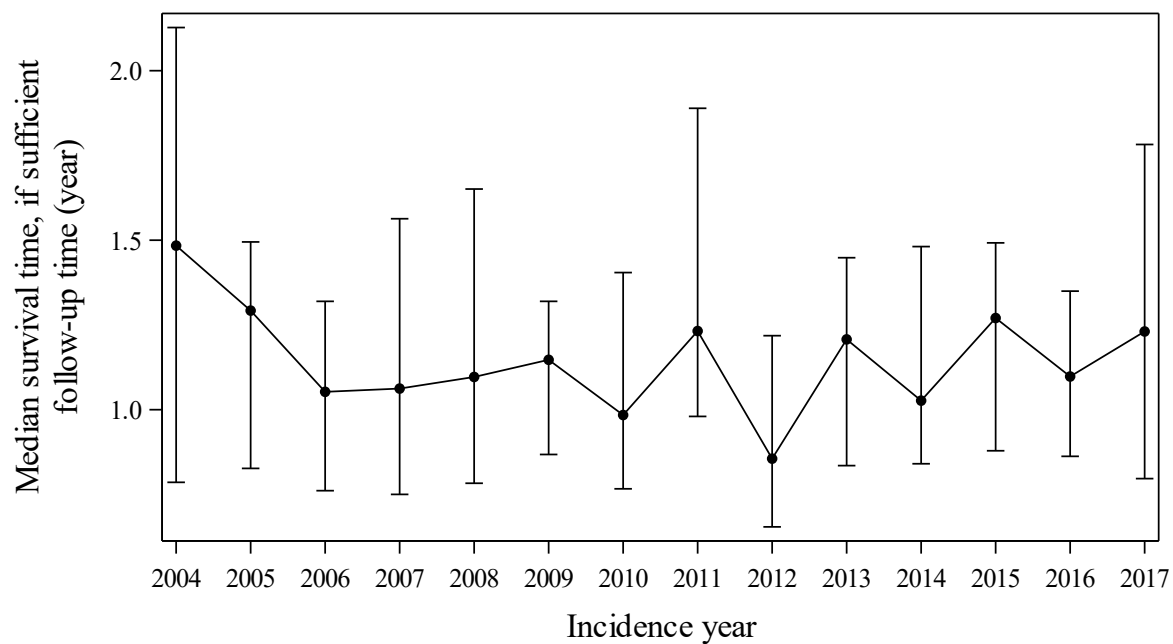
Note: the error bars represent the 95% CI.

**Figure 183 – Mesothelioma Flanders (2000-2017), combined stage III/IV/X, time trend relative survival with incidence year**

Note: the error bars represent the 95% CI.



Figure 184 – Mesothelioma Flanders (2000-2017), combined stage III/IV/X, median time observed survival



Note: the error bars represent the 95% CI. When the upper error is not plotted, the upper limit could not be determined with the follow-up available.



2015	11	N<35	—	N<35	—	N<35	—	N<35	—	N<35	—	N<35	—
2016	14	N<35	—	N<35	—	N<35	—	N<35	—	N<35	—	N<35	—
2017	4	N<35	—	N<35	—	N<35	—	N<35	—	N<35	—	N<35	—
Combined Stage III/IV/X													
2000	11	N<35	—	N<35	—	N<35	—	N<35	—	N<35	—	N<35	—
2001	12	N<35	—	N<35	—	N<35	—	N<35	—	N<35	—	N<35	—
2002	12	N<35	—	N<35	—	N<35	—	N<35	—	N<35	—	N<35	—
2003	17	N<35	—	N<35	—	N<35	—	N<35	—	N<35	—	N<35	—
2004	40	60.0	[43.2, 73.3]	40.0	[25.0, 54.6]	20.0	[9.4, 33.5]	12.5	[4.6, 24.6]	7.5	[1.9, 18.2]	1.5	[0.8, 2.1]
2005	45	55.6	[40.0, 68.6]	22.2	[11.5, 35.1]	8.9	[2.8, 19.3]	2.2	[0.2, 10.1]	0		1.3	[0.8, 1.5]
2006	54	51.9	[37.9, 64.1]	24.1	[13.7, 36.0]	9.3	[3.4, 18.7]	9.3	[3.4, 18.7]	7.4	[2.4, 16.3]	1.1	[0.8, 1.3]
2007	48	52.1	[37.2, 65.0]	20.8	[10.8, 33.2]	16.7	[7.8, 28.4]	6.3	[1.6, 15.5]	2.1	[0.2, 9.6]	1.1	[0.8, 1.6]
2008	66	51.5	[38.9, 62.7]	31.8	[21.0, 43.1]	13.6	[6.7, 23.0]	7.6	[2.8, 15.5]	4.5	[1.2, 11.5]	1.1	[0.8, 1.7]
2009	71	59.2	[46.8, 69.5]	21.1	[12.5, 31.2]	11.3	[5.3, 19.8]	5.6	[1.8, 12.7]	2.8	[0.5, 8.8]	1.1	[0.9, 1.3]
2010	82	50.0	[38.8, 60.2]	19.5	[11.8, 28.7]	11.0	[5.4, 18.8]	8.5	[3.8, 15.8]	4.9	[1.6, 11.1]	1.0	[0.8, 1.4]
2011	85	60.0	[48.8, 69.5]	36.5	[26.4, 46.6]	18.8	[11.4, 27.7]	10.6	[5.2, 18.2]	5.9	[2.2, 12.3]	1.2	[1.0, 1.9]
2012	76	43.4	[32.2, 54.2]	15.8	[8.7, 24.8]	7.9	[3.2, 15.3]	3.9	[1.1, 10.1]	2.6	[0.5, 8.2]	0.9	[0.7, 1.2]
2013	76	56.6	[44.7, 66.8]	19.7	[11.7, 29.3]	5.3	[1.7, 11.9]	3.9	[1.1, 10.1]	3.9	[1.1, 10.1]	1.2	[0.8, 1.4]
2014	93	50.5	[40.0, 60.2]	30.1	[21.1, 39.6]	17.2	[10.4, 25.5]	10.8	[5.5, 18.0]	9.7	[4.8, 16.7]	1.0	[0.8, 1.5]
2015	89	56.2	[45.3, 65.7]	29.2	[20.2, 38.8]	16.9	[10.0, 25.3]	9.0	[4.2, 16.0]	5.4	[1.9, 11.6]	1.3	[0.9, 1.5]
2016	76	52.6	[40.9, 63.1]	22.3	[13.7, 32.2]	9.8	[4.3, 17.8]	no FU	—	no FU	—	1.1	[0.9, 1.3]
2017	68	54.4	[41.9, 65.3]	36.8	[25.5, 48.1]	25.6	[15.1, 37.4]	no FU	—	no FU	—	1.2	[0.8, 1.8]

Survival results based on small number of persons initially at risk (N<35) can be too variable to be practically meaningful and are therefore not reported.



Table 91 – Mesothelioma Flanders (2000-2017), time trend relative survival with incidence year

Unadjusted relative survival, %											
Characteristic	N at risk	1 year		2 year		3 year		4 year		5 year	
		%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI
All											
2000	18	N<35	—	N<35	—	N<35	—	N<35	—	N<35	—
2001	16	N<35	—	N<35	—	N<35	—	N<35	—	N<35	—
2002	23	N<35	—	N<35	—	N<35	—	N<35	—	N<35	—
2003	34	N<35	—	N<35	—	N<35	—	N<35	—	N<35	—
2004	55	67.0	[52.4, 78.4]	37.4	[24.4, 50.7]	18.4	[9.3, 30.2]	9.5	[3.5, 19.4]	5.6	[1.4, 14.6]
2005	64	57.9	[45.2, 68.9]	24.4	[14.6, 35.8]	9.0	[3.5, 17.9]	1.6	[0.2, 7.3]	no FU	—
2006	77	61.7	[49.8, 71.8]	28.2	[18.5, 38.8]	13.1	[6.7, 21.7]	12.0	[5.8, 20.7]	10.9	[5.0, 19.7]
2007	71	60.0	[47.8, 70.5]	27.7	[17.8, 38.8]	22.4	[13.2, 33.3]	12.1	[5.6, 21.5]	7.0	[2.3, 15.6]
2008	88	57.5	[46.6, 67.1]	32.1	[22.5, 42.3]	16.6	[9.5, 25.5]	8.9	[4.0, 16.5]	6.1	[2.2, 13.2]
2009	91	62.9	[51.8, 72.3]	22.7	[14.6, 32.0]	13.1	[7.0, 21.2]	5.5	[1.9, 12.1]	1.7	[0.2, 6.7]
2010	105	58.4	[48.3, 67.3]	27.3	[19.2, 36.1]	16.6	[10.0, 24.8]	12.5	[6.8, 20.3]	7.3	[3.1, 13.9]
2011	112	65.4	[55.7, 73.6]	36.6	[27.5, 46.0]	18.7	[11.9, 26.9]	10.9	[5.8, 18.0]	5.9	[2.4, 11.8]
2012	96	50.5	[40.2, 60.0]	20.8	[13.2, 29.7]	8.9	[3.9, 16.5]	3.7	[1.0, 9.8]	2.7	[0.5, 8.4]
2013	103	64.5	[54.2, 73.3]	26.8	[18.6, 35.8]	7.8	[3.7, 14.1]	5.9	[2.4, 11.8]	6.1	[2.5, 12.1]
2014	123	56.9	[47.6, 65.2]	31.9	[23.6, 40.6]	18.7	[12.0, 26.5]	11.5	[6.4, 18.4]	10.0	[5.2, 16.7]
2015	120	62.9	[53.4, 71.1]	31.2	[23.0, 40.0]	19.0	[12.4, 27.0]	11.1	[6.0, 18.1]	5.4	[1.9, 11.9]
2016	113	59.8	[50.0, 68.4]	28.2	[20.0, 37.1]	12.3	[6.8, 19.7]	no FU	—	no FU	—
2017	127	58.3	[49.2, 66.5]	39.5	[30.6, 48.5]	26.1	[17.4, 35.7]	no FU	—	no FU	—
Combined Stage I											
2000	6	N<35	—	N<35	—	N<35	—	N<35	—	N<35	—
2001	3	N<35	—	N<35	—	N<35	—	N<35	—	N<35	—
2002	11	N<35	—	N<35	—	N<35	—	N<35	—	N<35	—
2003	10	N<35	—	N<35	—	N<35	—	N<35	—	N<35	—



2004	12	N<35	–	N<35	–	N<35	–	N<35	–	N<35	–
2005	7	N<35	–	N<35	–	N<35	–	N<35	–	N<35	–
2006	10	N<35	–	N<35	–	N<35	–	N<35	–	N<35	–
2007	9	N<35	–	N<35	–	N<35	–	N<35	–	N<35	–
2008	7	N<35	–	N<35	–	N<35	–	N<35	–	N<35	–
2009	8	N<35	–	N<35	–	N<35	–	N<35	–	N<35	–
2010	11	N<35	–	N<35	–	N<35	–	N<35	–	N<35	–
2011	11	N<35	–	N<35	–	N<35	–	N<35	–	N<35	–
2012	12	N<35	–	N<35	–	N<35	–	N<35	–	N<35	–
2013	14	N<35	–	N<35	–	N<35	–	N<35	–	N<35	–
2014	16	N<35	–	N<35	–	N<35	–	N<35	–	N<35	–
2015	20	N<35	–	N<35	–	N<35	–	N<35	–	N<35	–
2016	23	N<35	–	N<35	–	N<35	–	N<35	–	N<35	–
2017	55	58.4	[44.3, 70.4]	36.2	[23.3, 49.7]	25.2	[13.0, 39.9]	no FU	–	no FU	–
Combined Stage II											
2000	1	N<35	–	N<35	–	N<35	–	N<35	–	N<35	–
2001	1	N<35	–	N<35	–	N<35	–	N<35	–	N<35	–
2003	7	N<35	–	N<35	–	N<35	–	N<35	–	N<35	–
2004	3	N<35	–	N<35	–	N<35	–	N<35	–	N<35	–
2005	12	N<35	–	N<35	–	N<35	–	N<35	–	N<35	–
2006	13	N<35	–	N<35	–	N<35	–	N<35	–	N<35	–
2007	14	N<35	–	N<35	–	N<35	–	N<35	–	N<35	–
2008	15	N<35	–	N<35	–	N<35	–	N<35	–	N<35	–
2009	12	N<35	–	N<35	–	N<35	–	N<35	–	N<35	–
2010	12	N<35	–	N<35	–	N<35	–	N<35	–	N<35	–
2011	16	N<35	–	N<35	–	N<35	–	N<35	–	N<35	–
2012	8	N<35	–	N<35	–	N<35	–	N<35	–	N<35	–
2013	13	N<35	–	N<35	–	N<35	–	N<35	–	N<35	–



2014	14	N<35	—	N<35	—	N<35	—	N<35	—	N<35	—
2015	11	N<35	—	N<35	—	N<35	—	N<35	—	N<35	—
2016	14	N<35	—	N<35	—	N<35	—	N<35	—	N<35	—
2017	4	N<35	—	N<35	—	N<35	—	N<35	—	N<35	—
Combined Stage III/IV/X											
2000	11	N<35	—	N<35	—	N<35	—	N<35	—	N<35	—
2001	12	N<35	—	N<35	—	N<35	—	N<35	—	N<35	—
2002	12	N<35	—	N<35	—	N<35	—	N<35	—	N<35	—
2003	17	N<35	—	N<35	—	N<35	—	N<35	—	N<35	—
2004	40	61.9	[44.7, 75.6]	42.4	[26.5, 57.9]	21.2	[9.9, 35.8]	13.5	[4.9, 26.9]	7.9	[1.9, 20.1]
2005	45	60.1	[44.6, 72.8]	26.0	[14.3, 39.6]	11.6	[4.2, 23.4]	2.4	[0.2, 11.3]	no FU	—
2006	54	53.3	[39.2, 65.6]	23.7	[13.3, 36.0]	10.3	[4.1, 19.9]	10.5	[4.2, 20.4]	8.8	[3.1, 18.4]
2007	48	56.0	[41.1, 68.8]	23.7	[12.9, 36.7]	19.7	[9.6, 32.7]	8.2	[2.4, 18.9]	3.1	[0.3, 12.2]
2008	66	54.4	[41.7, 65.5]	35.3	[23.8, 47.1]	15.4	[7.7, 25.7]	8.9	[3.4, 17.8]	4.8	[1.1, 13.0]
2009	71	61.1	[48.3, 71.9]	21.3	[12.6, 31.7]	12.2	[5.8, 21.2]	5.8	[1.8, 13.6]	2.6	[0.4, 9.2]
2010	82	52.9	[41.6, 63.1]	22.6	[14.3, 32.1]	13.0	[6.6, 21.7]	10.2	[4.6, 18.7]	6.2	[2.1, 13.5]
2011	85	64.0	[52.9, 73.4]	40.0	[29.2, 50.8]	21.2	[12.9, 31.1]	11.8	[5.7, 20.3]	6.3	[2.2, 13.6]
2012	76	48.2	[36.7, 59.0]	19.0	[11.0, 28.9]	9.0	[3.6, 17.8]	4.7	[1.2, 12.0]	3.4	[0.7, 10.3]
2013	76	58.7	[46.5, 69.2]	21.5	[13.1, 31.4]	4.6	[1.4, 11.0]	3.4	[0.8, 9.4]	3.5	[0.8, 9.8]
2014	93	54.0	[43.4, 63.6]	33.0	[23.4, 43.0]	19.0	[11.5, 28.1]	11.6	[5.8, 19.7]	10.7	[5.2, 18.7]
2015	89	59.7	[48.7, 69.3]	31.7	[22.1, 41.9]	19.2	[11.5, 28.4]	9.4	[4.2, 17.4]	4.3	[1.1, 11.4]
2016	76	57.3	[45.3, 67.8]	25.1	[15.8, 35.8]	11.4	[5.1, 20.5]	no FU	—	no FU	—
2017	68	58.2	[45.4, 69.3]	41.0	[28.7, 53.3]	27.3	[15.6, 40.7]	no FU	—	no FU	—

Survival results based on small number of persons initially at risk (N<35) can be too variable to be practically meaningful and are therefore not reported.



Appendix 6.1.3. Uptake of selected drugs

Table 92 – Mesothelioma stage III-IV-X: proportion of patients who received at least one dose during 5-year period after diagnosis

Drug/incidence year (n)	2004 (66)	2005 (76)	2006 (84)	2007 (77)	2008 (104)	2009 (101)	2010 (114)	2011 (120)	2012 (117)	2013 (114)	2014 (127)	2015 (135)	2016 (113)	2017 (112)
Pemetrexed	9.1%	17.1%	56.0%	59.7%	71.2%	63.4%	67.5%	69.2%	59.8%	64.9%	63.8%	69.6%	69.0%	56.3%

* Number in yellow indicates the first calendar year of reimbursement. For example, pemetrexed was first reimbursed in 2006. The columns in this table indicate the incidence year. For example, for incidence year 2009, 63.4% of patients received reimbursed pemetrexed during the five years after diagnosis. Source: BCR-IMA.

Appendix 6.2. Reimbursement criteria for selected drugs

Table 93 – reimbursement criteria selected drugs in Mesothelioma

Drug	Trade name	Date start reimbursement	Indication NI	Indication Fr
Pemetrexed	Alimta	1/7/2006	in associatie met cisplatine voor de behandeling van chemotherapie-naïeve patiënten met inoperabel maligne mesotheliom van de pleura van het epitheliale type. De patiënt moet, voor het starten van de behandeling, een Karnofsky (performance status) score van ≥ 80 vertonen	en association avec le cisplatine, pour le traitement des patients atteints de mésothéliome pleural malin non résécable, de type épithélial. Le patient ne pourra pas avoir reçu de chimiothérapie antérieure et devra avoir, avant traitement, un score de Karnofsky (performance status) supérieur ou égal à 80

Appendix 6.3. Medical literature: search for evidence

Appendix 6.3.1. Search medical literature (systematic reviews)

The search for systematic reviews in MEDLINE, PreMedline and the Cochrane library of systematic reviews (inception to search date) specifically developed for this research question, yielded 13 records (Figure 278). After de-duplication, 13 of the 13 remaining reviews were screened based on title and abstract, of which 9 were excluded. In total 4 full text articles were assessed for eligibility. Based on full text evaluation, 3 reviews were excluded (Figure 279).



Figure 185 – Pleural mesothelioma – Selection of SRs - Study flow

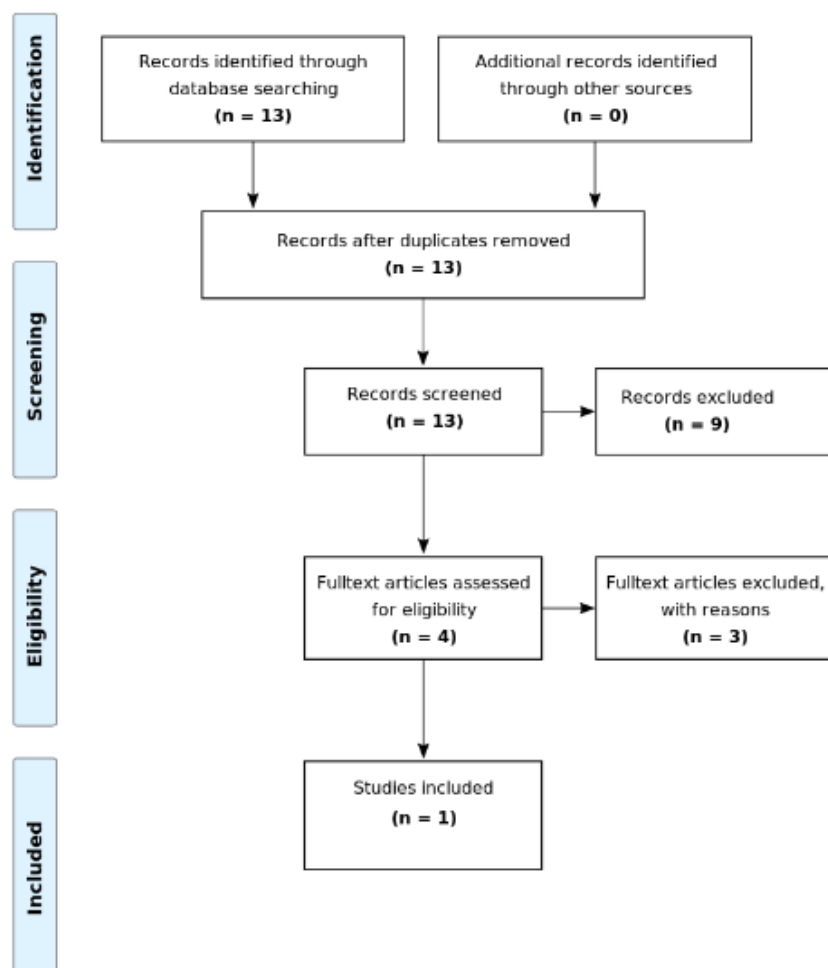


**Table 94 – Mesothelioma: excluded reviews and reason for exclusion**

	Year	Publication	Reason for exclusion
1	2008	Fennell, D. A. Gaudino, G. O'Byrne, K. J. et al. Advances in the systemic therapy of malignant pleural mesothelioma. <i>Nat Clin Pract Oncol</i> 2008; 5(3):136-147	Full text awaited
2	2007	Green, J., Dunder, Y., Dodd, S. et al. Pemetrexed disodium in combination with cisplatin versus other cytotoxic agents or supportive care for the treatment of malignant pleural mesothelioma. <i>Cochrane Database Syst Rev</i> 2007;1: CD005574	Included
3	2007	Dunder, Y. Bagust, A. Dickson, R. et al. Pemetrexed disodium for the treatment of malignant pleural mesothelioma: a systematic review and economic evaluation. <i>Health Technol Assess</i> 2007;11(1):1-90	No additional information. This document was included in the economic literature overview.
4	2006	Ellis, P. Davies, A. M. Evans, W. K. et al. The use of chemotherapy in patients with advanced malignant pleural mesothelioma: a systematic review and practice guideline. <i>J Thorac Oncol</i> 2006;1(6):591-601	No additional information

Appendix 6.3.2. Critical appraisal systematic reviews

Green 2007 ¹³⁴		
	Score	Rationale/comment
1. PICO	Y	
2. A priori study design	N	
3. Inclusion study designs	Y	
4. Comprehensive literature search	Partial yes	No search of trial registries
5. Duplicate study selection	Y	
6. Duplicate data extraction	Y	
7. List of excluded studies and rationale	Y	
8. Characteristics of included studies provided	Y	
9. Assessment of risk of bias	Partial Yes	No assessment regarding selective reporting of outcomes
10. Sources of funding reported	Y	
11. Appropriate methods to combine findings	Y	NA
12. Assessment of impact RoB in included studies on results MA	Y	
13. RoB assessment used in interpretation of results and in conclusions	Y	



Green 2007 ¹³⁴		
	Score	Rationale/comment
14. Explanation for and discussion of any observed heterogeneity	Y	NA
15. Adequate investigation of publication bias and its impact on the results	N	NA
16. Potential sources of conflict of interest reported	Y	

Appendix 6.3.3. Search strategy

Appendix 6.3.3.1. Cochrane library of systematic reviews

Date	24/06/2020 00:22:53	
Database	Cochrane@Wiley.com	
Search strategy		
#1	[mh "Mesothelioma"]	186
#2	mesotheliom*:ab,ti	643
#3	celothelioma:ab,ti	0
#4	((neoplasm? or cancer* or tumor? or tumour? or carcinom* or metasta* or adenocarcinom* or maligna*) NEAR/2 mesothelia*):ab,ti	4
#5	((neoplasm? or cancer* or tumor? or tumour? or carcinom* or metasta* or adenocarcinom* or maligna*) NEAR/2 submesothelia*):ab,ti	0
#6	pleuramesotheliom*:ab,ti	1
#7	#2 or #3 or #4 or #5 or #6	646
#8	#1 or #7	665
#9	[mh ^"pemetrexed"]	613
#10	pemetrexed:ab,ti	1737
#11	Alimta:ab,ti	138
#12	PEMFEXY:ab,ti	0
#13	armisarte:ab,ti	5
#14	ciambra:ab,ti	0
#15	elimta:ab,ti	0
#16	pemta:ab,ti	1
#17	MTA:ab,ti	615
#18	"LY 231514":ab,ti	0



#19	LY231514:ab,ti	22
#20	04Q9AIZ7NO:ab,ti	0
#21	"NSC-698037":ab,ti	0
#22	NSC698037:ab,ti	0
#23	"137281-23-3":ab,ti	32
#24	"150399-23-8":ab,ti	26
#25	#10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24	2362
#26	#9 or #25	2476
#27	#8 and #26	227
#28	[mh ^"Folic Acid"/AA]	12
#29	[mh ^"Antimetabolites"]	187
#30	[mh ^"Antimetabolites, Antineoplastic"]	1003
#31	#29 or #30	1190
#32	antimetabolite?:ab,ti	259
#33	#31 or #32	1409
#34	[mh "Folic Acid"]	3407
#35	(folic or folate):ab,ti	4652
#36	folacin:ab,ti	9
#37	folvite:ab,ti	0
#38	(vitamin NEAR/3 (m or b9)):ab,ti	154
#39	#35 or #36 or #37 or #38	4787
#40	#34 or #39	6596
#41	#33 and #40	168
#42	[mh ^"Thymidylate Synthase"/AI]	18
#43	[mh "Folic Acid Antagonists"]	114
#44	[mh ^"tetrahydrofolate reductase"/AI]	10130
#45	[mh ^"Hydroxymethyl and Formyl Transferases"/AI]	0
#46	[mh ^"Thymidylate Synthase"/AI]	18
#47	#42 or #43 or #44 or #45 or #46	10242
#48	(dihydrofolate NEAR/5 (inhibit* or antagonist? or target* or block* or against or anti or "multi-target" or "multi-targets" or "multi-targeting" or reduc*)):ab,ti	68
#49	((folic or folate) NEAR/5 (inhibit* or antagonist? or target* or block* or against or anti or "multi-target" or "multi-targets" or "multi-targeting" or reduc*)):ab,ti	523
#50	(dhfr NEAR/5 (inhibit* or antagonist? or target* or block* or against or anti or "multi-target" or "multi-targets" or "multi-targeting" or reduc*)):ab,ti	25
#51	(formyltransferase NEAR/5 (inhibit* or antagonist? or target* or block* or against or anti or "multi-target" or "multi-targets" or "multi-targeting" or reduc*)):ab,ti	2



#52	(garft NEAR/5 (inhibit* or antagonist? or target* or block* or against or anti or "multi-target" or "multi-targets" or "multi-targeting" or reduc*)):ab,ti	0
#53	#48 or #49 or #50 or #51 or #52	580
#54	#47 or #53	10808
#55	#28 or #41 or #54	10970
#56	#8 and #55	10
#57	((("new class" or "new classes" or innovative or target*) NEAR/3 (drug? or therapy or therapies or therapeutic* or treatment? or chemotherap*)):ab,ti	11940
#58	#8 and #57	30
#59	#27 or #56 or #58	247
Comments	Only one references out of Cochrane database of systematic reviews,	

Appendix 6.3.3.2. Medline + PreMedline

Date	June 22, 2020	
Database	Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946 to June 22, 2020>	
Search strategy		
1	exp Mesothelioma/	14125
2	mesotheliom*.ab,ti,kf.	16344
3	celothelioma.ab,ti,kf.	10
4	((neoplasm? or cancer* or tumor? or carcinom* or metasta* or adenocarcinom* or maligna*) adj2 mesothelia*).ab,ti,kf.	473
5	((neoplasm? or cancer* or tumor? or carcinom* or metasta* or adenocarcinom* or maligna*) adj2 submesothelia*).ab,ti,kf.	3
6	pleuramesotheliom*.ab,ti,kf.	13
7	2 or 3 or 4 or 5 or 6	16553
8	1 or 7	18869
9	pemetrexed/	2032
10	pemetrexed.ab,ti,kf,rn.	3444
11	Alimta.ab,ti,kf,rn.	172
12	PEMFEXY.ab,ti,kf,rn.	0
13	armisarte.ab,ti,kf,rn.	0
14	ciambra.ab,ti,kf,rn.	0
15	elimta.ab,ti,kf,rn.	0
16	pemta.ab,ti,kf,rn.	0
17	MTA.ab,ti,kf,rn.	4515
18	LY 231514.ab,ti,kf,rn.	11
19	LY231514.ab,ti,kf,rn.	113



20	04Q9AIZ7NO.ab,ti,kf,rn.	2033
21	NSC-698037.ab,ti,kf,rn.	0
22	NSC698037.ab,ti,kf,rn.	0
23	137281-23-3.ab,ti,kf,rn.	1
24	150399-23-8.ab,ti,kf,rn.	0
25	10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24	7883
26	9 or 25	7883
27	8 and 26	802
28	Folic Acid/aa [Analogues & Derivatives]	1380
29	Antimetabolites/	8007
30	Antimetabolites, Antineoplastic/	20091
31	29 or 30	28059
32	antimetabolite?.ab,ti,kf,rn.	11340
33	31 or 32	30807
34	exp Folic Acid/	37673
35	(folic or folate).ab,ti,kf,rn.	47404
36	folacin.ab,ti,kf,rn.	233
37	folvite.ab,ti,kf,rn.	3
38	(vitamin adj3 (m or b9)).ab,ti,kf,rn.	450
39	35 or 36 or 37 or 38	47731
40	34 or 39	57489
41	33 and 40	1806
42	Thymidylate Synthase/ai [Antagonists & Inhibitors]	1293
43	exp Folic Acid Antagonists/	58463
44	tetrahydrofolate reductase/ai	11
45	"Hydroxymethyl and Formyl Transferases"/ai [Antagonists & Inhibitors]	51
46	Thymidylate Synthase/ai [Antagonists & Inhibitors]	1293
47	42 or 43 or 44 or 45 or 46	59331
48	(dihydrofolate adj5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)).ab,ti,kf.	6548
49	((folic or folate) adj5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)).ab,ti,kf.	8100
50	(dhfr adj5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)).ab,ti,kf.	2884
51	(formyltransferase adj5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)).ab,ti,kf.	116
52	(garft adj5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)).ab,ti,kf.	41
53	48 or 49 or 50 or 51 or 52	14195
54	47 or 53	68471
55	28 or 41 or 54	70046
56	8 and 55	554



57	((new class* or innovative or target*) adj3 (drug? or therapy or therapies or therapeutic* or treatment? or chemotherap*)).ab,ti,kf.	330072
58	8 and 57	744
59	27 or 56 or 58	1508
60	((systematic review or systematic literature review or systematic scoping review or systematic narrative review or systematic qualitative review or systematic evidence review or systematic quantitative review or systematic meta-review or systematic critical review or systematic mixed studies review or systematic mapping review or systematic cochrane review or "systematic search and review" or systematic integrative review).ti. not comment.pt. not (protocol or protocols).ti. not medline.st.) or (Cochrane Database Syst Rev.ja. and review.pt.) or systematic review.pt.	159328
61	meta-analys*.ti.	108916
62	meta-analysis.pt.	116279
63	exp Technology Assessment, Biomedical/	11062
64	health technology assessment.ti,kf.	1917
65	HtA.ti,kf.	593
66	60 or 61 or 62 or 63 or 64 or 65	252947
67	59 and 66	12
Comments		



Appendix 6.4. Economic literature

Appendix 6.4.1. Search economic literature (HTA reports)

The search strategy in CRD's HTA database identified eight references (Table 95). In a first round, two references were selected based on a review of title, keywords and abstract. The six remaining references were excluded for the following reasons: intervention (5) or design (1). In a second round, the full text of the two selected references was reviewed. Both references were retained. These references are indicated in Table 42 with an asterix (*).

Furthermore, in May 2020, the website of the National Institute for Health Research (NIHR) was searched for relevant reports. The following search term was used: pemetrexed (34 hits, 1 with a focus on mesothelioma, which was already identified).

Finally, also in May 2020, the website of the National Institute for Health and Care Excellence (NICE) was searched. The following search term was used: pemetrexed (27 hits, 1 relevant Technology Assessment (TA), which was already identified).

An overview of the identified references is provided in Table 96.

Table 95 – Search strategy and results for CRD: HTA

Date	19 February 2020		
Date covered	All		
Search Strategy	1	MeSH DESCRIPTOR Mesothelioma EXPLODE ALL TREES	35
	2	MeSH DESCRIPTOR Solitary Fibrous Tumor, Pleural EXPLODE ALL TREES	0
	3	#1 OR #2	35
	4	* IN HTA	17351
	5	#3 AND #4	8 references
Note	/		

**Table 96 – Mesothelioma – Identified HTA reports for the selected drugs****Selected reports****Pemetrexed**

- NICE, TA135. January 2008. Pemetrexed for the treatment of malignant pleural mesothelioma. * β^{135}
 - Dundar Y, Bagust A, Dickson R, Dodd S, Green J. Pemetrexed disodium for the treatment of malignant pleural mesothelioma: a systematic review and economic evaluation. Health Technol Assess 2007;11(1). * α^{136}

* These references were identified in CRD's HTA database. α Reference identified on NIHR's website. β Reference identified on NICE's website.

Appendix 6.4.2. Results economic literature (HTA reports)**Appendix 6.4.2.1. NICE, TA135 (2008): pemetrexed**

- QoL:
 - "The results of the EMPHACIS trial suggest that pemetrexed plus cisplatin confers a survival benefit of approximately 3 months compared with cisplatin alone. The combination treatment also appears to demonstrate advantages in terms of 1-year survival, median time to progressive disease, tumour response rate and quality of life."¹³⁵
 - "Quality of life was evaluated using the Lung Cancer Symptom Scale–Meso instrument. Several aspects of quality of life were evaluated, including pain, dyspnoea, fatigue, anorexia and cough. Over 18 weeks, patients treated with pemetrexed plus cisplatin demonstrated statistically significant symptomatic improvements when compared with those who received cisplatin alone. For global quality of life in the ITT population, a least squares mean score of 56 out of 100 was reported for patients randomised to pemetrexed plus cisplatin versus a score of 53 out of 100 for patients in the cisplatin arm (p value for the difference between arms = 0.012). A similar result was observed in the fully supplemented population."¹³⁵
 - "Utility scores were taken from an ongoing observational study in patients with non-small-cell lung cancer (NSCLC) who completed the EQ-5D health-related quality of life questionnaire before chemotherapy. The base-case utility scores in both economic models were similar for both arms (0.68 for the pemetrexed plus cisplatin arm and 0.69 for the cisplatin alone arm) and did not take account of loss of quality of life in people with MPM [malignant pleural mesothelioma] as their disease progresses."¹³⁵
 - "The Committee discussed the possibility that differences in symptom relief (including pain and dyspnoea) and quality of life between pemetrexed plus cisplatin and cisplatin alone may not have been captured fully by the economic model because the utilities for both treatment and comparator had been estimated based on data from people with NSCLC. The Committee noted that there was some evidence from the EMPHACIS trial showing that pemetrexed plus cisplatin was associated with statistically significant symptomatic improvements (especially with pain relief) compared with cisplatin alone. The Committee agreed that the economic analyses may have underestimated the overall quality of life benefits of pemetrexed in people with MPM."¹³⁵



- “The information on QoL, which might be expected to capture the patient’s perception of the balance between benefit and toxicity and of effective palliative care, is limited at present, and for the economic evaluation presented here it has been necessary to assume that data from other forms of lung cancer apply in this condition also.”¹³⁶
- Results:
 - “The economic analyses carried out by the manufacturer and the Assessment Group, using model 1 [comparing pemetrexed plus cisplatin with cisplatin alone], both indicated an incremental cost per QALY gained of greater than £60,000 when pemetrexed plus cisplatin was compared with cisplatin alone in the fully supplemented population. Pemetrexed plus cisplatin, when compared with cisplatin alone, appears to have lower ICERs in patients with advanced disease and/or good performance status. The manufacturer’s economic analyses (based on indirect comparisons) using model 2 indicated more favourable ICERs for pemetrexed plus cisplatin when compared with MVP [mitomycin C, vinblastine and cisplatin combination], vinorelbine and ASC [active symptom control]. However, the assumptions underpinning model 2 are subject to high levels of uncertainty. When the assumptions were modified to reflect performance-status-adjusted survival, and resource use based on published data, the ICERs from model 2 were in line with those of pemetrexed plus cisplatin versus cisplatin alone.”¹³⁵
 - “The Assessment Group’s analysis resulted in an ICER of £60,600 per QALY gained in the fully supplemented population. The results were more favourable in fully supplemented patients with advanced disease (£49,100 per QALY gained), fully supplemented patients with good performance status (£50,400 per QALY gained) and fully supplemented patients with advanced disease and good performance status (£37,700 per QALY gained). The Assessment Group also calculated the cost effectiveness of pemetrexed plus cisplatin versus cisplatin alone in fully supplemented patients with advanced disease and good performance status under the assumption that a smaller 100-mg vial of pemetrexed becomes available. In this case the ICER was £34,500 per QALY gained.”¹³⁵
 - “In a later document, the manufacturer suggested that the ICERs for pemetrexed plus cisplatin might be lower if treatment was stopped in patients who did not experience a tumour response after their fourth cycle. It was suggested that this would lower overall costs without reducing aggregate health benefit, because only those who respond to treatment would experience survival gains. No clinical evidence or economic analysis to support this proposal was submitted.”¹³⁵
- Uncertainty/sensitivity:
 - “A wide-ranging sensitivity analysis was undertaken, in which survival and drug costs were found to be the key parameters. Results from the univariate analysis indicate that drug costs would need to be more than 20% lower for the therapy to be in the generally acceptable range of cost-effectiveness.”¹³⁶
 - “Model 2 [indirectly compared pemetrexed plus cisplatin with mitomycin C, vinblastine and cisplatin combination (MVP), vinorelbine (with or without platinum) and active symptom control (ASC)] There is a fundamental problem with the evidence provided to support outcome gains claimed in Model 2, which is highlighted by the following passage from the company submission: ‘There have been few studies investigating the use of MVP, vinorelbine (± platinum) in MPM, however most are small, non-randomised phase II trials. There are no randomised controlled trials comparing chemotherapy to ASC. The patient population characteristics varied widely between studies that make comparison of agents problematic and hence inconclusive.’”¹³⁶



- Conclusions:
 - “The Committee discussed the ICERs of pemetrexed plus cisplatin versus cisplatin alone produced by the manufacturer and the Assessment Group, and observed that the range of ICERs was higher than is normally considered acceptable.”¹³⁵
 - “Committee agreed that a direct RCT comparison of the efficacy of pemetrexed plus cisplatin versus other chemotherapy treatments and [active symptom control] ASC would be an informative addition to the evidence base. ... The Committee concluded that it could not base its decision on the indirect comparison model.”¹³⁵
 - “Having considered the likelihood of lower numbers of treatment cycles in clinical practice, the potential availability of a 100-mg pemetrexed vial and the likelihood of greater quality of life benefits than assumed by the cost-effectiveness analyses, the Committee agreed that the ICER for pemetrexed plus cisplatin in the fully supplemented subgroup with advanced disease and good performance status was likely to fall within acceptable levels.”¹³⁵
 - “The Committee also noted that MPM is a rare and aggressive malignancy caused by occupational exposure to asbestos and was mindful that this disease has a very poor prognosis.
 - The Committee concluded that pemetrexed in combination with cisplatin should be recommended as an option for the treatment of MPM only in people who are considered to have advanced disease and who have a WHO performance status of 0 or 1, in whom surgical resection is not considered appropriate.”¹³⁵
- (Confidential) prices:
 - No reference to confidential prices is made.

Reference Costs (list prices & remarks)	Population, Intervention & comparator IC, IE and ICERs	Remarks on use of generic utility instrument (e.g. EQ- 5D) to measure impact on QoL in economic evaluations	Most uncertain variables or important variables in sensitivity analysis
Pemetrexed			
NICE, TA135 (2008) ¹³⁵ Dundar (2007) ¹³⁶	Patients with malignant pleural mesothelioma. Pemetrexed plus cisplatin versus cisplatin alone.		
List prices: Pemetrexed costs £800 for a 500-mg vial (excluding VAT, 'British national formulary' [BNF] 53rd edition). The cost per patient, assuming an average of five treatment	Results of the incremental analysis (with list prices): Model 1: pemetrexed plus cisplatin compared with cisplatin alone. A) Manufacturer's model: FS population FS with advanced disease (Stage III/IV)	QoL was not measured with a generic utility instrument in the underlying trial. Utility scores were taken from an ongoing observational study in patients with non- small-cell lung cancer	Survival Drug costs Quality of life.
	ICER (£/QALY) 68 598 53 314		



cycles and a body surface area of 1.8m², is approximately £8000.

FS with good performance (0/1)

48 099

FS with advanced disease and good performance:47 567

(NSCLC) who completed the EQ-5D health-related quality of life questionnaire before chemotherapy.

B) Assessment Group's analysis (base-case pemetrexed costs):

ICER (£/QALY)

FS population

60,561

FS with advanced disease (Stage III/IV)

49,051

FS with good performance (0/1)

50,357

FS with advanced disease and good performance:37,664

Details on incremental costs and effects are available in the underlying report.¹³⁶

Remark: Model 2 compared pemetrexed plus cisplatin with standard care (as defined by the manufacturer on the basis of a market research survey - mitomycin C, vinblastine and cisplatin combination (MVP), vinorelbine (with or without platinum) and active symptom control (ASC)).

The evidence base underpinning Model 2 is not credible since it is not founded upon direct or even indirect comparisons of RCTs, and there is no evidence to support comparability of the patient populations between the various studies quoted, or with the EMPHACIS trial. The crucial issue is the extent of survival gain to be expected between pemetrexed plus cisplatin and the various comparators offered, and we have concluded that there is no objective basis on which to estimate such gains or to assess the uncertainty associated with such estimates. Without these figures, the Model 2 endeavour is fruitless, and therefore we have not pursued this approach any further.

FS: fully supplemented patients



APPENDIX 7. MULTIPLE MYELOMA

Appendix 7.1. BCR data

Appendix 7.1.1. Descriptive statistics

Appendix 7.1.1.1. Multiple myeloma, exploration

Table 97 – Multiple myeloma (2004-2017): Frequency table of patient and tumour characteristics

Characteristic	Total	Incidence period		
		2004-2008	2009-2013	2014-2017
Overall	10,578	3,295	3,809	3,474
Gender				
Male	5,814 (55.0)	1,772 (53.8)	2,142 (56.2)	1,900 (54.7)
Female	4,764 (45.0)	1,523 (46.2)	1,667 (43.8)	1,574 (45.3)
Age at diagnosis (year)				
<50 years	625 (5.9)	216 (6.6)	220 (5.8)	189 (5.4)
50-59 years	1,508 (14.3)	499 (15.1)	528 (13.9)	481 (13.8)
60-69 years	2,637 (24.9)	834 (25.3)	948 (24.9)	855 (24.6)
70-79 years	3,549 (33.6)	1,148 (34.8)	1,297 (34.1)	1,104 (31.8)
80+ years	2,259 (21.4)	598 (18.1)	816 (21.4)	845 (24.3)
WHO - Performance Status				
0 – Asymptomatic	1,714 (16.2)	432 (13.1)	671 (17.6)	611 (17.6)
1 – Symptomatic but completely ambulatory	4,560 (43.1)	1,040 (31.6)	1,793 (47.1)	1,727 (49.7)
2 – Symptomatic, <50% in bed during the day	1,101 (10.4)	330 (10.0)	367 (9.6)	404 (11.6)
3 – Symptomatic, >50% in bed, but not bedbound	454 (4.3)	113 (3.4)	162 (4.3)	179 (5.2)
4 – Bedbound	117 (1.1)	28 (0.8)	41 (1.1)	48 (1.4)
Not reported	2,632 (24.9)	1,352 (41.0)	775 (20.3)	505 (14.5)
Combined stage				
NA	10,578 (100.0)	3,295 (100.0)	3,809 (100.0)	3,474 (100.0)

Note: the values between parentheses are column percentages.



Appendix 7.1.1.2. Multiple myeloma, Observed and Relative Survival graphs

Multiple myeloma (2004-2017)

Figure 186 – Multiple myeloma (2004-2017), Kaplan-Meier graphs observed survival by incidence period

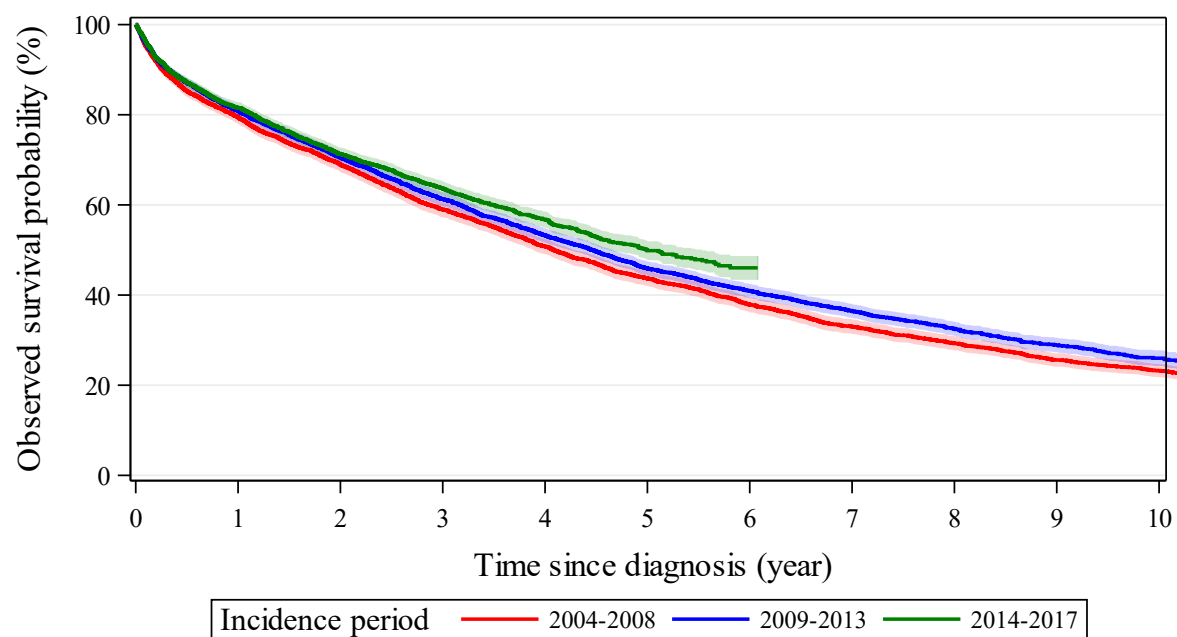
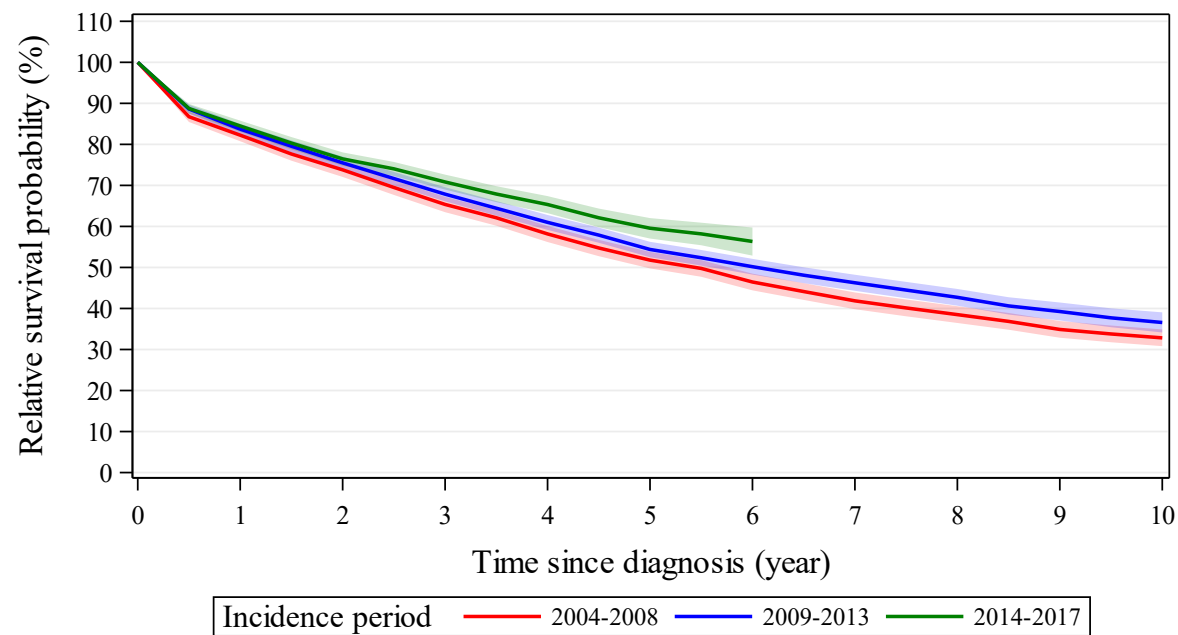




Figure 187 – Multiple myeloma (2004-2017), relative survival graphs by incidence period

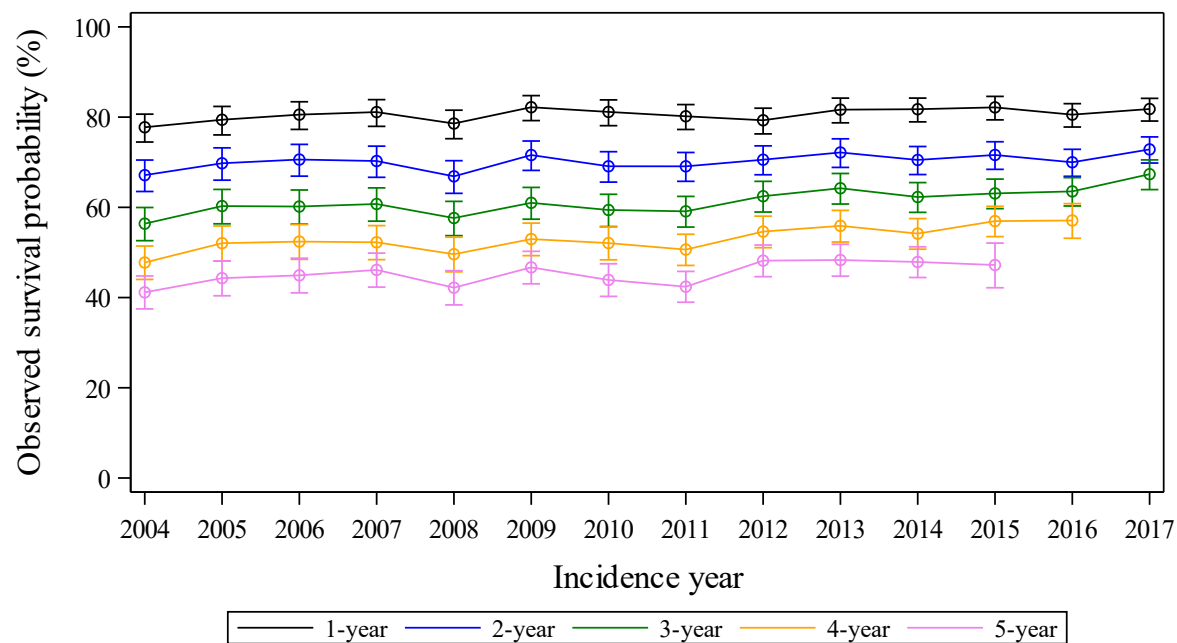




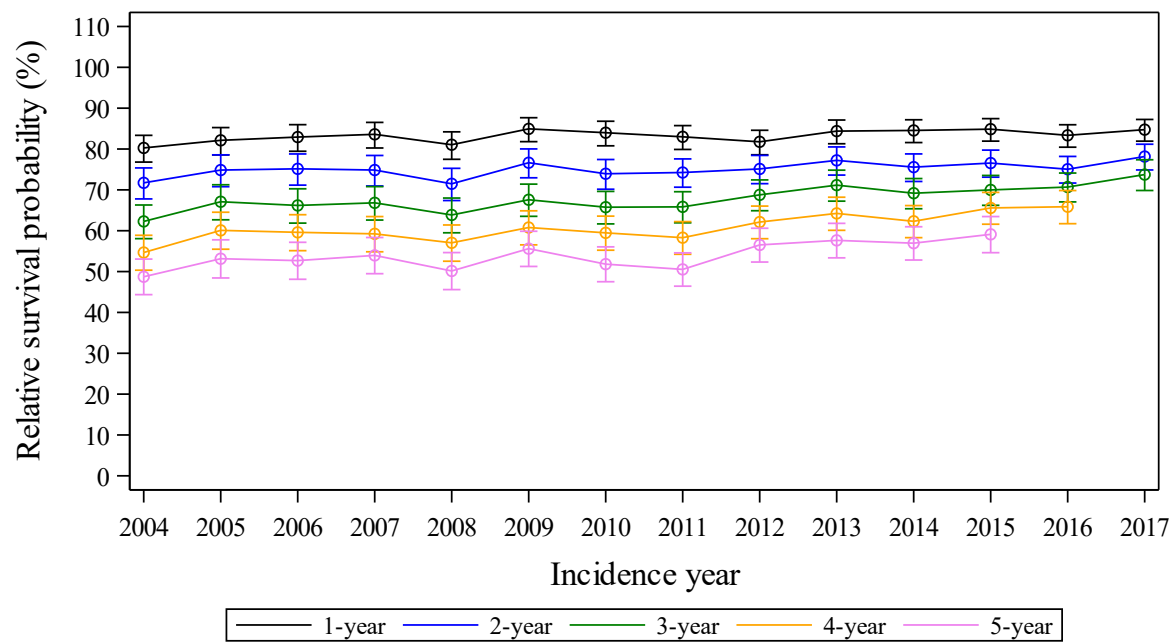
Appendix 7.1.1.3. Multiple myeloma, time trend Observed and Relative Survival

Multiple myeloma (2004-2017)

Figure 188 – Multiple myeloma (2004-2017), time trend observed survival with incidence year

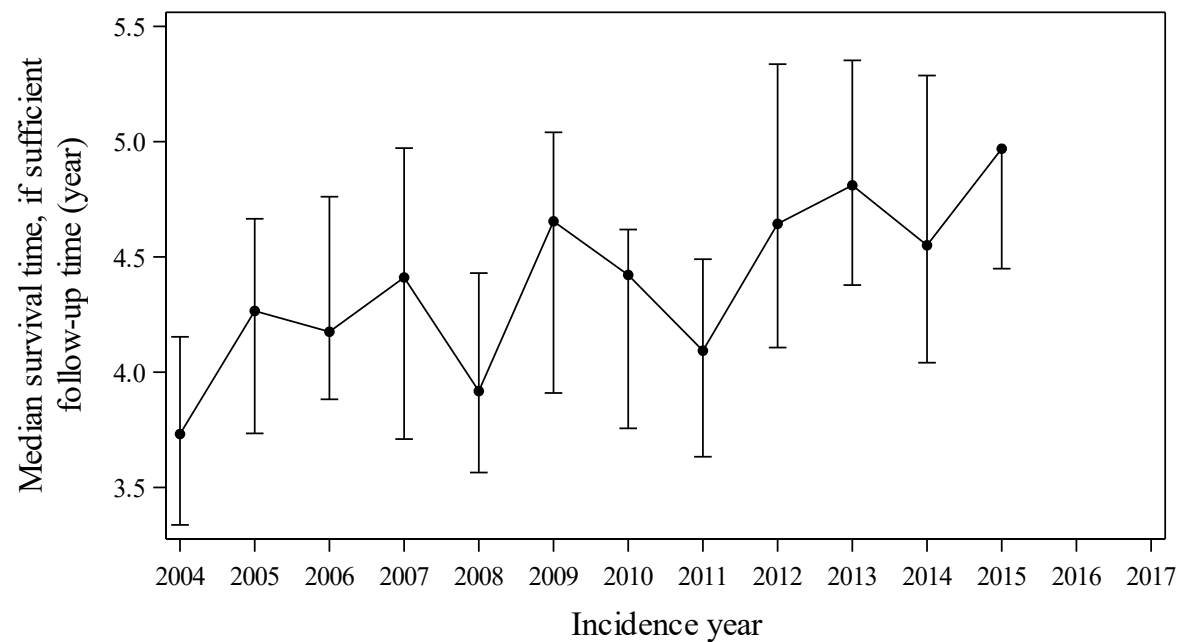


Note: the error bars represent the 95% CI.

**Figure 189 – Multiple myeloma (2004-2017), time trend relative survival with incidence year**

Note: the error bars represent the 95% CI.

Figure 190 – Multiple myeloma (2004-2017), Median time observed survival



Note: the error bars represent the 95% CI. When the upper error is not plotted, the upper limit could not be determined with the follow-up available.



Appendix 7.1.1.4. Multiple myeloma, time trend tables Observed and Relative Survival

Table 98 – Multiple myeloma (2004-2017), time trend observed survival with incidence year

Characteristic	N at risk	Unadjusted observed survival, %											
		1 year		2 year		3 year		4 year		5 year		Median survival time (year)	
		%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI	T	95% CI
All													
2004	697	77.8	[74.5, 80.7]	67.1	[63.5, 70.5]	56.4	[52.6, 60.0]	47.8	[44.0, 51.4]	41.2	[37.5, 44.8]	3.7	[3.3, 4.2]
2005	632	79.4	[76.1, 82.4]	69.8	[66.0, 73.2]	60.3	[56.4, 64.0]	52.1	[48.1, 55.9]	44.3	[40.4, 48.1]	4.3	[3.7, 4.7]
2006	643	80.6	[77.3, 83.4]	70.6	[66.9, 74.0]	60.2	[56.3, 63.9]	52.4	[48.5, 56.2]	44.9	[41.0, 48.7]	4.2	[3.9, 4.8]
2007	673	81.1	[78.0, 83.9]	70.3	[66.7, 73.6]	60.7	[56.9, 64.3]	52.3	[48.4, 56.0]	46.1	[42.3, 49.9]	4.4	[3.7, 5.0]
2008	650	78.6	[75.2, 81.5]	66.9	[63.1, 70.4]	57.6	[53.7, 61.3]	49.6	[45.7, 53.4]	42.2	[38.4, 46.0]	3.9	[3.6, 4.4]
2009	736	82.2	[79.2, 84.8]	71.6	[68.2, 74.7]	61.0	[57.4, 64.4]	53.0	[49.3, 56.5]	46.7	[43.0, 50.3]	4.7	[3.9, 5.0]
2010	722	81.2	[78.1, 83.8]	69.1	[65.6, 72.3]	59.4	[55.7, 62.9]	52.1	[48.4, 55.7]	43.9	[40.3, 47.5]	4.4	[3.8, 4.6]
2011	803	80.2	[77.3, 82.8]	69.1	[65.8, 72.2]	59.1	[55.6, 62.4]	50.6	[47.1, 54.0]	42.4	[39.0, 45.8]	4.1	[3.6, 4.5]
2012	779	79.3	[76.3, 82.0]	70.6	[67.2, 73.6]	62.5	[59.0, 65.8]	54.6	[51.1, 58.1]	48.2	[44.6, 51.6]	4.6	[4.1, 5.3]
2013	769	81.7	[78.7, 84.2]	72.2	[68.9, 75.2]	64.2	[60.7, 67.5]	55.9	[52.3, 59.3]	48.3	[44.7, 51.8]	4.8	[4.4, 5.4]
2014	830	81.8	[79.0, 84.2]	70.5	[67.3, 73.5]	62.3	[58.9, 65.5]	54.2	[50.7, 57.5]	47.9	[44.4, 51.3]	4.6	[4.0, 5.3]
2015	836	82.2	[79.4, 84.6]	71.6	[68.4, 74.5]	63.1	[59.7, 66.3]	57.0	[53.5, 60.2]	47.2	[42.2, 52.1]	5.0	[4.4, .]
2016	901	80.6	[77.8, 83.0]	70.0	[66.9, 72.9]	63.5	[60.3, 66.6]	57.1	[53.1, 60.8]	no FU	—	>4	
2017	907	81.8	[79.1, 84.2]	72.8	[69.8, 75.6]	67.4	[63.9, 70.5]	no FU	—	no FU	—	>3	


Table 99 – Multiple myeloma (2004-2017), time trend relative survival with incidence year

Unadjusted relative survival, %											
	N at risk	%	1 year 95% CI	%	2 year 95% CI	%	3 year 95% CI	%	4 year 95% CI	%	5 year 95% CI
All											
2004	697	80.3	[76.8, 83.3]	71.7	[67.8, 75.4]	62.3	[58.1, 66.3]	54.7	[50.3, 58.9]	48.7	[44.4, 53.1]
2005	632	82.1	[78.6, 85.2]	74.8	[70.8, 78.6]	67.1	[62.7, 71.2]	60.1	[55.5, 64.5]	53.1	[48.4, 57.8]
2006	643	82.9	[79.4, 86.0]	75.2	[71.2, 78.8]	66.2	[61.9, 70.3]	59.6	[55.1, 63.9]	52.7	[48.1, 57.2]
2007	673	83.6	[80.3, 86.5]	74.9	[71.0, 78.4]	66.8	[62.6, 70.8]	59.2	[54.8, 63.5]	54.0	[49.5, 58.3]
2008	650	81.1	[77.5, 84.2]	71.5	[67.4, 75.3]	63.9	[59.5, 68.0]	57.0	[52.5, 61.4]	50.1	[45.6, 54.6]
2009	736	84.9	[81.8, 87.7]	76.6	[73.0, 80.0]	67.6	[63.5, 71.4]	60.8	[56.5, 64.9]	55.6	[51.3, 59.9]
2010	722	84.0	[80.8, 86.8]	73.9	[70.2, 77.4]	65.8	[61.7, 69.6]	59.5	[55.2, 63.6]	51.8	[47.5, 56.0]
2011	803	83.0	[79.9, 85.7]	74.3	[70.7, 77.6]	65.8	[61.9, 69.5]	58.3	[54.2, 62.2]	50.5	[46.4, 54.6]
2012	779	81.8	[78.6, 84.6]	75.1	[71.5, 78.4]	68.8	[64.9, 72.4]	62.1	[58.0, 66.0]	56.5	[52.3, 60.6]
2013	769	84.4	[81.3, 87.1]	77.2	[73.6, 80.5]	71.2	[67.2, 74.8]	64.2	[60.1, 68.2]	57.6	[53.4, 61.8]
2014	830	84.5	[81.6, 87.2]	75.6	[72.1, 78.8]	69.2	[65.4, 72.8]	62.3	[58.3, 66.2]	56.9	[52.8, 61.0]
2015	836	84.9	[81.9, 87.4]	76.6	[73.1, 79.7]	70.0	[66.2, 73.5]	65.6	[61.6, 69.4]	59.1	[54.6, 63.5]
2016	901	83.4	[80.4, 85.9]	75.1	[71.7, 78.2]	70.7	[67.1, 74.1]	65.9	[61.7, 69.8]	no FU	—
2017	907	84.7	[81.9, 87.2]	78.2	[74.9, 81.2]	73.7	[69.8, 77.4]	no FU	—	no FU	—

Appendix 7.1.2. Uptake of selected drugs

Table 100 – Proportion of patients diagnosed with multiple myeloma who received at least one dose during 5-year period after diagnosis

Drug/incidence year (n)	2004 698	2005 633	2006 645	2007 673	2008 651	2009 739	2010 723	2011 803	2012 780	2013 770	2014 831	2015 837	2016 902	2017 910
lenalidomide	8.2%	16.7%	24.2%	28.2%	32.4%	36.0%	39.3%	38.9%	39.0%	46.6%	42.6%	42.5%	44.5%	48.9%
bortezomib	28.8%	38.5%	39.8%	44.7%	43.5%	54.9%	59.6%	61.0%	62.3%	65.3%	67.3%	67.1%	54.7%	56.8%
pomalidomide						0.3%	3.9%	6.7%	11.2%	13.2%	13.0%	11.1%	5.9%	2.9%
daratumumab									3.7%	8.3%	9.1%	9.8%	10.6%	8.1%



* Numbers in yellow indicate the first calendar year of reimbursement. For example, lenalidomide was first reimbursed in 2008. The columns in this table indicate the incidence year. For example, for incidence year 2006, 24.2% of patients received reimbursed lenalidomide during the 5 years after diagnosis.

Appendix 7.2. reimbursement criteria for selected drugs

Table 101 – Targeted drugs in multiple myeloma: reimbursement criteria in Belgium

Drug	Trade name	Date start reimbursement	Indication NI	Indication Fr
Lenalidomide	Revlimid	1/4/2008	De specialiteit komt voor vergoeding in aanmerking indien ze wordt toegediend, in combinatie met dexamethasone, aan een patiënt met multipel myeloom bij wie minstens één voorafgaande behandeling heeft gefaald. Daarnaast moet aan één van de volgende voorwaarden voldaan worden: <ul style="list-style-type: none"> • ofwel moet in de voorafgaande behandeling minstens één stamceltransplantatie vervat geweest zijn • ofwel komt de patiënt niet in aanmerking voor een stamceltransplantatie. • Alle behandelingen toegediend in het kader van de stamceltransplantatie worden als één behandelingsschema beschouwd met inbegrip van de stamceltransplantatie. 	La spécialité fait l'objet d'un remboursement si elle est administrée, en association avec la dexaméthasone, pour le traitement d'un patient atteint de myélome multiple chez qui au moins un traitement antérieur a échoué. En outre une des conditions suivantes doit être remplie : <ul style="list-style-type: none"> • - ou le traitement antérieur doit avoir comporté au moins une greffe de cellules souches • - ou le patient doit être inéligible pour une telle greffe de cellules souche. • Tous les traitements qui ont été administrés dans le cadre d'une greffe de cellules souches sont considérés comme un seul schéma de traitement, y compris la greffe de cellules souches.
		1/3/2016	De specialiteit komt voor vergoeding in aanmerking indien ze wordt toegediend voor de behandeling van een niet eerder behandeld multipel myeloom bij een volwassen patiënt die niet in aanmerking komt voor een stamceltransplantatie.	La spécialité fait l'objet d'un remboursement si elle est administrée, pour le traitement du myélome multiple non préalablement traité chez les patients adultes non éligibles à une greffe de cellules souches.
		1/12/2017	De specialiteit wordt vergoed indien ze wordt toegediend als monotherapie voor de onderhoudsbehandeling van volwassen patiënten met nieuw gediagnosticeerd multipel myeloom die een autologe stamceltransplantatie hebben ondergaan. De patiënt komt in aanmerking voor deze onderhoudsbehandeling indien de patiënt na de autologe transplantatie minstens een stabiele ziekte vertoont.	La spécialité fait l'objet d'un remboursement si elle est administrée en monothérapie pour le traitement d'entretien du myélome multiple non préalablement traité chez les patients adultes ayant reçu une autogreffe de cellules souches. Le patient est éligible pour le traitement d'entretien s'il présente au moins une maladie stable après la greffe autologue. La posologie journalière maximale remboursable est limitée à 15 mg,



Drug	Trade name	Date start reimbursement	Indication NI	Indication Fr
Bortezomib	Velcade			consistant en un maximum de 1 gélule par jour de traitement.
		1/4/2009	toegediend in combinatie met melfalan en prednison, in het kader van de eerstelijnsbehandeling van patiënten met multipel myeloom die niet in aanmerking komen voor een hooggedoseerde chemotherapie met een hematopoëtische stamceltransplantatie;	administrée en association avec melfalan et prednison, dans le cadre d'un traitement de première ligne des patients atteints d'un myélome multiple qui n'entre pas en ligne de compte pour un chimiothérapie à haute dose avec une transplantation de cellules souches hématopoïétiques
		1/9/2014	toegediend in combinatie met dexamethason, of met dexamethason en thalidomide, in het kader van de inductiebehandeling van patiënten met niet eerder behandeld multipel myeloom die in aanmerking komen voor een hooggedoseerde chemotherapie met een hematopoëtische stamceltransplantatie.	administrée en association avec la dexaméthasone, ou avec la dexaméthasone et le thalidomide, dans le cadre d'un traitement d'induction des patients atteints d'un myélome multiple non traité précédemment qui entrent en ligne de compte pour une chimiothérapie à haute dose avec une transplantation de cellules souches hématopoïétiques.
		1/2/2005	toegediend in het kader van de behandeling van patiënten met multipel myeloom, die een progressie van de ziekte vertonen en die minstens één voorafgaande behandeling hebben gehad. In de voorafgaande behandeling moet minstens één hematopoëtische stamceltransplantatie vervat geweest zijn behalve indien de patiënt hiervoor niet in aanmerking komt. Alle behandelingen toegediend in het kader van de hematopoëtische stamceltransplantatie worden als één behandeling beschouwd met inbegrip van de hematopoëtische stamceltransplantatie.	administrée en association avec la dexaméthasone, ou avec la dexaméthasone et le thalidomide, dans le cadre d'un traitement d'induction des patients atteints d'un myélome multiple non traité précédemment qui entrent en ligne de compte pour une chimiothérapie à haute dose avec une transplantation de cellules souches hématopoïétiques.
pomalidomide	Imnovid	1/9/2014	in combinatie met dexamethasone voor de behandeling van een gerecidiveerd en refractair multipel myeloom bij een volwassen patiënt die al minstens twee voorafgaande lijnen behandeling heeft gekregen waaronder een behandeling met een proteasoomremmer en een immunomodulerend middel, en bij wie de ziekte progressie heeft vertoond na de laatste behandeling.	en combinaison avec la dexaméthasone pour le traitement du myélome multiple en rechute et réfractaire chez les patients adultes ayant déjà reçu au moins deux lignes de traitement antérieures comportant un inhibiteur du protéasome et un immunomodulateur, et dont la maladie a progressé après le dernier traitement.
Daratumumab	Darzalex	1/3/2017	vergoeding in monotherapie voor de behandeling van een gerecidiveerd en refractair multipel myeloom bij een volwassen patiënt die al minstens twee voorafgaande lijnen behandeling heeft gekregen waaronder een	remboursement en monothérapie pour le traitement du myélome multiple en rechute et réfractaire chez les patients adultes ayant déjà reçu au moins deux lignes de traitement antérieures comportant un inhibiteur du



Drug	Trade name	Date start reimbursement	Indication NI	Indication Fr
			<p>behandeling met een proteasoomremmer en een immunomodulerend middel, en bij wie de ziekte progressie heeft vertoond na de laatste behandeling. De patiënt moet ofwel:</p> <p>1) Gerecidiveerd zijn en refractair zijn (progressie tijdens of binnen de 2 maanden na de behandeling) aan de voorafgaande behandeling met een proteasoomremmer en/of immunomodulerend middel</p> <p>2) Ofwel een vroegtijdig recidief vertonen na een proteasoomremmer en/of immunomodulerend middel (dit wil zeggen binnen een interval van 6 maanden na beste respons)</p> <p>3) Ofwel intolerant zijn voor een proteasoomremmer en/of immunomodulerend middel (intolerantie die stopzetting van de behandeling noodzakelijk maakte).</p>	<p>protéasome et un immunomodulateur, et dont la maladie a progressé après le dernier traitement. Le patient doit être soit:</p> <p>1) En rechute et réfractaire (progression pendant ou endéans les 2 mois après le traitement) au traitement préalable par un inhibiteur du protéasome et/ou un immunomodulateur</p> <p>2) Soit en rechute précoce après un inhibiteur du protéasome et/ou un immunomodulateur (c'est-à-dire dans un délai de moins de 6 mois après la meilleure réponse)</p> <p>3) Soit intolérant à un inhibiteur du protéasome et/ou à un immunomodulateur (intolérance nécessitant l'arrêt du traitement).</p>
		1/3/2018	<p>vergoeding indien ze wordt toegediend, in combinatie met lenalidomide en dexamethason, aan volwassen patiënten met multipel myeloom die progressie van de ziekte vertonen en die minstens één voorafgaande behandeling hebben gehad. In de voorafgaande behandeling moet minstens één hematopoëtische stamceltransplantatie vervat geweest zijn behalve indien de patiënt hiervoor niet in aanmerking komt. Alle behandelingen toegediend in het kader van de stamceltransplantatie worden als één behandeling beschouwd met inbegrip van de stamceltransplantatie. De specialiteit komt niet in aanmerking voor vergoeding indien ze wordt toegediend aan patiënten die minstens twee voorafgaande behandelingen hebben gehad als deze patiënten in de voorafgaande behandeling progressie vertonen op een op lenalidomide-bevattende combinatiebehandeling.</p>	<p>remboursement si elle est administrée en combinaison avec lenalidomide et dexaméthasone chez des patients adultes atteints de myélome multiple, présentant une progression de la maladie, et qui ont reçu au moins un schéma de traitement antérieur ayant comporté au moins une greffe de cellules souches sauf s'ils sont inéligibles pour une telle greffe de cellules souche. Tous les traitements qui ont été administrés dans le cadre d'une greffe de cellules souches sont considérés comme un seul traitement, en ce, y compris la greffe de cellules souches. La spécialité ne fait pas l'objet d'un remboursement si elle est administrée aux patients ayant au moins deux traitements antérieurs, si ces patients dans le traitement précédent montrent une progression avec une thérapie combinée contenant lenalidomide.</p>
		1/3/2018	<p>vergoeding indien ze wordt toegediend, in combinatie met bortezomib en dexamethason, aan volwassen patiënten met multipel myeloom die progressie van de ziekte vertonen en die minstens één voorafgaande behandeling hebben gehad. In de voorafgaande behandeling moet minstens één hematopoëtische</p>	<p>remboursement si elle est administrée en combinaison avec bortezomib et dexaméthasone chez des patients adultes atteints de myélome multiple, présentant une progression de la maladie, et qui ont reçu au moins un schéma de traitement antérieur ayant comporté au moins une greffe de cellules souches sauf s'ils sont</p>



Drug	Trade name	Date start reimbursement	Indication NI	Indication Fr
			stamceltransplantatie vervat geweest zijn behalve indien de patiënt hiervoor niet in aanmerking komt. Alle behandelingen toegediend in het kader van de stamceltransplantatie worden als één behandeling beschouwd met inbegrip van de stamceltransplantatie. De specialiteit komt niet in aanmerking voor vergoeding indien ze wordt toegediend aan patiënten die minstens twee voorafgaande behandelingen hebben gehad als deze patiënten in de voorafgaande behandeling progressie vertonen op een op bortezomib-bevattende combinatiebehandeling.	inéligibles pour une telle greffe de cellules souches. Tous les traitements qui ont été administrés dans le cadre d'une greffe de cellules souches sont considérés comme un seul traitement, en ce, y compris la greffe de cellules souches. La spécialité ne fait pas l'objet d'un remboursement si elle est administrée aux patients ayant au moins deux traitements antérieurs, si ces patients dans le traitement précédent montrent une progression avec une thérapie combinée contenant bortezomib.

Appendix 7.3. Medical literature: Search for evidence

Appendix 7.3.1. Search medical literature (systematic reviews)

The search for systematic reviews in MEDLINE, PreMedline, and the Cochrane library of systematic reviews (inception to search date) specifically developed for this research question, yielded 202 records (Figure 292). After de-duplication, 86 (2020-2017) of the remaining 181 reviews were screened based on title and abstract, of which 58 were excluded. In total 28 full text articles were assessed for eligibility. Based on full text evaluation, 23 reviews were excluded (Figure 293).



Figure 191 – Multiple myeloma – Selection of SRs - Study flow

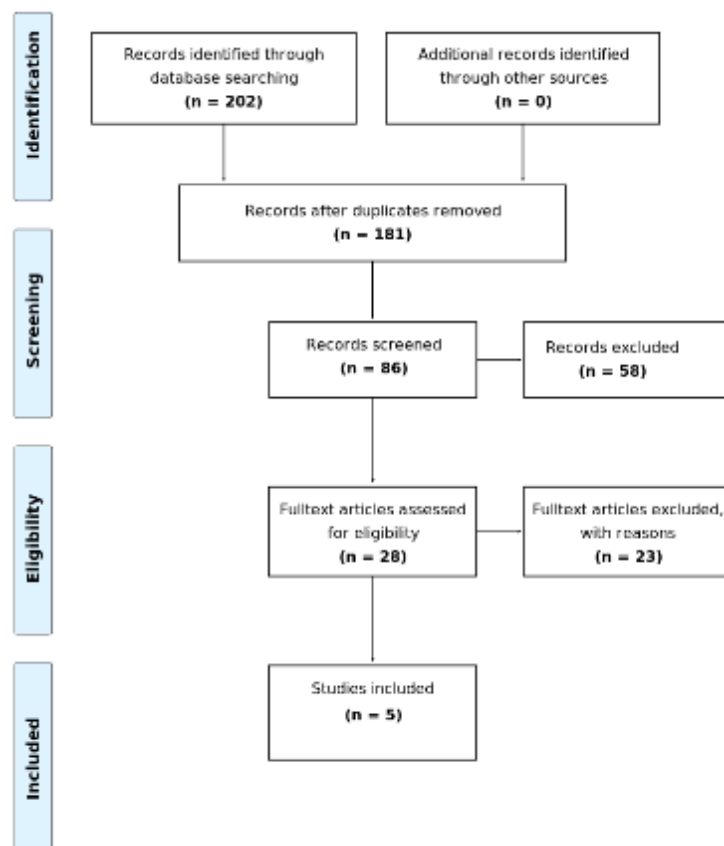


**Table 102 – Multiple myeloma: excluded reviews and reason for exclusion**

	Year	Publication	Reason for exclusion
1	2020	Chakraborty, R. Bin Riaz, I. Malik, S. U. et al. Venous thromboembolism risk with contemporary lenalidomide-based regimens despite thromboprophylaxis in multiple myeloma: A systematic review and meta-analysis. <i>Cancer</i> 2020;126(8):1640-1650	wrong outcomes
2	2020	Dhakal, B. Narra, R. K. Giri, S. et al. Association of adverse events and associated cost with efficacy for approved relapsed and/or refractory multiple myeloma regimens: A Bayesian network meta-analysis of phase 3 randomized controlled trials. <i>Cancer</i> 2020;126(12):2791-2801	Included for search (wrong outcomes)
3	2020	Musto, P. La Rocca, F. Monoclonal antibodies in relapsed/refractory myeloma: updated evidence from clinical trials, real-life studies, and meta-analyses. <i>Expert Rev Hematol</i> 2020;13(4):331-349	not a systematic review
4	2020	Zhang, S. Kulkarni, A. A. Xu, B. et al. Bortezomib-based consolidation or maintenance therapy for multiple myeloma: a meta-analysis. <i>Blood Cancer J</i> 2020;10(3):33	No additional information
5	2019	Zhao, A. L. Shen, K. N. Wang, J. N. Early or deferred treatment of smoldering multiple myeloma: a meta-analysis on randomized controlled studies. <i>Cancer Manag Res</i> 2019;11:5599-5611	wrong research question
6	2019	Cao, Y. Wan, N. Liang, Z. et al. Treatment Outcomes in Patients With Newly Diagnosed Multiple Myeloma Who Are Ineligible for Stem-Cell Transplantation: Systematic Review and Network Meta-analysis. <i>Clin Lymphoma Myeloma Leuk</i> 2019;19(8):e478-e488	No critical appraisal of included studies
7	2019	Mushtaq, A. Iftikhar, A. Hassan, H. et al. Pomalidomide-Based Regimens for Treatment of Relapsed and Relapsed/Refractory Multiple Myeloma: Systematic Review and Meta-analysis of Phase 2 and 3 Clinical Trials. <i>Clin Lymphoma Myeloma Leuk</i> 2019;19(7):447-461	No critical appraisal of included studies
8	2019	Piechotta, V. Jakob, T. Langer, P. et al. Multiple drug combinations of bortezomib, lenalidomide, and thalidomide for first-line treatment in adults with transplant-ineligible multiple myeloma: a network meta-analysis. <i>Cochrane Database of Systematic Reviews</i> 2019;11	Included
9	2019	Sekine, L. Ziegelmann, P. K. Manica, D. et al. Upfront treatment for newly diagnosed transplant-ineligible multiple myeloma patients: A systematic review and network meta-analysis of 14,533 patients over 29 randomized clinical trials. <i>Crit Rev Oncol Hematol</i> 2019;143:102-116	No additional information
10	2019	Blommestein, H. M. van Beurden-Tan, C. H. Y. Franken, M. G. Efficacy of first-line treatments for multiple myeloma patients not eligible for stem cell transplantation: a network meta-analysis. <i>Haematologica</i> 2019;104(5):1026-1035	No new information
11	2019	Li, T. Timmins, H. C. King, T. et al. Characteristics and risk factors of bortezomib induced peripheral neuropathy: A systematic review of phase III trials. <i>Hematol Oncol</i> 2019;24	wrong outcomes
12	2019	Sekine, L. Ziegelmann, P. K. Manica, D. et al. Frontline treatment for transplant-eligible multiple myeloma: A 6474 patients network meta-analysis. <i>Hematol Oncol</i> 2019;37(1):62-74	Included
13	2020	Ramasamy, K. Dhanasiri, S. Thom, H. et al. Relative efficacy of treatment options in transplant-ineligible newly diagnosed multiple myeloma: results from a systematic literature review and network meta-analysis. <i>Leuk Lymphoma</i> 2020 Mar;61(3):668-679	No new information



	Year	Publication	Reason for exclusion
14	2019	Su, B. Zhu, X. Jiang, Y. et al. A meta-analysis of autologous transplantation for newly diagnosed multiple myeloma in the era of novel agents. <i>Leuk Lymphoma</i> 2019;60(6):1381-1388	Wrong research question
15	2019	Weisel, K. Sonneveld, P. Spencer, A. et al. A comparison of the efficacy of immunomodulatory-free regimens in relapsed or refractory multiple myeloma: a network meta-analysis. <i>Leuk Lymphoma</i> 2019;60(1):151-162	No additional information
16	2019	Fu, S. Wu, C. F. Wang, M. Lairson, D. R. Cost Effectiveness of Transplant, Conventional Chemotherapy, and Novel Agents in Multiple Myeloma: A Systematic Review. <i>Pharmacoeconomics</i> 2019;37(12):1421-1449	No full HTA report with primary economic evaluation
17	2019	Fu, S. Wu, C. F. Wang, M. Lairson, D. R. Cost Effectiveness of Transplant, Conventional Chemotherapy, and Novel Agents in Multiple Myeloma: A Systematic Review. <i>Pharmacoeconomics</i> 2019;37(12):1421-1449	Duplicate
18	2018	Sparano, F. Cavo, M. Niscola, P. et al. Patient-reported outcomes in relapsed/refractory multiple myeloma: a systematic review. <i>Support Care Cancer</i> 2018;26(7):2075-2090	Included
19	2018	Maiese, E. M. Ainsworth, C. Le Moine, J. G. et al. Comparative Efficacy of Treatments for Previously Treated Multiple Myeloma: A Systematic Literature Review and Network Meta-analysis. <i>Clin Ther</i> 2018;40(3):480-494	Wrong outcomes
20	2018	Luo, X. W. Du, X. Q. Li, J. L. et al. Treatment options for refractory/relapsed multiple myeloma: an updated evidence synthesis by network meta-analysis. <i>Cancer Manag Res</i> 2018;10:2817-2823	searched only one database, no critical appraisal
21	2018	Gay, F. Jackson, G. Rosinol, L. et al. Maintenance Treatment and Survival in Patients With Myeloma: A Systematic Review and Network Meta-analysis. <i>JAMA Oncol</i> 2018;4(10):1389-1397	No additional information
22	2018	Dimopoulos, M. A. Kaufman, J. L. White, D. et al. A Comparison of the Efficacy of Immunomodulatory-containing Regimens in Relapsed/Refractory Multiple Myeloma: A Network Meta-analysis. <i>Clin Lymphoma Myeloma Leuk</i> 2018;18(3):163-173	No additional information
23	2018	Buyukkaramikli, N. C. de Groot, S. Fayter, D. et al. Pomalidomide with Dexamethasone for Treating Relapsed and Refractory Multiple Myeloma Previously Treated with Lenalidomide and Bortezomib: An Evidence Review Group Perspective of an NICE Single Technology Appraisal. <i>Pharmacoeconomics</i> 2018;36(2):145-159	Not a systematic review
24	2017	Zhang, T. Wang, S. Lin, T. et al. Systematic review and meta-analysis of the efficacy and safety of novel monoclonal antibodies for treatment of relapsed/refractory multiple myeloma. <i>Oncotarget</i> 2017;8(20):34001-34017	No additional information
25	2017	van Beurden-Tan, C. H. Y. Franken, M. G. Blommestein, H. M. et al. Systematic Literature Review and Network Meta-Analysis of Treatment Outcomes in Relapsed and/or Refractory Multiple Myeloma. <i>J Clin Oncol</i> 2017;35(12):1312-1319	no critical appraisal, PFS only
26	2017	Chen, R. Wang, Y. Luan, C. et al. Effect of pomalidomide on relapsed/refractory multiple myeloma: a systematic review and meta-analysis. <i>J of Cancer</i> 2017;8(10):1801-1808	Included (OS taken from original study)



	Year	Publication	Reason for exclusion
27	2017	Botta, C. Ciliberto, D. Rossi, M. et al. Network meta-analysis of randomized trials in multiple myeloma: efficacy and safety in relapsed/refractory patients. Blood Adv 2017;1(7):455-466	No additional information
28	2017	Aguiar, P. M. de Mendonca Lima, T. Colleoni, G. W. B. Storpirtis, S. Efficacy and safety of bortezomib, thalidomide, and lenalidomide in multiple myeloma: An overview of systematic reviews with meta-analyses. Crit Rev Oncol Hematol 2017;113:195-212	Review of reviews

Appendix 7.3.2. Critical appraisal systematic reviews

		Piechotta 2019 ¹³⁷		Chen 2017 ¹³⁸	
		Score	Rationale/comment	score	Rationale/comment
1.	PICO	Y		Y	
2.	A priori study design	(partial) Y	Did not check content	N	
3.	Inclusion study designs	Y		Y	
4.	Comprehensive literature search	Y		Partial Yes	No search of trial registries
5.	Duplicate study selection	Y		N	(unclear)
6.	Duplicate data extraction	Y		Y	
7.	List of excluded studies and rationale	Y		N	
8.	Characteristics of included studies provided	Y		Y	
9.	Assessment of risk of bias	Y		Y	
10.	Sources of funding reported	Y		N	
11.	Appropriate methods to combine findings	Y		NA	
12.	Assessment of impact RoB in included studies on results MA	Y		N	
13.	RoB assessment used in interpretation of results and in conclusions	Y		N	
14.	Explanation for and discussion of any observed heterogeneity	Y		NA	
15.	Adequate investigation of publication bias and its impact on the results	N		N	



	Piechotta 2019 ¹³⁷		Chen 2017 ¹³⁸	
	Score	Rationale/comment	score	Rationale/comment
16. Potential sources of conflict of interest reported	Y		Y	

	Sekine 2019 ¹³⁹		Sparano 2018 ¹⁴⁰	
	Score	Rationale/comment	Score	Rationale/comment
1. PICO	Y		Y	
2. A priori study design	(partial) Y	Did not check content	N	
3. Inclusion study designs	Y		Y	
4. Comprehensive literature search	partial Y	No search of trial registries, no involvement of content experts	Partial Y	No search of trial registries
5. Duplicate study selection	Y		Y	
6. Duplicate data extraction	Y		Y	(unclear)
7. List of excluded studies and rationale	N		N	
8. Characteristics of included studies provided	Y		Y	
9. Assessment of risk of bias	Y		N	
10. Sources of funding reported	N	No funding received for NMA, funding of individual studies not reported	N	
11. Appropriate methods to combine findings	Y		NA	
12. Assessment of impact RoB in included studies on results MA	N		N	
13. RoB assessment used in interpretation of results and in conclusions	Y		N	
14. Explanation for and discussion of any observed heterogeneity	N	Only general statement 'Heterogeneity among protocols included in the same group of comparison should not be overlooked.'	NA	
15. Adequate investigation of publication bias and its impact on the results	N		N	



Sekine 2019 ¹³⁹			Sparano 2018 ¹⁴⁰	
	Score	Rationale/comment	Score	Rationale/comment
16. Potential sources of conflict of interest reported	Y	None declared	Y	

Dhakal 2020 ¹⁴¹			
	Score	Rationale/comment	
1. PICO	Y		
2. A priori study design	Y		
3. Inclusion study designs	Y		
4. Comprehensive literature search	Partial Y	reference lists not searched	
5. Duplicate study selection	N	Unclear	
6. Duplicate data extraction	Y		
7. List of excluded studies and rationale	N		
8. Characteristics of included studies provided	Y		
9. Assessment of risk of bias	Y		
10. Sources of funding reported	N	funding of included studies not reported	
11. Appropriate methods to combine findings	Y		
12. Assessment of impact RoB in included studies on results MA	N		
13. RoB assessment used in interpretation of results and in conclusions	N		
14. Explanation for and discussion of any observed heterogeneity	N		
15. Adequate investigation of publication bias and its impact on the results	N		
16. Potential sources of conflict of interest reported	Y		



Appendix 7.3.3. Search strategy

Appendix 7.3.3.1. Cochrane library of systematic reviews

Date	23/06/2020 23:51:17	
Database	Cochrane@Wiley.com	
Search strategy		
#1	[mh "multiple myeloma"]	1554
#2	((('plasma cell' or 'plasma cells') NEAR/3 myeloma?):ab,ti	254
#3	((kahler or "kahler's" or kahlers) NEAR/3 disease):ab,ti	7
#4	(multiple NEAR/3 myeloma?):ab,ti	4385
#5	((neoplasm* or cancer* or tumor* or tumour*) NEAR/3 ("plasma cell" or "plasma cells")):ab,ti	37
#6	("myeloma-multiple" or "myelomas-multiple"):ab,ti	0
#7	myelomatos*:ab,ti	38
#8	"morbus kahler":ab,ti	0
#9	"myeloma multiplex":ab,ti	1
#10	((leucemia? or leucaemia? or leukemia? or leukaemia?) NEAR/3 ('plasma cell' or 'plasma cells')):ab,ti	787
#11	((leucemia? or leucaemia? or leukemia? or leukaemia?) NEAR/3 (plasmocyt* or plasmacyt*)):ab,ti	1
#12	#2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11	5214
#13	#1 or #12	5444
#14	[mh ^"lenalidomide"]	373
#15	lenalidomide:ab,ti	1787
#16	Revlimid:ab,ti	167
#17	Revimid:ab,ti	0
#18	"IMiD3 Cpd":ab,ti	0
#19	"imid 3":ab,ti	3
#20	"CC 5013":ab,ti	64
#21	CC5013:ab,ti	1
#22	F0P408N6V4:ab,ti	0
#23	"SYP-1512":ab,ti	1
#24	SYP1512:ab,ti	0
#25	"CDC-501":ab,ti	4
#26	CDC501:ab,ti	0
#27	cdc5013:ab,ti	0
#28	"cdc 5013":ab,ti	2
#29	"enmd 0997":ab,ti	0
#30	enmd0997:ab,ti	0



#31	"191732-72-6":ab,ti	69
#32	#15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31	1821
#33	#14 or #32	1832
#34	[mh ^"bortezomib"]	424
#35	bortezomib:ab,ti	1763
#36	Velcade:ab,ti	252
#37	"LDP 341":ab,ti	0
#38	LDP341:ab,ti	1
#39	"PS 341":ab,ti	27
#40	PS341:ab,ti	3
#41	69G8BD63PP:ab,ti	0
#42	"NSC-681239":ab,ti	2
#43	NSC681239:ab,ti	0
#44	"mg 341":ab,ti	0
#45	mg341:ab,ti	0
#46	"mln 341":ab,ti	0
#47	mln341:ab,ti	1
#48	"179324-69-7":ab,ti	57
#49	"197730-97-5":ab,ti	0
#50	#35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49	1828
#51	#34 or #50	1854
#52	pomalidomide:ab,ti	294
#53	ACTIMID:ab,ti	0
#54	IMNOVID:ab,ti	14
#55	POMALYST:ab,ti	5
#56	D2UX06XLB5:ab,ti	0
#57	"IMID 3":ab,ti	3
#58	"CC-4047":ab,ti	19
#59	CC4047:ab,ti	5
#60	"IMID-3":ab,ti	3
#61	IMID3:ab,ti	0
#62	aminothalidomide:ab,ti	0
#63	"19171-19-8":ab,ti	17
#64	"443912-23-0":ab,ti	0
#65	"443919-33-3":ab,ti	0
#66	#52 or #53 or #54 or #55 or #56 or #57 or #58 or #59 or #60 or #61 or #62 or #63 or #64 or #65	299
#67	#33 or #51 or #66	3163
#68	#13 and #67	2078



#69	[mh "angiogenesis inhibitors"]	1093
#70	[mh "proteasome inhibitors"]	30
#71	[mh ^"Ikaro Transcription Factor"/AI]	0
#72	[mh "immunologic factors"]	8153
#73	#69 or #70 or #71 or #72	9266
#74	(angiogenesis NEAR/5 (inhibit* or antagonist? or target* or block* or against or anti or "multi-target" or "multi-targets" or "multi-targeting" or reduc*)):ab,ti	668
#75	(proteasome NEAR/5 (inhibit* or antagonist? or target* or block* or against or anti or "multi-target" or "multi-targets" or "multi-targeting" or reduc*)):ab,ti	503
#76	(ikaros NEAR/5 (inhibit* or antagonist? or target* or block* or against or anti or "multi-target" or "multi-targets" or "multi-targeting" or reduc*)):ab,ti	9
#77	(ikzf* NEAR/5 (inhibit* or antagonist? or target* or block* or against or anti or "multi-target" or "multi-targets" or "multi-targeting" or reduc*)):ab,ti	3
#78	immunomodulator?:ti	580
#79	#74 or #75 or #76 or #77 or #78	1751
#80	#73 or #79	10798
#81	#13 and #80	488
#82	((("new class" or "new classes" or innovative or target*) NEAR/3 (drug? or therapy or therapies or therapeutic* or treatment? or chemotherap*)):ab,ti	11940
#83	#13 and #82	83
#84	#68 or #81 or #83	2280
Comments	Cochrane database of systematic reviews: 3	



Appendix 7.3.3.2. Medline + PreMedline

Date	June 22, 2020	
Database	Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946 to June 22, 2020>	
Search strategy		
1	exp multiple myeloma/	40919
2	('plasma cell?' adj3 myeloma?).ab,ti,kf.	3186
3	((kahler or kahler's or kahlers) adj3 disease).ab,ti,kf.	226
4	(multiple adj3 myeloma?).ab,ti,kf.	37621
5	((neoplasm* or cancer* or tumor*) adj3 plasma-cell?).ab,ti,kf.	1833
6	myeloma?-multiple.ab,ti,kf.	57
7	myelomatos*.ab,ti,kf.	767
8	morbus kahler.ab,ti,kf.	3
9	myeloma multiplex.ab,ti,kf.	33
10	(leu#?emia? adj3 plasma cell?).ab,ti,kf.	1181
11	(leu#?emia? adj3 plasm#cyt*).ab,ti,kf.	178
12	2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11	41622
13	1 or 12	53277
14	lenalidomide/	2613
15	lenalidomide.ab,ti,kf,rn.	4617
16	Revlimid.ab,ti,kf,rn.	131
17	Revimid.ab,ti,kf,rn.	9
18	IMiD3 Cpd.ab,ti,kf,rn.	0
19	imid 3.ab,ti,kf,rn.	6
20	CC 5013.ab,ti,kf,rn.	57
21	CC5013.ab,ti,kf,rn.	10
22	F0P408N6V4.ab,ti,kf,rn.	2613
23	SYP-1512.ab,ti,kf,rn.	0
24	SYP1512.ab,ti,kf,rn.	0
25	CDC-501.ab,ti,kf,rn.	1
26	CDC501.ab,ti,kf,rn.	0
27	cdc5013.ab,ti,kf,rn.	0
28	cdc 5013.ab,ti,kf,rn.	0
29	"enmd 0997".ab,ti,kf,rn.	2
30	enmd0997.ab,ti,kf,rn.	0
31	191732-72-6.ab,ti,kf,rn.	0
32	15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31	4650



33	14 or 32	4650
34	bortezomib/	5618
35	bortezomib.ab,ti,kf,rn.	8981
36	Velcade.ab,ti,kf,rn.	530
37	LDP 341.ab,ti,kf,rn.	5
38	LDP341.ab,ti,kf,rn.	1
39	PS 341.ab,ti,kf,rn.	377
40	PS341.ab,ti,kf,rn.	47
41	69G8BD63PP.ab,ti,kf,rn.	5618
42	NSC-681239.ab,ti,kf,rn.	2
43	NSC681239.ab,ti,kf,rn.	0
44	mg 341.ab,ti,kf,rn.	5
45	mg341.ab,ti,kf,rn.	2
46	mln 341.ab,ti,kf,rn.	1
47	mln341.ab,ti,kf,rn.	3
48	179324-69-7.ab,ti,kf,rn.	0
49	197730-97-5.ab,ti,kf,rn.	0
50	35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49	9106
51	34 or 50	9106
52	pomalidomide.ab,ti,kf,rn.	745
53	ACTIMID.ab,ti,kf,rn.	27
54	IMNOVID.ab,ti,kf,rn.	7
55	POMALYST.ab,ti,kf,rn.	17
56	D2UX06XLB5.ab,ti,kf,rn.	389
57	IMID 3.ab,ti,kf,rn.	6
58	CC-4047.ab,ti,kf,rn.	57
59	CC4047.ab,ti,kf,rn.	4
60	IMID-3.ab,ti,kf,rn.	6
61	IMID3.ab,ti,kf,rn.	4
62	aminothalidomide.ab,ti,kf,rn.	2
63	19171-19-8.ab,ti,kf,rn.	1
64	443912-23-0.ab,ti,kf,rn.	0
65	443919-33-3.ab,ti,kf,rn.	0
66	52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65	782
67	33 or 51 or 66	12380
68	13 and 67	6501
69	exp angiogenesis inhibitors/	57134
70	exp proteasome inhibitors/	4345



71	Ikaros Transcription Factor/ai [Antagonists & Inhibitors]	10
72	exp immunologic factors/	1373981
73	69 or 70 or 71 or 72	1404340
74	(angiogenesis adj5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)).ab,ti,kf.	24149
75	(proteasome adj5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)).ab,ti,kf.	14414
76	(ikaros adj5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)).ab,ti,kf.	133
77	(ikzf* adj5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)).ab,ti,kf.	59
78	immunomodulator?.ti,kf.	9326
79	74 or 75 or 76 or 77 or 78	47785
80	73 or 79	1433903
81	13 and 80	18668
82	((new class* or innovative or target*) adj3 (drug? or therapy or therapies or therapeutic* or treatment? or chemotherap*)).ab,ti,kf.	330072
83	13 and 82	2416
84	68 or 81 or 83	22417
85	((systematic review or systematic literature review or systematic scoping review or systematic narrative review or systematic qualitative review or systematic evidence review or systematic quantitative review or systematic meta-review or systematic critical review or systematic mixed studies review or systematic mapping review or systematic cochrane review or "systematic search and review" or systematic integrative review).ti. not comment.pt. not (protocol or protocols).ti. not medline.st.) or (Cochrane Database Syst Rev.ja. and review.pt.) or systematic review.pt.	159328
86	meta-analys*.ti.	108916
87	meta-analysis.pt.	116279
88	exp Technology Assessment, Biomedical/	11062
89	health technology assessment.ti,kf.	1917
90	HtA.ti,kf.	593
91	85 or 86 or 87 or 88 or 89 or 90	252947
92	84 and 91	174
Comments		



Appendix 7.4. Economic literature

Appendix 7.4.1. Search economic literature (HTA reports)

The search strategy in CRD's HTA database identified 71 references (Table 103). In a first round, 12 references were selected based on a review of title, keywords and abstract. The 59 remaining references were excluded for the following reasons: intervention (43), design (10), or language (6). In a second round, the full text of the 12 selected references was reviewed. Seven references were excluded because of the wrong design (13). Five references were retained. These references are indicated in Table 104 with an asterix (*).

Furthermore, in May 2020, the website of the National Institute for Health Research (NIHR) was searched for relevant reports. The following search terms were used: lenalidomide (15 hits, 7 with a focus on multiple myeloma, all not previously identified); pomalidomide (7 hits, 3 with a focus on multiple myeloma, none not previously identified); and bortezomib (19 hits, 11 with a focus on multiple myeloma, 2 not previously identified). In November 2020, we also applied the search term daratumumab (5 hits, 3 with a focus on multiple myeloma, 1 not previously identified).

Finally, also in May 2020, the website of the National Institute for Health and Care Excellence (NICE) was searched. The following search terms were used: lenalidomide (38 hits, 6 relevant Technology Assessments (TAs), 5 not previously identified); pomalidomide (15 hits, 4 relevant TAs, 4 not previously identified); and bortezomib (36 hits, 7 relevant TAs, 4 not previously identified). In November 2020, we also applied the search term daratumumab (13 hits, 4 relevant TAs, 2 not previously identified).

An overview of the identified references is provided in Table 104.

Table 103 – Search strategy and results for CRD: HTA

Date			
Date covered	All		
Search Strategy	1	MeSH DESCRIPTOR Multiple Myeloma EXPLODE ALL TREES	180
	2	* IN HTA	17351
	3	#1 AND #2	71 references
Note	/		

**Table 104 – Multiple myeloma – Identified HTA reports for the selected drugs**

Selected reports	
Lenalidomide	
•	NICE, TA603. September 2019. Lenalidomide with bortezomib and dexamethasone for untreated multiple myeloma (terminated appraisal). ^{142 β}
•	NICE, TA587. June 2019. Lenalidomide plus dexamethasone for previously untreated multiple myeloma. ^{143 β} <ul style="list-style-type: none"> ○ Lenalidomide in combination with dexamethasone for previously untreated multiple myeloma [ID474] ^α → no link to full report.
•	NICE, TA586. June 2019. Lenalidomide plus dexamethasone for multiple myeloma after 1 treatment with bortezomib. ^{144 β} <ul style="list-style-type: none"> ○ Bacelar M, Durand A, Cooper C, Hyde C, Latimer N, Murray, D. The clinical and cost-effectiveness of lenalidomide for people who have received at least one prior therapy with bortezomib (partial review of TA171). Single Technology Appraisal NIHR HTA Programme (13/07/01), Matrix and Peninsula Technology Assessment Group, 2014.^{145 α}
•	NICE, TA171. June 2009 (updated June 2019). Lenalidomide for the treatment of multiple myeloma in people who have received at least 2 prior therapies. ^{146 * β} <ul style="list-style-type: none"> ○ Hoyle M, Rogers G, Garside R, Moxham T, Stein K. The clinical- and cost-effectiveness of lenalidomide for multiple myeloma in people who have received at least one prior therapy: an evidence review of the submission from celgene. Peninsula Technology Assessment Group (PenTAG). September 2008.^{147 α}
Pomalidomide	
•	NICE, TA602. September 2019. Pomalidomide with bortezomib and dexamethasone for treating relapsed or refractory multiple myeloma (terminated appraisal). ^{148 β}
•	NICE, TA427. January 2017. Pomalidomide for multiple myeloma previously treated with lenalidomide and bortezomib. ^{149 β} <ul style="list-style-type: none"> ○ Fayter D, Büyükkaramikli N, et al. (2016). Pomalidomide with dexamethasone for treating relapsed and refractory multiple myeloma after at least two regimens including lenalidomide and bortezomib (review of TA338): a Single Technology Assessment. York, Kleijnen Systematic Reviews Ltd.^{150 α}
Bortezomib	
•	NICE, TA603. September 2019. Lenalidomide with bortezomib and dexamethasone for untreated multiple myeloma (terminated appraisal). ^{142 β} <ul style="list-style-type: none"> ○ See lenalidomide
•	NICE, TA602. September 2019. Pomalidomide with bortezomib and dexamethasone for treating relapsed or refractory multiple myeloma (terminated appraisal). ^{148 β} <ul style="list-style-type: none"> ○ See pomalidomide
•	NICE, TA453. July 2017. Bortezomib for treating multiple myeloma after second or subsequent relapse (terminated appraisal). ^{151 β}
•	NICE, TA311. April 2014. Bortezomib for induction therapy in multiple myeloma before high-dose chemotherapy and autologous stem cell transplantation. ^{152 β} <ul style="list-style-type: none"> ○ Cooper K, Hartwell D, Copley V, Pickett K, Bryant J. Bortezomib for induction therapy in multiple myeloma before high dose chemotherapy and autologous stem cell transplantation: A Single Technology Appraisal. SHTAC. 2013.^{153 * α}
•	NICE, TA228. July 2011. Bortezomib and thalidomide for the first-line treatment of multiple myeloma. ^{154 β} <ul style="list-style-type: none"> ○ Picot J, Cooper K, Bryant J, Clegg A. The clinical effectiveness and cost-effectiveness of bortezomib and thalidomide in combination regimens with an alkylating agent and a corticosteroid for the first-line treatment of multiple myeloma: a systematic review and economic evaluation. Health Technol Assess 2011;15(41).^{155 * α} ○ Cooper K, Picot J, Bryant J, Clegg A. Comparative cost-effectiveness models for the treatment of multiple myeloma. Int J Technol Assess Health Care. 2014;30(1):90-7.^{156 α} → the above full report was considered.
•	NICE, TA129. October 2007. Bortezomib monotherapy for relapsed multiple myeloma. ^{157 * β}



- Bryant J, Takeda A, Cooper K, Clegg A, Smith A, Stephens M. Bortezomib for the treatment of multiple myeloma patients. Southampton Health Technology Assessments Centre. April 2006.^{158 α}
- Green C, Bryant J, Takeda A, Cooper K, Clegg A, Smith A, et al. Bortezomib for the treatment of multiple myeloma patients. Health Technol Assess 2009;13(Suppl 1 Article 5).^{159 * α}

Daratumumab

- NICE, TA573. April 2019. Daratumumab with bortezomib and dexamethasone for previously treated multiple myeloma.^{160 β}
 - Kalita N, Pickett K, Lord J, Frampton G, Yao GL, Picot J. Daratumumab in combination with bortezomib and dexamethasone for treating relapsed or refractory multiple myeloma: A Single Technology Appraisal. SHTAC 2018.^{161 α}
- NICE, TA510. March 2018. Daratumumab monotherapy for treating relapsed and refractory multiple myeloma.^{162 β}
 - Daratumumab for treating relapsed and refractory multiple myeloma [ID933] ^α → no link to full report.
- NICE, TA634. June 2020. Daratumumab with lenalidomide and dexamethasone for untreated multiple myeloma (terminated appraisal).^{163 β}
- NICE, TA454. July 2017. Daratumumab with lenalidomide and dexamethasone for treating relapsed or refractory multiple myeloma (terminated appraisal).^{164 β}

Excluded reports**Lenalidomide**

- NICE, TA505. February 2018. Ixazomib with lenalidomide and dexamethasone for treating relapsed or refractory multiple myeloma.^{165 β}
 - Armoiry X, Cummins E, Connock M, Tsertsvadze A, Melendez-Torres GJ, Royle P, Munro K, Court R, Clarke A. Ixazomib citrate in combination with lenalidomide and dexamethasone for relapsed refractory multiple myeloma: A Single Technology Appraisal. Warwick Evidence, 2017.^{166 α}
 - The intervention assessed in this technology appraisal is ixazomib.
- NICE, TA454. July 2017. Daratumumab with lenalidomide and dexamethasone for treating relapsed or refractory multiple myeloma (terminated appraisal).¹⁶⁴
 - No details on the intervention and the comparator were found as the appraisal is terminated.

Pomalidomide

- NICE, TA338. March 2015. Pomalidomide for relapsed and refractory multiple myeloma previously treated with lenalidomide and bortezomib.^{167 β}
 - Pomalidomide for treating relapsed and refractory multiple myeloma previously treated with both lenalidomide and bortezomib(ID666) ^α → No link to full report.
 - Only link to journal article: Büyükkaramikli NC, de Groot S, Fayter D, Wolff R, Armstrong N, Stirk L et al. Pomalidomide with Dexamethasone for Treating Relapsed and Refractory Multiple Myeloma Previously Treated with Lenalidomide and Bortezomib: An Evidence Review Group Perspective of an NICE Single Technology Appraisal Pharmacoeconomics 2018.^{168 α}
 - This guidance has been updated and replaced by NICE technology appraisal guidance 427.
- NICE, Evidence summary ESNM32. February 2014. Relapsed and refractory multiple myeloma: pomalidomide. ^β
 - This evidence summary has been replaced by NICE technology appraisal guidance 338 [Replaced by NICE technology appraisal guidance 427].

* These references were identified in CRD's HTA database. ^α References identified on NIHR's website. ^β References identified on NICE's website.



Appendix 7.4.2. Results economic literature (HTA reports)

Appendix 7.4.2.1. NICE, TA603 (2019): lenalidomide

- “NICE is unable to make a recommendation about the use in the NHS of lenalidomide with bortezomib and dexamethasone for untreated multiple myeloma in adults because Celgene did not provide an evidence submission.”¹⁴²

Appendix 7.4.2.2. NICE, TA587 (2019): lenalidomide

- QoL:
 - “EQ-5D data were collected directly in FIRST for lenalidomide plus dexamethasone. The company mapped EQ-5D data for bortezomib plus melphalan plus prednisone from European Organisation for Research and Treatment of Cancer (EORTC) data from the clinical trial.”¹⁴³
 - No underlying HTA report with further QoL details was identified.
- Results:
 - “The company's estimated deterministic incremental cost-effectiveness ratio (ICER) is £11,886 per quality-adjusted life year (QALY) gained for lenalidomide plus dexamethasone compared with bortezomib plus melphalan plus prednisone.”¹⁴³
 - “With the committee's preferred assumptions, the ICER was £19,654 per QALY gained (using the new, simple-discount PAS in the intervention arm and the existing complex PAS in the comparator arm) or was £26,713 per QALY gained (using the new, simple-discount PAS in both the intervention and comparator arms), which is within the range NICE usually considers a cost-effective use of NHS resources.”¹⁴³
 - No underlying HTA report with further details on the results (IE, IC) was identified.
- Uncertainty and sensitivity:
 - “Because there was no trial directly comparing lenalidomide plus dexamethasone with bortezomib plus melphalan plus prednisone, the company did an indirect treatment comparison to compare them.” ... “(...) there was uncertainty because the network included few trials overall.”¹⁴³
 - “Based on the evidence presented, and acknowledging potential confounding, the committee concluded that lenalidomide plus dexamethasone was more clinically effective than bortezomib plus melphalan plus prednisone, although by how much was uncertain.”¹⁴³
 - “The tornado diagram showed that the ICER was insensitive to varying most parameters, except the hazard ratio for overall survival between lenalidomide plus dexamethasone and bortezomib plus melphalan plus prednisone. The committee recalled that the credible interval for this parameter in the indirect comparison was wide.”¹⁴³



- Conclusions:
 - “The most plausible cost-effectiveness estimate for lenalidomide plus dexamethasone for people unable to take thalidomide is within the range that NICE normally considers a cost-effective use of NHS resources. Because of this and the high unmet need, lenalidomide plus dexamethasone can be recommended for people unable to take thalidomide.”¹⁴³
 - “The committee concluded that, despite the uncertainties, lenalidomide plus dexamethasone would be a cost-effective first-line treatment option for people who are not eligible for a stem cell transplant and who cannot take thalidomide. It therefore recommended lenalidomide plus dexamethasone for routine commissioning.”¹⁴³
- (Confidential) price:
 - “The company has a commercial arrangement. This makes lenalidomide available to the NHS with a discount. The size of the discount is commercial in confidence.”¹⁴³
 - “The committee was aware that both the company's and ERG's ICERs included the new, simple-discount patient access scheme (PAS) in the intervention arm and the existing complex PAS (cost capped after 26 cycles) in the comparator arm to reflect the assumption that the new PAS would take effect only if NICE produces positive guidance. However, the committee was aware that, because NHS England had concerns about the operation of the complex PAS, it had renegotiated this scheme with the company. Therefore, the committee considered that there was merit in considering ICERs with the simple-discount PAS applied in both the intervention and comparator arms.”¹⁴³



Reference Costs (list prices & remarks)	Population, Intervention & comparator IC, IE and ICERs	Remarks on use of generic utility instrument (e.g. EQ-5D) to measure impact on QoL in economic evaluations	Most uncertain variables or important variables in sensitivity analysis
Lenalidomide plus dexamethasone			
NICE, TA587 (2019) ¹⁴³	Adults with previously untreated multiple myeloma who are not eligible for transplant and in whom thalidomide is unsuitable. Lenalidomide plus dexamethasone compared with bortezomib plus melphalan plus prednisone		
List prices, negotiated discounts (PAS) are hidden. Drug cost per 28-day cycle: the list price of lenalidomide varies from £3426 (2.5 mg) to £4368 (25 mg) for 21 capsules*	Results of the incremental analysis (ERG): - using the new, simple-discount PAS in the intervention arm and the existing complex PAS in the comparator arm: £19 654/QALY gained - using the new, simple-discount PAS in both the intervention and comparator arms: £26 713/QALY gained. Conclusion: despite the uncertainties, lenalidomide plus dexamethasone is a cost-effective first-line treatment option for people who are not eligible for a stem cell transplant and who cannot take thalidomide	There was no head-to-head trials comparing the interventions under consideration. Utility estimates: - For the intervention: EQ-5D data collected from the FIRST trial - For the comparator: EQ-5D mapped data	Results sensitive to the hazard ratio for overall survival

* The list price of Lenalidomide for a 21-capsule pack varies according to capsule size: £3426 (2.5 mg), £3570 (5 mg), £3675 (7.5 mg), £3780 (10 mg), £3969 (15 mg), £4168 (20 mg) and £4368 (25 mg). ERG: evidence review group, PAS: patient access scheme.



Appendix 7.4.2.3. NICE, TA586 (2019): lenalidomide

- QoL:
 - “It [The committee] noted that the company took EQ-5D utility values from a model by van Agthoven et al. (2004). The original source of these utility values was a 2002 PhD thesis which, to the committee's knowledge, had not been published in a peer-reviewed journal when discussed at the committee's first meeting.”¹⁴⁴
 - No further information on QoL was identified in the underlying HTA report from Bacelar (2014).¹⁴⁵ This report is 5 years older than the NICE TA586.
- Results:
 - “The company's ICER corresponding with this scenario [with the simple-discount PAS applied in both the intervention and comparator arms] exceeded £30,000 per QALY gained. The committee took into account the ERG's different estimate of progression-free survival with dexamethasone, noting that this resulted in a broadly similar ICER to the company's.”¹⁴⁴
 - “The committee was aware that both the company's and ERG's analyses still assumed that melphalan had the same clinical effectiveness as dexamethasone, and the committee agreed that melphalan was likely to be more effective than dexamethasone. This meant that the ICERs were underestimated.”¹⁴⁴
 - Therefore, the committee considered that the most plausible ICER for lenalidomide plus dexamethasone compared with melphalan was higher than the company's and ERG's ICERs, although how much higher was uncertain. It concluded that the most plausible ICER may be higher than £30,000 per QALY gained.
 - No further information was identified in the underlying HTA report from Bacelar (2014).¹⁴⁵ This report is 5 years older than the NICE TA586.
- Uncertainty and sensitivity:
 - “The committee concluded that there was a limited evidence base to support the utility values and this added to the uncertainty in the model.”¹⁴⁴
 - “The June 2016 modelling used direct trial data from MM-009 and MM-010 and assumed that melphalan had the same clinical effectiveness as dexamethasone” (...) “The company stated that the assumption of equivalence was supported by a randomised controlled trial comparing 4 treatments, including melphalan plus prednisolone and including dexamethasone in patients who had not had previous treatment (Facon et al. 2006). The trial showed no difference in overall survival (the primary endpoint) between dexamethasone and melphalan. The committee was not convinced that melphalan had the same clinical effectiveness as dexamethasone because Facon et al. showed that progression-free survival was longer with melphalan. It was also aware that Facon et al. did not recruit enough patients, based on the sample size calculations, to detect a difference in survival. (...) The committee concluded that the analysis assuming equivalence may have underestimated the incremental cost-effectiveness ratio (ICER) for lenalidomide plus dexamethasone compared with melphalan.”¹⁴⁴



- Conclusions:
 - “The committee noted that the most plausible ICER may be above the range usually considered a cost-effective use of NHS resources. However, when making its decision, the committee took into account:
 - the unmet need for an alternative treatment option to cytotoxic chemotherapy for people who had 1 previous treatment, which included bortezomib
 - that lenalidomide is a cost-effective first-line treatment for people who cannot have thalidomide in a separate parallel appraisal
 - that the treatment pathway for multiple myeloma is likely to change and, if lenalidomide were to be available as a first-line treatment for people who cannot have thalidomide, fewer people would have lenalidomide as a second-line treatment after bortezomib
 - that, if it did not recommend lenalidomide for use after 1 previous treatment including bortezomib, people currently having bortezomib first line would continue to have less effective cytotoxic chemotherapy before moving on to more effective treatments, which it agreed was inappropriate.

Taking all these factors into account, the committee concluded that it was appropriate to recommend lenalidomide plus dexamethasone for treating multiple myeloma in adults who have had only 1 previous therapy, which included bortezomib.”¹⁴⁴
- (Confidential) price:
 - “The committee was aware that this [company] ICER included the new, simple-discount patient access scheme (PAS) in the intervention arm and the existing complex PAS (cost capped after 26 cycles) in the comparator arm to reflect the assumption that the new PAS would take effect only if NICE produces positive guidance. However, the committee was aware that, because NHS England had concerns about the operation of the complex PAS, it had renegotiated this scheme with the company. Therefore, the committee considered that there was merit in considering ICERs with the simple-discount PAS applied in both the intervention and comparator arms.”¹⁴⁴



Reference Costs (list prices & remarks)	Population, Intervention & comparator IC, IE and ICERs	Remarks on use of generic utility instrument (e.g. EQ- 5D) to measure impact on QoL in economic evaluations	Most uncertain variables or important variables in sensitivity analysis
Lenalidomide plus dexamethasone			
NICE, TA586 (2019) ¹⁴⁴ Bacelar (2014) ¹⁴⁵	Adult patients with multiple myeloma who cannot have a stem cell transplant or first-line thalidomide, and who have already had bortezomib Lenalidomide plus dexamethasone compared with cytotoxic chemotherapy (melphalan plus prednisolone)		
List prices, negotiated discounts (PAS) are hidden. Drug cost per 28-day cycle: the list price of lenalidomide varies from £3426 (2.5 mg) to £4368 (25 mg) for 21 capsules*	Results from the company's base-case analyses (with the simple-discount PAS applied in both the intervention and comparator arms): over £30 000/QALY gained. ERG estimate resulted in similar ICER to the company. Remark: The underlying HTA report dates back to 2014. No further information was identified in this report. Conclusion: Lenalidomide plus dexamethasone is recommended in this indication despite the ICER exceeding the threshold (see text).	There was no head-to-head trials comparing the interventions under consideration. EQ-5D utilities taken from Agthoven et al. (2004). ¹⁶⁹ The source is an unpublished PhD thesis (2002).	Impact on OS and QoL was uncertain.

* The list price of Lenalidomide for a 21-capsule pack varies according to capsule size: £3426 (2.5 mg), £3570 (5 mg), £3675 (7.5 mg), £3780 (10 mg), £3969 (15 mg), £4168 (20 mg) and £4368 (25 mg). OS: overall survival, PAS: patient access scheme.



Appendix 7.4.2.4. NICE, TA171 (2009): lenalidomide

- QoL:
 - “No utility or quality of life data was collected in the MM-009 and MM-010 trials. Utility values used in the Celgene model were taken from a cost-utility study carried out by van Agthoven and colleagues (2004) in people with myeloma of intensive chemotherapy alone versus intensive chemotherapy followed by myeloablative therapy with autologous stem cell rescue.”¹⁴⁷
 - “For the complete response, partial response and stable disease states [=progression-free survival], a utility value of 0.81 was used. (...) A utility value of 0.64 was applied to the progressive disease state. After 2 years, a utility value of 0.77 was applied to those patients whose disease had not progressed.”¹⁴⁶
- Results:
 - Manufacturer updated base-case: “(...) for patients who had received two or more prior therapies the incremental life-year gain was 2.77, the incremental QALY gain was 1.86 and the ICER was £30,350 per QALY gained. For patients who had received thalidomide as one of the prior therapies the incremental life-year gain was 2.51, the incremental QALY gain was 1.7 and the ICER was £28,941 per QALY gained.”¹⁴⁶
 - ERG base-case: “The ERG repeated the exploratory analysis on the updated model [of the manufacturer] using their preferred approach with the dexamethasone overall survival curve calibrated to the mean survival predicted from the MRC trials and the patient access scheme implemented in the model. For the subgroup of patients who had received two or more prior therapies, the incremental life-year gain was 1.81 and the incremental QALY gain was 1.24 at an incremental cost of £54,291, giving an ICER of £43,800 per QALY gained. For patients who had received thalidomide as one of the prior therapies, the incremental life-year gain was 1.71 and the incremental QALY gain was 1.15 at an incremental cost of £47,531, giving an ICER of £41,300 per QALY gained.”¹⁴⁶
- Uncertainty and sensitivity:
 - “The Committee noted that the variable that had the greatest impact on cost effectiveness was the method of calibrating the dexamethasone overall survival curve in the economic model (that is, to the predicted median or mean survival for the trial population) from the risk equation for survival derived from the MRC trials.”¹⁴⁶
 - “Accurate estimates of the utilities of patients in progression-free survival and post-progression survival separately for Len/Dex and Dex would be useful to allow more accurate estimates of cost-effectiveness.”¹⁴⁷
- Conclusions:
 - “In summary, the Committee was satisfied that the population and the technology of interest meet the criteria for accepting that this is an appraisal of a life-extending, end-of-life treatment and that the evidence presented for this consideration was supported by robust data.”¹⁴⁶
 - “The Committee subsequently considered the ERG's cost-effectiveness estimates using the manufacturer's model in the context of a life-extending, end-of-life treatment. It noted that the QALY increment associated with the most plausible cost-effectiveness estimates was approximately 1.24 QALYs. The Committee concluded that the additional weights that need to be attached to the QALYs to achieve ICERs within the normal threshold range are acceptable in these circumstances.”¹⁴⁶



- (Confidential) price:
 - “The pricing arrangement considered during guidance development was that the manufacturer (Celgene) had agreed a complex patient access scheme with the Department of Health” (...) “A commercial arrangement has now been agreed. This makes lenalidomide available to the NHS with a discount. The size of the discount is commercial in confidence.”¹⁴⁶

Reference Costs (list prices & remarks)	Population, Intervention & comparator IC, IE and ICERs	Remarks on use of generic utility instrument (e.g. EQ- 5D) to measure impact on QoL in economic evaluations	Most uncertain variables or important variables in sensitivity analysis																								
Lenalidomide																											
NICE, TA171 (2009) ¹⁴⁶ Hoyle (2008) ¹⁴⁷	Adults with multiple myeloma who had received two or more prior therapies Lenalidomide compared with high-dose dexamethasone																										
List prices, negotiated discounts (PAS) are hidden. Drug cost per 28-day cycle: the list price for 21 capsules of lenalidomide 25 mg is £4368	Results of the incremental analysis (with PAS for intervention): A) Patients who had received two or more prior therapies <table> <tr> <th></th><th>IC</th><th>QALY gained</th><th>ICER</th></tr> <tr> <td>Manufacturer</td><td>-</td><td>1.86</td><td>£30 350</td></tr> <tr> <td>ERG*</td><td>£54 291</td><td>1.24</td><td>£43 800</td></tr> </table> B) Patients who had received thalidomide as one of the prior therapies <table> <tr> <th></th><th>IC</th><th>QALY gained</th><th>ICER</th></tr> <tr> <td>Manufacturer</td><td>-</td><td>1.7</td><td>£28 941</td></tr> <tr> <td>ERG*</td><td>£47 531</td><td>1.15</td><td>£41 300</td></tr> </table> Remark: the results are appraised in the context of an end-of-life treatment. Conclusion: “The Committee concluded that the additional weights that need to be attached to the QALYs to achieve ICERs within the normal threshold range are acceptable in these circumstances”		IC	QALY gained	ICER	Manufacturer	-	1.86	£30 350	ERG*	£54 291	1.24	£43 800		IC	QALY gained	ICER	Manufacturer	-	1.7	£28 941	ERG*	£47 531	1.15	£41 300	EQ-5D was not measured in MM-009 and MM-010 trials. EQ-5D utility values obtained from Agthoven et al. (2004). ¹⁶⁹ The source is an unpublished PhD thesis (2002).	Results sensitive to the OS curve calibration method. QoL measure uncertain.
	IC	QALY gained	ICER																								
Manufacturer	-	1.86	£30 350																								
ERG*	£54 291	1.24	£43 800																								
	IC	QALY gained	ICER																								
Manufacturer	-	1.7	£28 941																								
ERG*	£47 531	1.15	£41 300																								

* Results after amendments made by ERG to the manufacturer's model using the ERG preferred approach with the dexamethasone overall survival curve calibrated to the mean (instead of the median) survival predicted from the MRC trials. OS: overall survival, PAS: patient access scheme.



Appendix 7.4.2.5. NICE, TA602 (2019): pomalidomide

- “NICE is unable to make a recommendation about the use in the NHS of pomalidomide with bortezomib and dexamethasone for treating relapsed or refractory multiple myeloma in adults because Celgene did not provide an evidence submission. The company has confirmed that it does not intend to make a submission for the appraisal because the technology is unlikely to be a cost-effective use of NHS resources.”¹⁴⁸

Appendix 7.4.2.6. NICE, TA427 (2017): pomalidomide

- QoL:
 - EQ-5D data were obtained from the MM-003 trial (pomalidomide vs conventional chemotherapy) to describe the disease-related characteristics (stable disease, progressive disease...). This approach to include QoL was judged as appropriate in the NICE review of the original appraisal.¹⁵⁰
- Results:
 - “Compared with conventional chemotherapy, the company's base-case ICER (corrected by the ERG) for pomalidomide with low-dose dexamethasone was £48,673 per quality-adjusted life year (QALY) gained. The committee was aware this was based on data directly from the MM-003 trial and was therefore less uncertain than the other comparisons.”¹⁴⁹
 - “Compared with bendamustine, the company's base-case ICER (corrected by the ERG) for pomalidomide with low-dose dexamethasone was £45,082 per QALY gained. (...) The committee concluded that the ICER (...) was associated with uncertainty, but was likely to be less than £50,000 per QALY gained.”¹⁴⁹
 - “The precise ICERs for pomalidomide compared with panobinostat cannot be reported because of a confidential patient access scheme for panobinostat.”¹⁴⁹
- Uncertainty and sensitivity:
 - “Because there was no direct evidence other than for conventional chemotherapy, the company selected individual treatment arms from available studies and ran separate analyses comparing pomalidomide and low-dose dexamethasone with each of the comparators.” (...) “The ERG's main concern with the company's analyses was that because the company used different datasets for pomalidomide in each comparison, a fully incremental analysis was not possible.”¹⁴⁹
 - “The ICERs varied based on the clinical datasets included, and using crossover adjustment and covariate adjustment methods.”¹⁴⁹
 - “The committee noted that results were associated with uncertainty, but was satisfied that a survival gain of 3.0 months was plausible.”¹⁴⁹
- Conclusions:
 - “The most plausible ICERs for pomalidomide with low-dose dexamethasone compared with conventional chemotherapy and bendamustine with thalidomide and dexamethasone were below £50,000 per QALY gained, and the committee concluded that pomalidomide meets the end-of-life criteria compared with bendamustine and conventional chemotherapy.”¹⁴⁹



- “The committee noted its conclusion (...) that the savings per QALY lost for pomalidomide compared with panobinostat were high enough for it to be considered a cost-effective use of NHS resources without applying the end-of-life criteria.”¹⁴⁹
- “The committee concluded that it could recommend pomalidomide with low-dose dexamethasone for treating relapsed and refractory multiple myeloma at third or subsequent relapse; that is, after 3 previous treatments including lenalidomide and bortezomib, as a cost-effective use of NHS resources, only when the company provides pomalidomide with the discount agreed in the patient access scheme.”¹⁴⁹
- (Confidential) price:
 - “The company has agreed a patient access scheme with the Department of Health. (...) The level of the discount is commercial in confidence.”¹⁴⁹

Reference Costs (list prices & remarks)	Population, Intervention & comparator IC, IE and ICERs	Remarks on use of generic utility instrument (e.g. EQ-5D) to measure impact on QoL in economic evaluations	Most uncertain variables or important variables in sensitivity analysis
Pomalidomide			
NICE, TA427 (2017) ¹⁴⁹ Fayter (2016) ¹⁵⁰	Adults with multiple myeloma who have received 3 or more previous treatments, including both lenalidomide and bortezomib Pomalidomide plus low-dose dexamethasone compared with: A) conventional chemotherapy B) bendamustine with thalidomide and dexamethasone C) panobinostat with bortezomib and dexamethasone		
List prices, negotiated discounts (PAS) are hidden. Drug cost per 28-day cycle*: the list price for 21 capsules of pomalidomide is £8884	Results from the company's base-case analyses (corrected by the ERG) for pomalidomide (including PAS) compared with: A) conventional chemotherapy: £48 673/QALY gained B) bendamustine: £45 082/QALY gained C) panobinostat: confidential ICER as confidential patient access scheme for panobinostat Remark: results are not incremental (rather pairwise comparisons) as different datasets were used in each comparison. Remark: the results for A and B are appraised in the context of an end-of-life treatment Conclusions: pomalidomide is a cost-effective use of NHS resources, only when pomalidomide is provided with PAS.	There was no head-to-head trials for the comparisons B and C. EQ-5D data for the disease stages were obtained from the MM3 trial (comparison A).	Gain is OS uncertain (for comparisons B and C)

* The drug is taken orally once daily on days 1 to 21 of repeated 28-day cycles. The average cost of a course of treatment is £44 420. ERG: evidence review group, OS: overall survival, PAS: patient access scheme.



Appendix 7.4.2.7. NICE, TA453 (2017): bortezomib

- “NICE is unable to make a recommendation about the use in the NHS of bortezomib for treating multiple myeloma after second or subsequent relapse because no evidence submission was received from Janssen–Cilag.”¹⁵¹

Appendix 7.4.2.8. NICE, TA311 (2014): bortezomib

- QoL:
 - “To inform the cost-effectiveness evidence, the manufacturer conducted a systematic literature search to identify publications relevant to the decision problem in relation to health-related quality of life. The manufacturer selected the van Agthoven study as the base-case source of utility values because the utility values were obtained using EQ-5D.”¹⁵²
- Results:
 - “(...) for bortezomib, thalidomide and dexamethasone compared with thalidomide and dexamethasone, the manufacturer's base-case using the MRC Myeloma VII data as the source for long-term survival resulted in an ICER of £17,800 per QALY gained. (...) incorporating data from the ERG's preferred Alvares and NMSG 5/94 studies resulted in ICERs of £22,700 and £39,600 per QALY gained respectively.”¹⁵²
 - “For bortezomib and dexamethasone compared with cyclophosphamide, thalidomide and dexamethasone, using the MRC Myeloma VII, Alvares and NMSG 5/94 data sources to inform overall survival in the model, the ICERs were £20,600, £24,300 and £33,400 per QALY gained respectively.”¹⁵²
 - “The Committee concluded that the ICERs based on survival data from the MRC Myeloma VII and Alvares study were appropriate for its decision making.”¹⁵²
- Uncertainty and sensitivity:
 - The Committee acknowledged that there was no direct evidence available to compare the bortezomib, thalidomide and dexamethasone and the bortezomib and dexamethasone regimens with cyclophosphamide, thalidomide and dexamethasone, and it asked the manufacturer to further explore this by conducting a further indirect comparison using single arms from the relevant clinical trials.”¹⁵²
 - “It [the Committee] concluded that although there was uncertainty in the magnitude of overall survival gain associated with bortezomib, it was plausible that bortezomib's impact on induction response could be associated with improved overall survival.”¹⁵²
 - “The manufacturer's deterministic sensitivity analyses highlighted that the results were most sensitive to the mortality for patients who had a complete response after the induction therapy, and to drug costs.”¹⁵²
- Conclusions:
 - “The Committee considered and explored a range of ICERs using several studies included in the submissions, and concluded that, on balance, the ICERs for bortezomib, thalidomide and dexamethasone compared with thalidomide and dexamethasone, and for bortezomib and dexamethasone compared with cyclophosphamide, thalidomide and dexamethasone (...), were likely to be below £30,000 per QALY gained. Therefore both bortezomib regimens could be considered a cost-effective use of NHS resources.”¹⁵²



- (Confidential) price:
 - No reference to confidential discounts is made in the 'Summary of Appraisal Committee's key conclusions' of TA311.

Reference Costs (list prices & remarks)	Population, Intervention & comparator IC, IE and ICERs	Remarks on use of generic utility instrument (e.g. EQ- 5D) to measure impact on QoL in economic evaluations	Most uncertain variables or important variables in sensitivity analysis
Bortezomib			
NICE, TA311 (2014) ¹⁵² Cooper (2013) ¹⁵³	Adults with previously untreated multiple myeloma, who are eligible for high-dose chemotherapy with haematopoietic stem cell transplantation Interventions compared: A) bortezomib plus thalidomide and dexamethasone compared with thalidomide and dexamethasone B) bortezomib and dexamethasone compared with cyclophosphamide, thalidomide and dexamethasone		
List prices Bortezomib costs £762 per 3.5 mg vial Average cost of a treatment course: - £12 261 (bortezomib plus dexamethasone) - £24 840 (bortezomib plus dexamethasone plus thalidomide)	Results of the manufacturer updated model (using different data sources for informing OS, as suggested by ERG): Comparison A): - MRC Myeloma VII: £17 800/QALY gained - Alvares: £22 700/QALY gained Comparison B): - MRC Myeloma VII: £20 600/QALY gained - Alvares: £24 300/QALY gained Conclusion: "bortezomib regimens could be considered a cost-effective use of NHS resources." Remark: The additional information on IC, IE and incremental QALYs provided in the underlying report by Cooper et al. (2013) ¹⁵³ is not relevant as the manufacturer model assessed in this report is an older version of the model assessed in NICE TA311.	There was no head-to-head trial comparing the interventions under consideration. EQ-5D utility values taken from Agthoven et al. (2004). ¹⁶⁹ The source is an unpublished PhD thesis (2002).	Gain in OS uncertain. Results most sensitive to: - mortality for patients with a complete response after induction therapy - drug costs

OS: overall survival, PAS: patient access scheme.



Appendix 7.4.2.9. NICE, TA228 (2011): bortezomib

- QoL:
 - “Health-related quality of life data were from a systematic review of studies of health-related quality of life. The Assessment Group did not identify any generic preference-based studies of people with untreated multiple myeloma who were not eligible for high-dose chemotherapy with stem cell transplantation, but did identify a study not identified by the manufacturers that assessed health-related quality of life in this group using the EORTC QLQ-C30. The Assessment Group mapped the EORTC QLQ-C30 to the EQ-5D using a validated mapping algorithm. The utility estimates used were 0.58 for the treatment health state and 0.68 for the post-treatment state.”¹⁵⁴
 - “A targeted search was therefore conducted for studies that mapped data from the EORTC QLQ-C30 onto the EQ-5D to enable the estimation of health state values based on EORTC QLQ-C30 data.”¹⁵⁵
- Results:
 - “The Committee noted that the Assessment Group’s scenario that assumed four cycles (equivalent to 31 vials used) gave an ICER of £19,000 per QALY gained for VMP [bortezomib plus melphalan and prednisolone/prednisone] compared with MP [melphalan and prednisolone/prednisone] and £320,000 per QALY gained for VMP compared with MPT [thalidomide, melphalan and prednisolone/prednisone].”¹⁵⁴
- Uncertainty and sensitivity:
 - “The key drivers of cost effectiveness of VMP compared with MPT were the inclusion of data from studies with maintenance treatment and the number of vials of bortezomib used.”¹⁵⁴
- Conclusions:
 - “Bortezomib in combination with an alkylating agent and a corticosteroid is recommended as an option for the first-line treatment of multiple myeloma if:
 - high-dose chemotherapy with stem cell transplantation is considered inappropriate **and**
 - the person is unable to tolerate or has contraindications to thalidomide.”¹⁵⁴
- (Confidential) price:
 - No reference to confidential discounts is made in the ‘Summary of Appraisal Committee’s key conclusions’ of TA228.



Reference Costs (list prices & remarks)	Population, Intervention & comparator IC, IE and ICERs	Remarks on use of generic utility instrument (e.g. EQ- 5D) to measure impact on QoL in economic evaluations	Most uncertain variables or important variables in sensitivity analysis
Bortezomib			
NICE, TA228 (2011) ¹⁵⁴ Picot (2011) ¹⁵⁵	Adults with newly diagnosed MM, who are not eligible for high-dose chemotherapy with stem cell transplantation Interventions compared: A) Bortezomib plus melphalan and prednisone (VMP) compared with melphalan and prednisone (MP) B) Bortezomib plus melphalan and prednisone (VMP) compared with thalidomide plus melphalan and prednisone (MPT)		
List prices Bortezomib costs £762 per 3.5 mg vial	Results of the ERG incremental analysis: A) £19 000/QALY gained for VMP versus MP B) £320 000/QALY gained for VMP versus MPT Conclusion: Bortezomib in combination with an alkylating agent and a corticosteroid is recommended for the first-line treatment of multiple myeloma if high-dose chemotherapy with stem cell transplantation is considered inappropriate and the person is unable to tolerate or has contraindications to thalidomide. Remark: No additional information on IC, IE and incremental QALYs was found in the underlying report by Picot (2011) ¹⁵⁵ as the cost-effectiveness model developed in this report is an older version of the model assessed in NICE TA228.	QoL was not measured in the underlying clinical trial (VISTA) EQ-5D utilities derived by the ERG through mapping EORTC QLQ-C30 data to EQ-5D using a validated algorithm	The exact number of vials of bortezomib used is uncertain

ERG: evidence review group.



Appendix 7.4.2.10. NICE, TA129 (2007): bortezomib

- QoL:
 - “The QALYs were derived using utility values of 0.81 for the pre-progression state, and 0.64 after progression, based on a published study of patients with previously untreated multiple myeloma.”¹⁵⁷
 - “We have tried to base this estimate on the least flawed of the published utility data and based this on data from van Agthoven et al., 2004¹⁶⁹.”¹⁵⁸
- Results:
 - “The Committee noted that the most cost-effective approach to using bortezomib was to treat patients at first relapse, to measure serum M protein after four cycles, to discontinue and rebate treatment in people whose disease had responded less than partially, and to continue treatment only in those whose disease had responded at least partially. This approach resulted in an ICER of £20,700 per QALY.”¹⁵⁷
- Uncertainty and sensitivity:
 - “The Committee was concerned that the utilities assumed for patients with relapsed multiple myeloma may not accurately reflect the significant impairments in QoL that these patients can experience.”¹⁵⁷
 - “The Committee agreed that because of the degree of crossover that occurred between the arms of the APEX trial it was necessary and justified to adjust the APEX data. However, the Committee was concerned that there was uncertainty about the impact of using data from the Mayo Observational Study to make these adjustments in the model and that the modelling approach may have overestimated the effect of bortezomib treatment in the long term. (...) [This] would therefore influence the modelling of both time to progression and overall survival for both bortezomib and HDD arms.”¹⁵⁷
- Conclusions:
 - “Bortezomib monotherapy is recommended as an option for the treatment of progressive multiple myeloma in people who are at first relapse having received one prior therapy and who have undergone, or are unsuitable for, bone marrow transplantation, under the following circumstances:
 - the response to bortezomib is measured using serum M protein after a maximum of four cycles of treatment, and treatment is continued only in people who have a complete or partial response (that is, reduction in serum M protein of 50% or more or, where serum M protein is not measurable, an appropriate alternative biochemical measure of response) and
 - the manufacturer rebates the full cost of bortezomib for people who, after a maximum of four cycles of treatment, have less than a partial response (as defined above).”¹⁵⁷
- (Confidential) price:
 - The Department of Health proposed response-based rebate scheme to the manufacturer, the ‘Velcade Response Scheme’. The manufacturer model was revised to reflect this rebate of bortezomib costs.



Reference Costs (list prices & remarks)	Population, Intervention & comparator IC, IE and ICERs	Remarks on use of generic utility instrument (e.g. EQ- 5D) to measure impact on QoL in economic evaluations	Most uncertain variables or important variables in sensitivity analysis
Bortezomib			
NICE, TA129 (2007) ¹⁵⁷ Bryant (2006) ¹⁵⁸ Green (2009) ¹⁵⁹	Adults at first relapse of multiple myeloma Bortezomib compared with high-dose dexamethasone (HDD)		
List prices Bortezomib costs £762 per 3.5 mg vial	ERG results (established from the manufacturer revised model to reflect a PAS applied to bortezomib costs): £20 700 per QALY gained for bortezomib versus HDD Remark: results including the manufacturer response-based rebate scheme. Remark: no additional information on IC, IE and incremental QALYs was found in the underlying reports by Bryant (2006) ¹⁵⁸ and Green (2009) ¹⁵⁹ as the manufacturer model assessed in those reports is an older version of the model assessed in NICE TA129. Conclusion: bortezomib is recommended provided the manufacturer rebates the full cost of bortezomib for people who, after a maximum of four cycles of treatment, have less than a partial response.	EQ-5D was not measured in the APEX trial. EQ-5D utility values taken from Agthoven et al. (2004). ¹⁶⁹ The source is an unpublished PhD thesis (2002).	Uncertain parameters: - Utilities for patients with relapsed multiple myeloma - Time to progression and overall survival for both bortezomib and HDD arms

ERG: evidence review group.



Appendix 7.4.2.11. NICE, TA573 (2019): daratumumab

- QoL:
 - Company model:
 - “The company model used health state utility values estimated from the CASTOR trial. As per the trial protocol, utility values obtained from EQ-5D-5L were assessed at the first day of each treatment cycle, end of treatment, post-treatment week 8 and post treatment week 16.”¹⁶¹
 - “Health state utilities are estimated from CASTOR, but are uncertain due to poor reporting. Health state utilities were estimated from the CASTOR trial, but the methods of analysis and results are poorly reported in the CS [company submission].”¹⁶¹
 - “The company state that there was no statistically significant difference in the utility scores between the two treatment arms. The company assumed the same utility for all patients in pre-progression health state across the two treatment arms: 0.7280 (95% CI 0.7062 to 0.7497). (...) For patients in the progressed health state, the company use an estimated utility of 0.6950 (95% CI 0.6511 to 0.7389).”¹⁶¹
 - ERG model:
 - “ENDEAVOR data mapped to EQ-5D with Proskorovsky algorithm.”¹⁶¹
 - “As such, it [the committee] considered that the ERG’s estimate of post-progression utility was more plausible than the company’s, even though it came from ENDEAVOR [which compared carfilzomib plus dexamethasone with bortezomib plus dexamethasone] and was not derived from EQ-5D data. (...) Either way, the committee agreed that the difference between the utility values before and after disease progression was underestimated, concluding that utility values from ENDEAVOR appeared more plausible.”¹⁶⁰
- Results:
 - “Because carfilzomib and some follow-on treatments in the model had confidential commercial access agreements, the exact incremental cost-effectiveness ratios (ICERs) for daratumumab plus bortezomib plus dexamethasone compared with bortezomib or carfilzomib (both plus dexamethasone) are confidential and cannot be reported here.”¹⁶⁰
 - “Using the company’s assumption on the long-term survival with daratumumab plus bortezomib plus dexamethasone (using an exponential extrapolation; see section 3.12) and utility values based on CASTOR (see section 3.14), the ICERs were between £30,000 and £40,000 per quality-adjusted life year (QALY) gained for both the comparison with bortezomib plus dexamethasone and with carfilzomib plus dexamethasone.”¹⁶⁰
 - “Using the ERG’s assumption on the long-term survival with daratumumab plus bortezomib plus dexamethasone (using a Weibull extrapolation) and utility values based on ENDEAVOR, the ICER was between £40,000 and £50,000 per QALY gained for the comparison with bortezomib plus dexamethasone and was higher for the comparison with carfilzomib plus dexamethasone.”¹⁶⁰
 - Precise ICERs and information about IC and IE are not provided in TA573¹⁶⁰ nor in the supporting HTA report.¹⁶¹



- Uncertainty and sensitivity:
 - “Overall survival data from CASTOR were immature because more than half the patients in both arms were still alive at the interim analysis presented in the company's original submission, after a median of 27 months' follow-up. This meant that the company extrapolated overall survival for a large proportion of patients (over 40%), based on few patients at risk of dying at the end of the trial (16 patients at 24 months, and 3 patients at 26 months), up to the end of the time horizon. The committee concluded that overall survival improved with daratumumab plus bortezomib plus dexamethasone, but that the long-term effect of treatment on survival was unknown because the data were immature.”¹⁶⁰
 - “The committee was aware of the substantial uncertainty in the extrapolation, which predicted survival up to 30 years based on a trial with a median follow-up of under 3 years, and in the relative treatment effect of daratumumab in the long term. (...) The choice of parametric curve for extrapolating trial data had a large effect on the overall survival estimates for daratumumab plus bortezomib plus dexamethasone.”¹⁶⁰
 - “The long-term survival on this treatment was unclear, and the company's and ERG's estimates of survival past the point for which there were trial data varied widely. Because of this the cost-effectiveness estimates also varied.”¹⁶⁰
 - “The evidence for the comparison of daratumumab plus bortezomib plus dexamethasone with bortezomib plus dexamethasone came from a clinical trial directly comparing the 2 treatments and was more robust than the comparison with carfilzomib plus dexamethasone, which came from an indirect comparison of data from 2 trials.”¹⁶⁰
- Conclusions:
 - “The committee concluded that, based on the current evidence, the ICERs for daratumumab plus bortezomib plus dexamethasone were over £30,000 per QALY gained, and were more likely to be closer to the ERG's ICER estimates using the Weibull survival curve (between £40,000 and £50,000 per QALY gained). It concluded that daratumumab plus bortezomib plus dexamethasone did not represent a cost-effective use of NHS resources.”¹⁶⁰
 - “The committee considered it was reasonable to consider that daratumumab plus bortezomib plus dexamethasone had the plausible potential to be a cost-effective use of NHS resources. It heard that the ongoing CASTOR trial is anticipated to provide a further 3 to 4 years of data, which the committee considered could address the uncertainty around survival estimates. It concluded that daratumumab plus bortezomib plus dexamethasone met the criteria to be considered in the Cancer Drugs Fund, and recommended it as an option for people with multiple myeloma who have had 1 previous treatment.”¹⁶⁰
 - “The estimates of cost effectiveness presented by the company and evidence review group differ greatly. These differences depend mostly on the estimates of how much longer people will live if they have daratumumab plus bortezomib plus dexamethasone rather than bortezomib plus dexamethasone. If the company's estimates are confirmed by extra trial data, there is potential for daratumumab plus bortezomib plus dexamethasone to be cost effective. Therefore it is recommended for use in the Cancer Drugs Fund while extra data on long-term survival are collected.”¹⁶⁰
 - “It is recommended only if the conditions in the managed access agreement for daratumumab plus bortezomib plus dexamethasone are followed.”¹⁶⁰



- (Confidential) price:
 - “The company has a managed access agreement, which includes a commercial arrangement, for daratumumab. There is also a commercial arrangement for bortezomib.”¹⁶⁰
 - “ (...) carfilzomib and some follow-on treatments in the model had confidential commercial access agreements (...).”¹⁶⁰
 - “There is a managed access agreement, which includes a patient access scheme and commercial access agreement for daratumumab. The commercial access agreement is an agreement for further data collection for daratumumab with bortezomib and dexamethasone for previously treated multiple myeloma. A positive recommendation within the context of a managed access agreement (MAA) has been decided by the appraisal committee.”¹⁶⁰

Reference Costs (list prices & remarks)	Population, Intervention & comparator IC, IE and ICERs	Remarks on use of generic utility instrument (e.g. EQ- 5D) to measure impact on QoL in economic evaluations	Most uncertain variables or important variables in sensitivity analysis
Daratumumab with bortezomib and dexamethasone			
NICE, TA573 (2019) ¹⁶⁰ Kalita (2018) ¹⁶¹	Adult patients with relapsed multiple myeloma who have received at least one prior treatment Daratumumab plus bortezomib and dexamethasone compared with: A) bortezomib plus dexamethasone B) carfilzomib plus dexamethasone		
List prices Daratumumab costs £360 for the 100 mg vial, and £1440 for the 400 mg vial (2018 costing year) There is a managed access agreement, which includes a patient access scheme (PAS) and commercial access agreement (CAA) for daratumumab.	Results including confidential PAS and CAA for the intervention and the comparators: <u>Comparison A:</u> Company model: between £30 000 and £40 000 per QALY gained ERG model: between £40 000 and £50 000 per QALY gained <u>Comparison B:</u> Company model: between £30 000 and £40 000 per QALY gained ERG model: above £50 000 per QALY gained Remark: due to confidential access agreements on the interventions and comparators, exact ICERs are kept confidential and only ranges are reported. IC and IE are not reported. Conclusion: daratumumab plus bortezomib plus dexamethasone cannot be recommended for routine use. However, due to its potential to be cost-effective, the combination daratumumab plus bortezomib plus dexamethasone is recommended for use in the Cancer Drug Fund while	Company model: EQ-5D data collected from the underlying trial (CASTOR, comparison A). PFS: 0.728, PD: 0.695 ERG model: health state utility values from the mapping of ENDEAVOR EORTC data to EQ-5D. PFS: 0.737 (0.741 from cycle 3 onwards), PD: 0.638	Key uncertainties: - Long-term overall survival for patients with daratumumab (immature data). - Extrapolation method to model long-term survival based on short-term trial data - Highly uncertain ICERs



extra data on long-term survival are collected (managed access agreement).

PAS: Patient Access Scheme; CAA: commercial access agreement.

Appendix 7.4.2.12. NICE, TA510 (2018): daratumumab

- QoL:
 - “The committee was aware that the early phase [single arm] trials presented by the company did not collect health-related quality-of-life data to estimate utility. In response to consultation, the company submitted utility data from an ongoing observational study providing early access to daratumumab for patients with relapsed or refractory multiple myeloma who had at least 3 previous lines of therapy.”¹⁶²
 - No underlying HTA report with further QoL details was identified.
- Results:
 - “It [the committee] noted that the ICERs for daratumumab compared with pomalidomide plus dexamethasone, and with panobinostat plus bortezomib and dexamethasone, varied widely. This reflected the high degree of uncertainty in daratumumab's clinical effectiveness compared with current NHS treatments.”¹⁶²
 - “The committee agreed that the degree of uncertainty in the current evidence was too high for it to be able to identify the most plausible ICER for decision-making.”¹⁶²
 - No underlying HTA report with further details on the results (IE, IC) was identified.
- Uncertainty and sensitivity:
 - “The evidence on the clinical effectiveness of daratumumab came from 2 single-arm clinical trials, MMY2002 and GEN501. The committee (...) noted that the data on overall survival were immature, with over 50% of patients alive at the end of the trials. (...) The original data on overall survival from MMY2002 and GEN501 were immature (see section 4.4). (...) This created considerable uncertainty about the long-term effect of daratumumab.”¹⁶²
 - “The committee noted that the model reflected the limitations of the clinical-effectiveness data. As a result, the model output was of limited use in estimating the cost effectiveness of daratumumab.”¹⁶²
 - “The committee was concerned about some of the company's assumptions in the model; extrapolating overall survival for a large proportion of patients over a lifetime time horizon based on few patients at risk of dying; comparing hazard ratios reflecting treatment effects in different trial populations; and including the effect of treatments taken after disease progression, but not the cost associated with them.”¹⁶²
 - “The committee noted that the results were highly sensitive to changes in the number of characteristics matched to derive the hazard ratio in the MAIC.”¹⁶²



- Conclusions:
 - “The committee concluded that it could not recommend daratumumab as a cost-effective use of NHS resources.”¹⁶²
 - “The committee concluded that the benefit of collecting further data through the Cancer Drugs Fund would enhance the evidence for daratumumab while providing it to NHS patients until daratumumab's clinical and cost effectiveness could be reappraised.”¹⁶²
- (Confidential) price:
 - “Daratumumab has been recommended according to the conditions in the managed access agreement. As part of this, NHS England and Janssen have agreed a commercial access agreement that makes daratumumab available to the NHS at a reduced cost. The financial terms of the agreement are commercial in confidence.”¹⁶²

Reference Costs (list prices & remarks)	Population, Intervention & comparator IC, IE and ICERs	Remarks on use of generic utility instrument (e.g. EQ- 5D) to measure impact on QoL in economic evaluations	Most uncertain variables or important variables in sensitivity analysis
Daratumumab			
NICE, TA510 (2018) ¹⁶²	Adults with relapsed and refractory multiple myeloma Daratumumab monotherapy compared with: A) pomalidomide plus dexamethasone B) panobinostat plus bortezomib and dexamethasone		
List prices, negotiated discounts (commercial access agreement) are hidden Daratumumab costs £360 for the 100 mg vial, and £1440 for the 400 mg vial.*	Results of the company and the ERG models for comparisons A and B (including confidential PAS and CAA for the intervention and confidential discounts for all comparators): - the ICERs varied considerably; - the degree of uncertainty in the current evidence is too high to be able to identify the most plausible ICERs. Remark: due to high uncertainty ICERs, IC and IE are not reported. Conclusion: Daratumumab monotherapy is recommended for use within the Cancer Drugs Fund. Daratumumab is recommended according to the conditions in the managed access agreement.	No head-to-head trial available. Utilities obtained from an ongoing observational study. Methods used and values are not reported.	The impact on the long-term OS is highly uncertain

* Assuming an average body weight of 73.91 kg, and an average treatment duration of 3.4 months, the cost of a course of treatment is £68 862 excluding administration costs, and £74 531 including administration costs. CAA: commercial access agreement; PAS: patient access scheme.



Appendix 7.4.2.13. NICE, TA634 (2020): daratumumab

- “NICE is unable to make a recommendation about the use in the NHS of daratumumab with lenalidomide and dexamethasone for untreated multiple myeloma because Janssen did not provide an evidence submission.”¹⁶³

Appendix 7.4.2.14. NICE, TA454 (2017): daratumumab

- “NICE is unable to make a recommendation about the use in the NHS of daratumumab, with lenalidomide and dexamethasone, for treating relapsed or refractory multiple myeloma because no evidence submission was received from Janssen-Cilag.”¹⁶⁴



APPENDIX 8. NON HODGKIN

Appendix 8.1. BCR data

Appendix 8.1.1. Descriptive statistics

Appendix 8.1.1.1. B-cell chronic lymphocytic leukaemia & small lymphocytic lymphoma, exploration

Table 105 – B-cell chronic lymphocytic leukaemia & small lymphocytic lymphoma: Frequency table of patient and tumour characteristics

Characteristic	Total	Incidence period		
		2004-2008	2009-2013	2014-2017
Overall	10,920	3,301	4,093	3,526
Gender				
Male	6,397 (58.6)	1,937 (58.7)	2,368 (57.9)	2,092 (59.3)
Female	4,523 (41.4)	1,364 (41.3)	1,725 (42.1)	1,434 (40.7)
Age at diagnosis (year)				
<50 years	625 (5.7)	226 (6.8)	229 (5.6)	170 (4.8)
50-59 years	1,743 (16.0)	534 (16.2)	656 (16.0)	553 (15.7)
60-69 years	3,001 (27.5)	881 (26.7)	1,144 (28.0)	976 (27.7)
70-79 years	3,392 (31.1)	1,111 (33.7)	1,218 (29.8)	1,063 (30.1)
80+ years	2,159 (19.8)	549 (16.6)	846 (20.7)	764 (21.7)
WHO - Performance Status				
0 – Asymptomatic	4,767 (43.7)	1,131 (34.3)	1,866 (45.6)	1,770 (50.2)
1 – Symptomatic but completely ambulatory	3,138 (28.7)	743 (22.5)	1,298 (31.7)	1,097 (31.1)
2 – Symptomatic, <50% in bed during the day	281 (2.6)	99 (3.0)	88 (2.2)	94 (2.7)
3 – Symptomatic, >50% in bed, but not bedbound	86 (0.8)	28 (0.8)	24 (0.6)	34 (1.0)
4 – Bedbound	47 (0.4)	20 (0.6)	10 (0.2)	17 (0.5)
Not reported	2,601 (23.8)	1,280 (38.8)	807 (19.7)	514 (14.6)

Note: the values between parentheses are column percentages.



Appendix 8.1.1.2. *B-cell chronic lymphocytic leukaemia & small lymphocytic lymphoma, Observed and Relative Survival graphs*

B-cell chronic lymphocytic leukaemia & small lymphocytic lymphoma (2004-2017)

Figure 192 – B-cell chronic lymphocytic leukaemia & small lymphocytic lymphoma, Kaplan-Meier graphs observed survival by incidence period

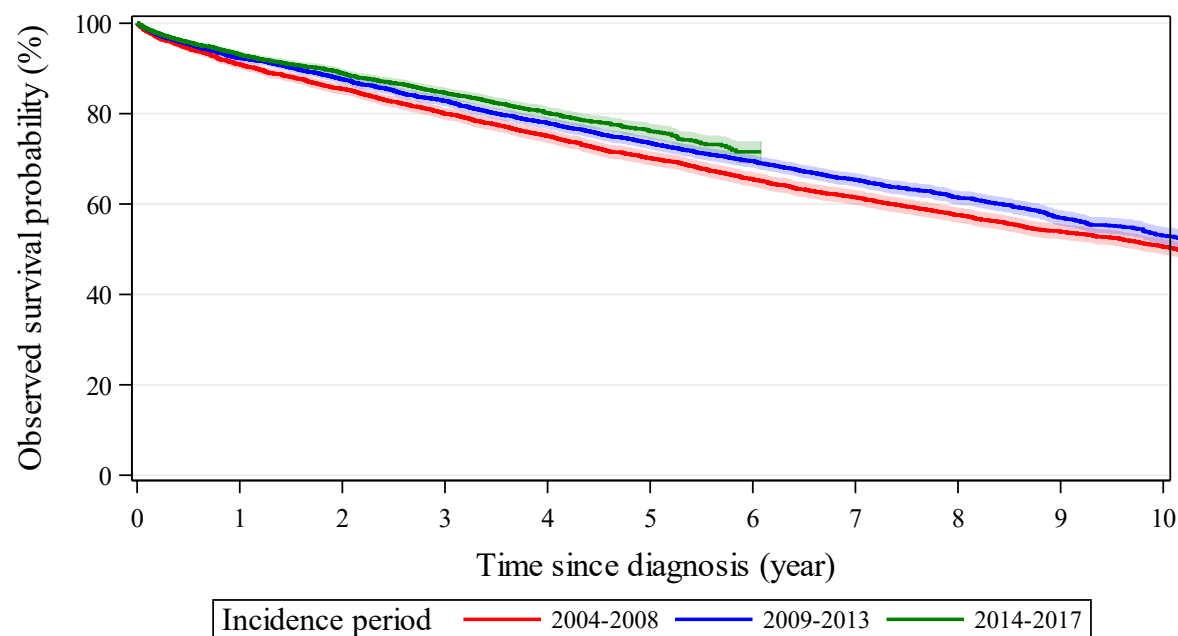
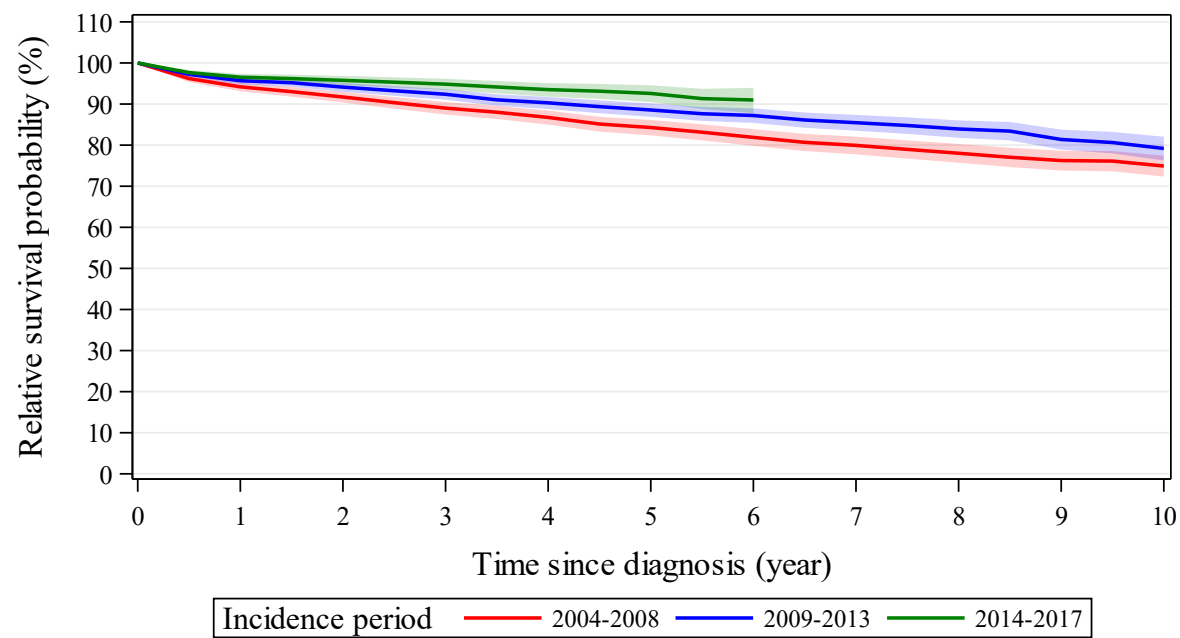




Figure 193 – B-cell chronic lymphocytic leukaemia & small lymphocytic lymphoma, relative survival graphs by incidence period

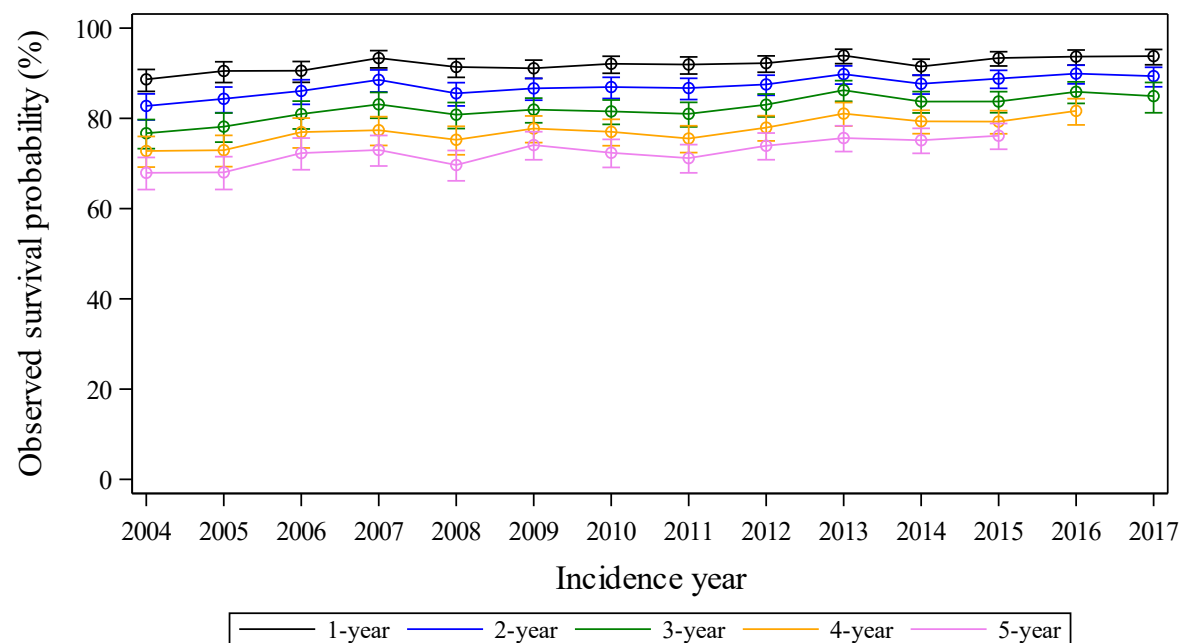




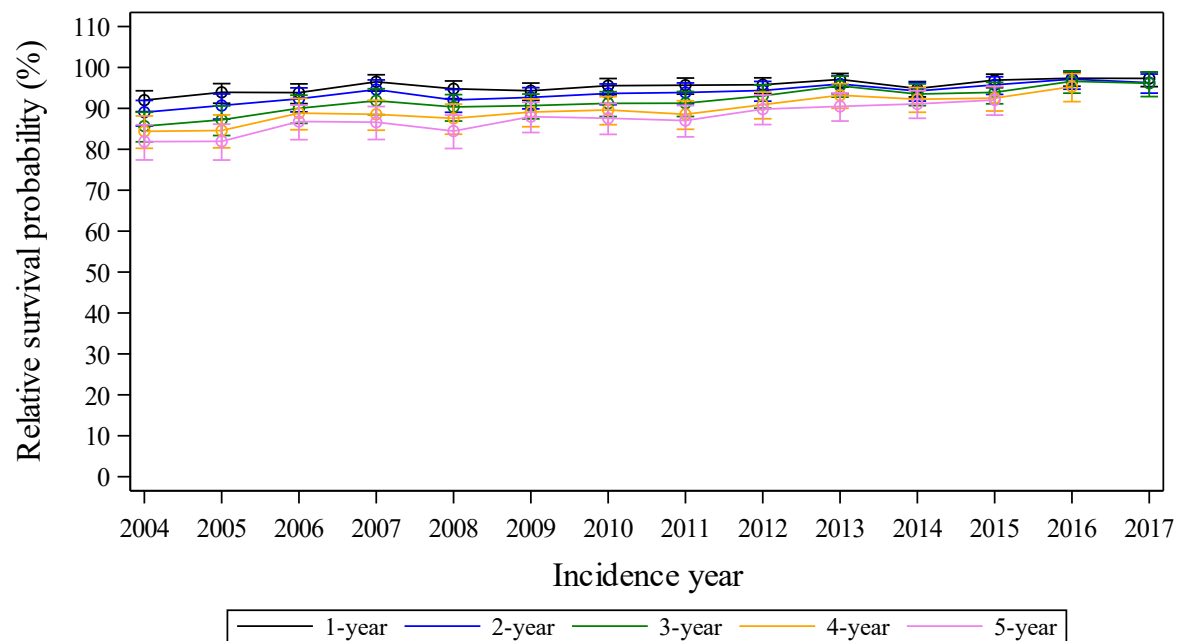
Appendix 8.1.1.3. B-cell chronic lymphocytic leukaemia & small lymphocytic lymphoma, time trend Observed and Relative Survival

B-cell chronic lymphocytic leukaemia & small lymphocytic lymphoma (2004-2017)

Figure 194 – B-cell chronic lymphocytic leukaemia & small lymphocytic lymphoma, time trend observed survival with incidence year



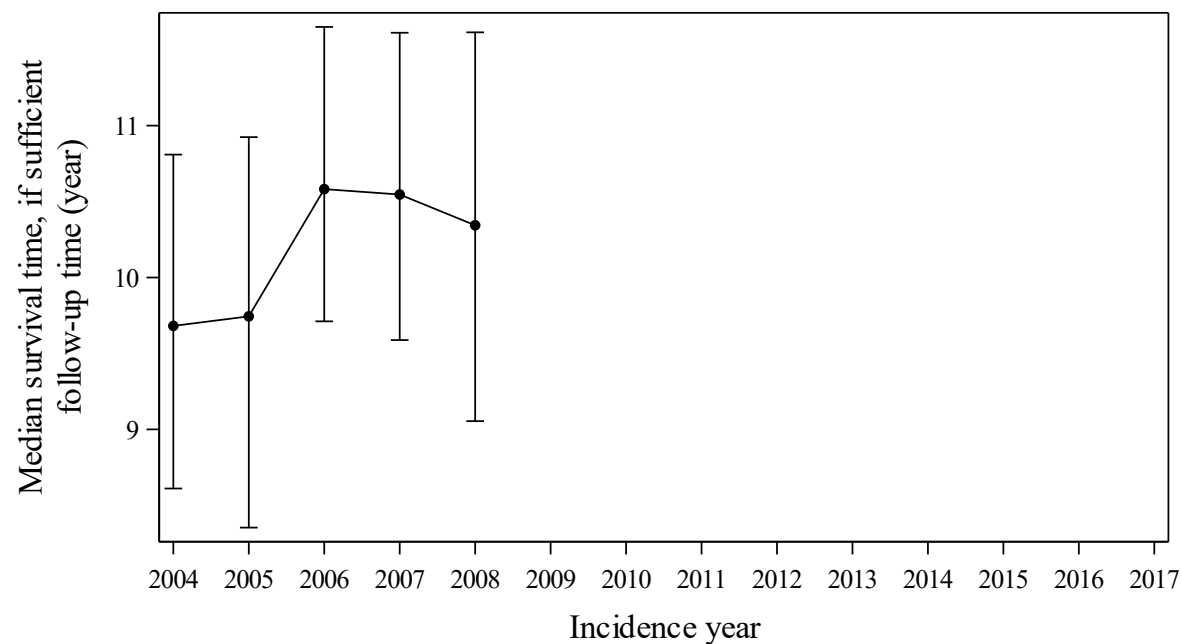
Note: the error bars represent the 95% CI.

**Figure 195 – B-cell chronic lymphocytic leukaemia & small lymphocytic lymphoma, time trend relative survival with incidence year**

Note: the error bars represent the 95% CI.



Figure 196 – B-cell chronic lymphocytic leukaemia & small lymphocytic lymphoma, Median time observed survival



Note: the error bars represent the 95% CI. When the upper error is not plotted, the upper limit could not be determined with the follow-up available.



Appendix 8.1.1.4. *B-cell chronic lymphocytic leukaemia & small lymphocytic lymphoma, time trend tables Observed and Relative Survival*

Table 106 – B-cell chronic lymphocytic leukaemia & small lymphocytic lymphoma, time trend observed survival with incidence year

Unadjusted observed survival, %													
Characteristic	N at risk	1 year		2 year		3 year		4 year		5 year		Median survival time (year)	
		%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI	T	95% CI
All													
2004	661	88.7	[86.0, 90.8]	82.8	[79.7, 85.4]	76.7	[73.3, 79.7]	72.8	[69.2, 76.0]	67.9	[64.2, 71.3]	9.7	[8.6, 10.8]
2005	632	90.5	[87.9, 92.5]	84.3	[81.3, 86.9]	78.2	[74.7, 81.2]	72.9	[69.3, 76.2]	68.0	[64.2, 71.5]	9.7	[8.4, 10.9]
2006	625	90.6	[88.0, 92.6]	86.1	[83.1, 88.6]	81.0	[77.7, 83.8]	77.0	[73.4, 80.1]	72.3	[68.6, 75.6]	10.6	[9.7, 11.6]
2007	663	93.4	[91.2, 95.0]	88.5	[85.9, 90.7]	83.1	[80.0, 85.8]	77.4	[74.0, 80.4]	73.0	[69.4, 76.2]	10.5	[9.6, 11.6]
2008	720	91.4	[89.1, 93.2]	85.5	[82.8, 87.9]	80.8	[77.7, 83.5]	75.3	[71.9, 78.2]	69.7	[66.2, 72.9]	10.3	[9.1, 11.6]
2009	765	91.1	[88.8, 92.9]	86.6	[84.0, 88.9]	81.9	[79.0, 84.5]	77.7	[74.6, 80.5]	74.1	[70.8, 77.0]	>11	
2010	797	92.1	[90.0, 93.8]	86.9	[84.4, 89.1]	81.5	[78.7, 84.1]	77.0	[73.9, 79.8]	72.4	[69.1, 75.3]	>10	
2011	807	91.9	[89.8, 93.6]	86.7	[84.2, 88.9]	81.0	[78.1, 83.5]	75.5	[72.4, 78.4]	71.2	[67.9, 74.2]	>9	
2012	850	92.2	[90.2, 93.8]	87.5	[85.1, 89.6]	83.0	[80.3, 85.4]	77.9	[75.0, 80.6]	73.9	[70.8, 76.7]	>8	
2013	874	93.9	[92.1, 95.3]	89.8	[87.6, 91.6]	86.2	[83.8, 88.4]	81.1	[78.3, 83.5]	75.6	[72.6, 78.4]	>7	
2014	942	91.5	[89.5, 93.1]	87.7	[85.4, 89.6]	83.7	[81.2, 85.9]	79.3	[76.6, 81.8]	75.1	[72.2, 77.8]	>6	
2015	967	93.4	[91.6, 94.8]	88.8	[86.7, 90.6]	83.7	[81.3, 85.9]	79.3	[76.6, 81.7]	76.2	[73.2, 78.9]	>5	
2016	826	93.7	[91.8, 95.2]	89.9	[87.7, 91.8]	85.9	[83.3, 88.1]	81.7	[78.5, 84.4]	no FU	—	>4	
2017	791	93.8	[91.9, 95.3]	89.4	[87.0, 91.3]	84.9	[81.2, 88.0]	no FU	—	no FU	—	>3	



Table 107 – B-cell chronic lymphocytic leukaemia & small lymphocytic lymphoma, time trend relative survival with incidence year

Unadjusted relative survival, %											
Characteristic	N at risk	%	1 year	%	2 year	%	3 year	%	4 year	%	5 year
			95% CI		95% CI		95% CI		95% CI		95% CI
All											
2004	661	92.0	[89.2, 94.3]	89.0	[85.7, 91.9]	85.7	[81.8, 89.1]	84.4	[80.2, 88.1]	81.9	[77.4, 86.0]
2005	632	93.9	[91.3, 96.0]	90.7	[87.4, 93.5]	87.2	[83.4, 90.6]	84.6	[80.4, 88.4]	81.9	[77.4, 86.1]
2006	625	93.8	[91.2, 96.0]	92.3	[89.1, 95.0]	90.0	[86.3, 93.2]	88.8	[84.8, 92.4]	86.8	[82.4, 90.8]
2007	663	96.5	[94.2, 98.2]	94.6	[91.7, 97.0]	91.9	[88.5, 94.8]	88.5	[84.7, 92.0]	86.6	[82.4, 90.4]
2008	720	94.8	[92.4, 96.7]	92.0	[89.0, 94.6]	90.3	[86.9, 93.4]	87.6	[83.7, 91.0]	84.4	[80.2, 88.4]
2009	765	94.3	[92.0, 96.2]	92.7	[89.9, 95.1]	90.7	[87.4, 93.5]	89.1	[85.5, 92.3]	88.0	[84.1, 91.5]
2010	797	95.5	[93.3, 97.3]	93.6	[90.9, 96.0]	91.2	[88.0, 94.1]	89.6	[86.0, 92.8]	87.6	[83.6, 91.2]
2011	807	95.7	[93.5, 97.4]	93.9	[91.1, 96.2]	91.3	[88.0, 94.1]	88.5	[84.9, 91.9]	87.0	[83.0, 90.7]
2012	850	95.8	[93.7, 97.5]	94.4	[91.8, 96.6]	93.1	[90.0, 95.7]	90.9	[87.5, 94.0]	89.8	[86.0, 93.2]
2013	874	97.1	[95.2, 98.5]	96.0	[93.6, 97.9]	95.5	[92.8, 97.9]	93.2	[90.0, 96.0]	90.5	[86.9, 93.7]
2014	942	94.9	[92.8, 96.5]	94.2	[91.8, 96.3]	93.5	[90.7, 96.0]	92.2	[89.0, 95.1]	91.1	[87.6, 94.3]
2015	967	96.9	[95.1, 98.4]	95.7	[93.4, 97.7]	93.9	[91.1, 96.4]	92.5	[89.4, 95.3]	92.0	[88.4, 95.4]
2016	826	97.4	[95.4, 98.9]	97.1	[94.7, 99.2]	96.6	[93.7, 99.1]	95.3	[91.6, 98.5]	no FU	—
2017	791	97.3	[95.3, 98.9]	96.3	[93.7, 98.4]	96.1	[92.9, 98.9]	no FU	—	no FU	—



Appendix 8.1.1.5. Diffuse Large B-cell Lymphoma, exploration

Table 108 – Diffuse Large B-cell Lymphoma (2004-2017): Frequency table of patient and tumour characteristics

Characteristic	Total	Incidence period		
		2004-2008	2009-2013	2014-2017
Overall	9,951	3,172	3,695	3,084
Gender				
Male	5,298 (53.2)	1,656 (52.2)	1,970 (53.3)	1,672 (54.2)
Female	4,653 (46.8)	1,516 (47.8)	1,725 (46.7)	1,412 (45.8)
Age at diagnosis (year)				
<50 years	1,230 (12.4)	456 (14.4)	451 (12.2)	323 (10.5)
50-59 years	1,280 (12.9)	427 (13.5)	465 (12.6)	388 (12.6)
60-69 years	2,064 (20.7)	638 (20.1)	758 (20.5)	668 (21.7)
70-79 years	2,966 (29.8)	976 (30.8)	1,118 (30.3)	872 (28.3)
80+ years	2,411 (24.2)	675 (21.3)	903 (24.4)	833 (27.0)
WHO - Performance Status				
0 – Asymptomatic	1,152 (11.6)	289 (9.1)	464 (12.6)	399 (12.9)
1 – Symptomatic but completely ambulatory	4,546 (45.7)	1,041 (32.8)	1,870 (50.6)	1,635 (53.0)
2 – Symptomatic, <50% in bed during the day	984 (9.9)	320 (10.1)	333 (9.0)	331 (10.7)
3 – Symptomatic, >50% in bed, but not bedbound	424 (4.3)	118 (3.7)	141 (3.8)	165 (5.4)
4 – Bedbound	180 (1.8)	47 (1.5)	69 (1.9)	64 (2.1)
Not reported	2,665 (26.8)	1,357 (42.8)	818 (22.1)	490 (15.9)

Note: the values between parentheses are column percentages.



Appendix 8.1.1.6. Diffuse Large B-cell Lymphoma, Observed and Relative Survival graphs

Diffuse Large B-cell Lymphoma (2004-2017)

Figure 197 – Diffuse Large B-cell Lymphoma (2004-2017), Kaplan-Meier graphs observed survival by incidence period

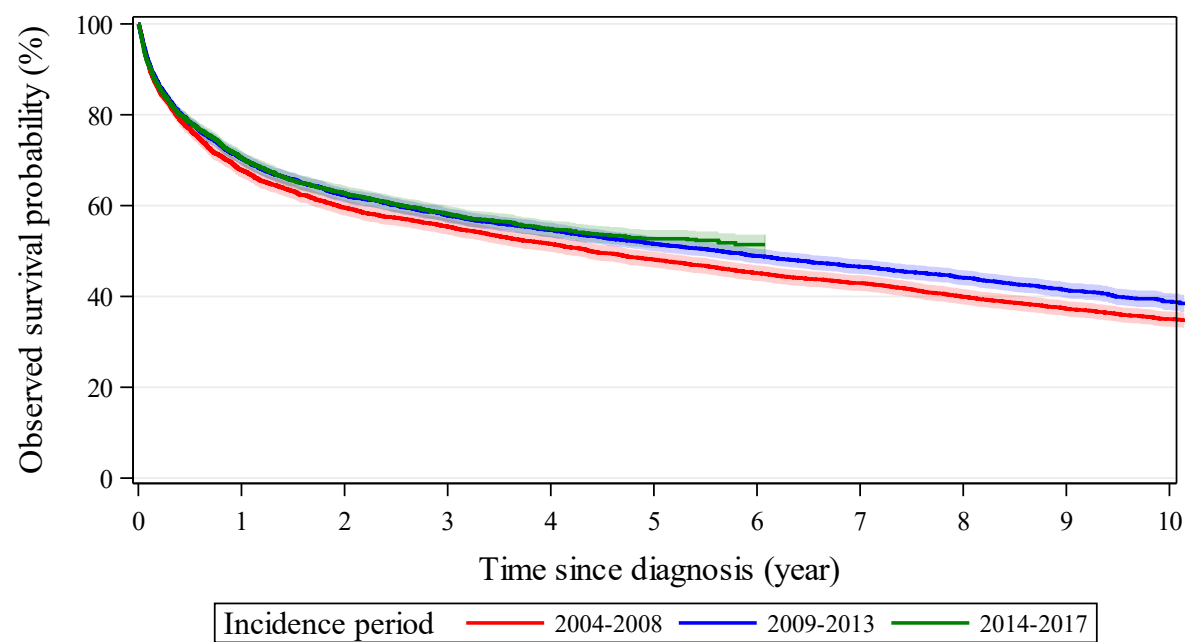
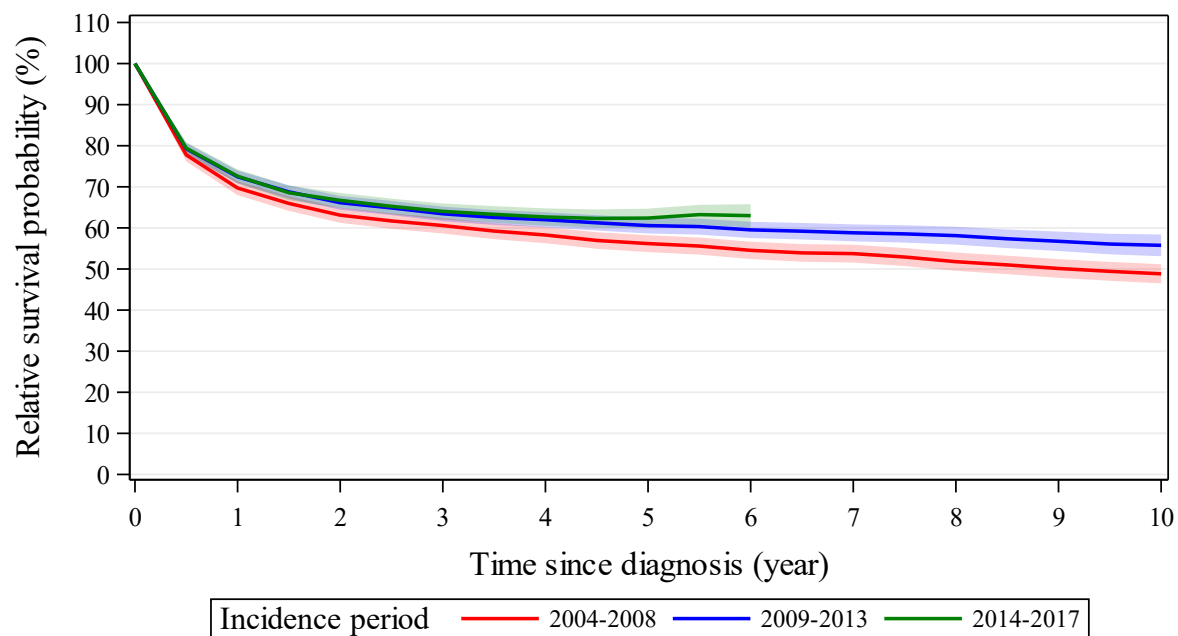


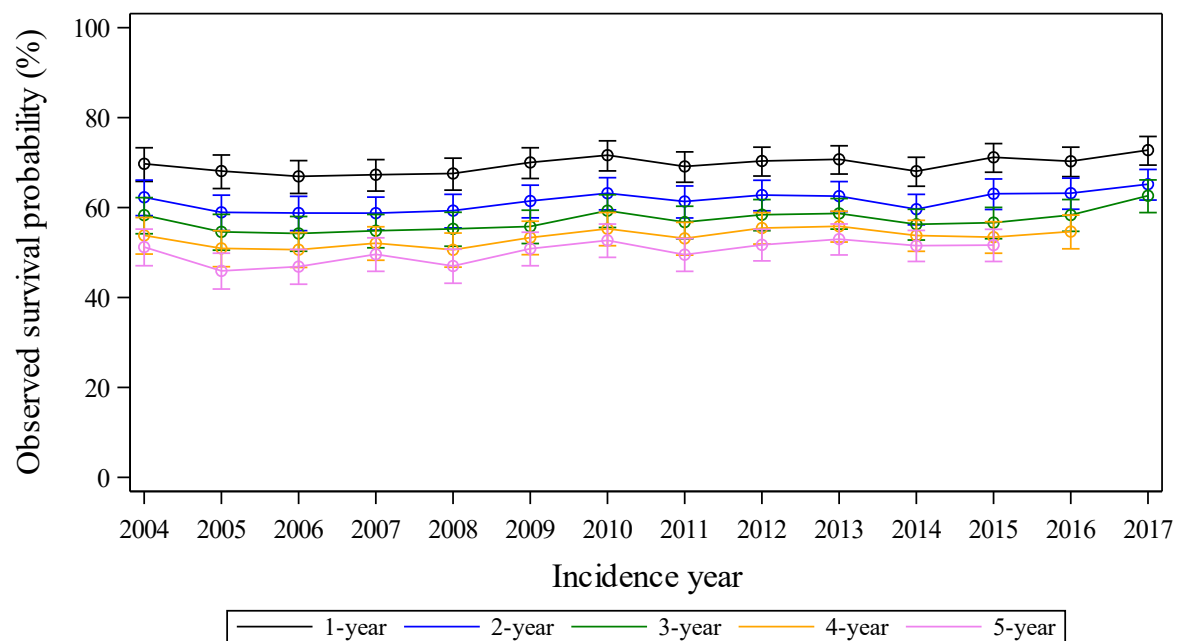
**Figure 198 – Diffuse Large B-cell Lymphoma (2004-2017), relative survival graphs by incidence period**



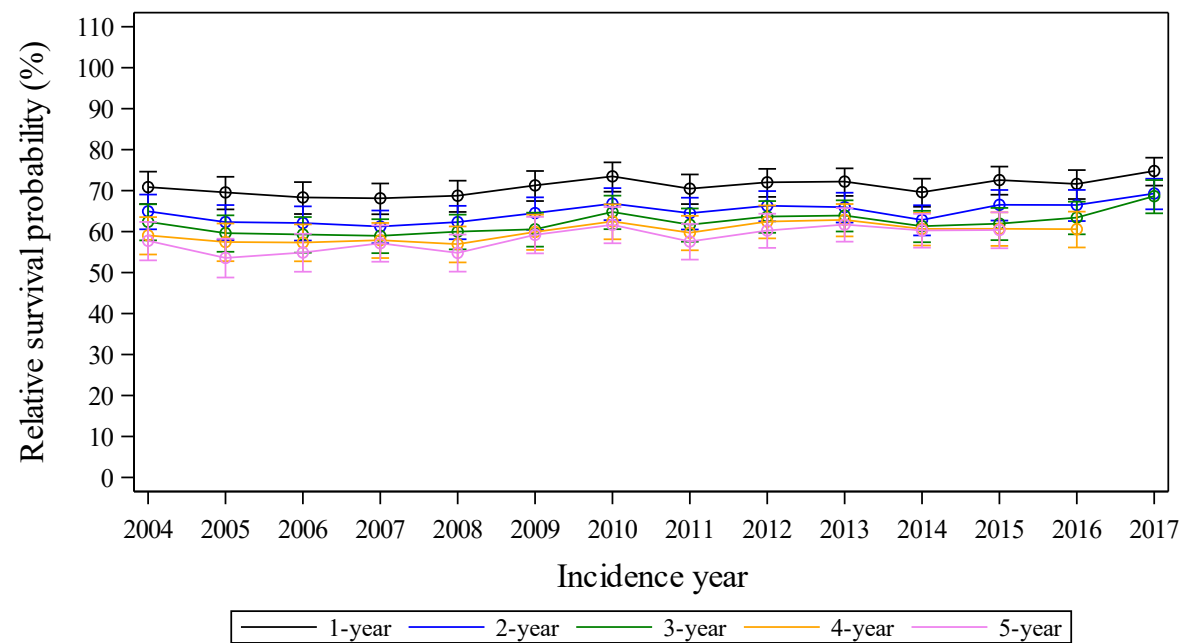
Appendix 8.1.1.7. Diffuse Large B-cell Lymphoma, time trend Observed and Relative Survival

Diffuse Large B-cell Lymphoma (2004-2017)

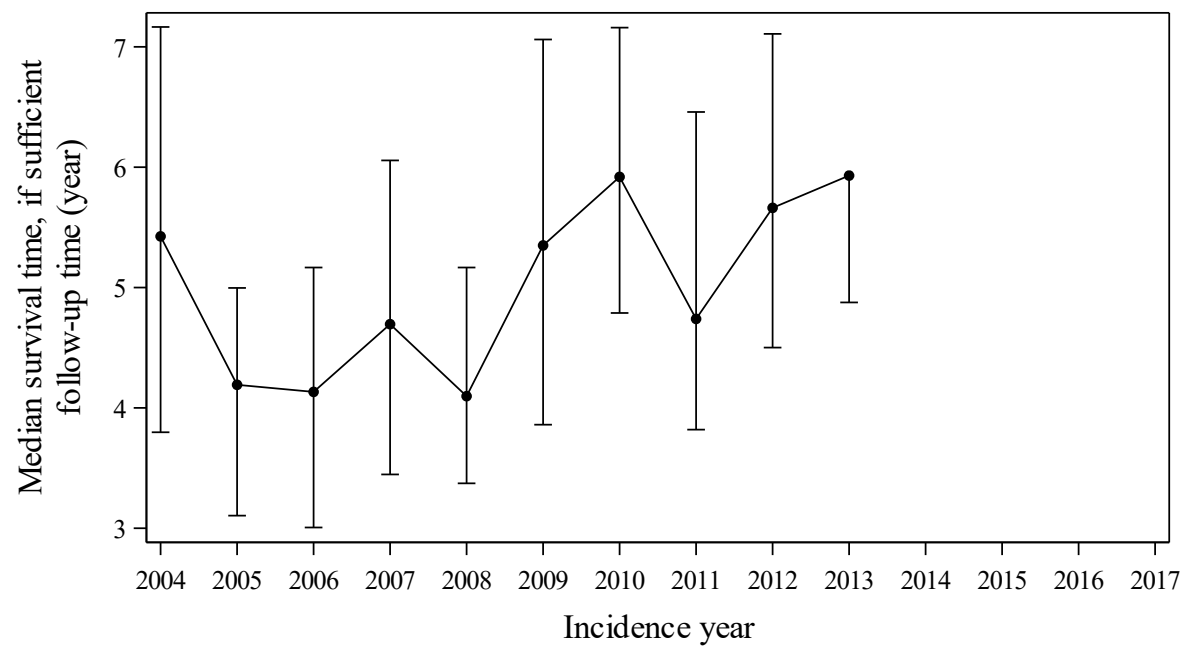
Figure 199 – Diffuse Large B-cell Lymphoma (2004-2017), time trend observed survival with incidence year



Note: the error bars represent the 95% CI.

**Figure 200 – Diffuse Large B-cell Lymphoma (2004-2017), time trend relative survival with incidence year**

Note: the error bars represent the 95% CI.

**Figure 201 – Diffuse Large B-cell Lymphoma (2004-2017), Median time observed survival**

Note: the error bars represent the 95% CI. When the upper error is not plotted, the upper limit could not be determined with the follow-up available.



Appendix 8.1.1.8. Diffuse Large B-cell Lymphoma, time trend tables Observed and Relative Survival

Table 109 – Diffuse Large B-cell Lymphoma (2004-2017), time trend observed survival with incidence year

Unadjusted observed survival, %													
Characteristic	N at risk	1 year		2 year		3 year		4 year		5 year		Median survival time (year)	
		%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI	T	95% CI
All													
2004	578	69.7	[65.8, 73.3]	62.3	[58.2, 66.1]	58.3	[54.2, 62.2]	53.8	[49.7, 57.8]	51.2	[47.1, 55.2]	5.4	[3.8, 7.2]
2005	599	68.1	[64.2, 71.7]	58.9	[54.9, 62.8]	54.6	[50.5, 58.5]	50.9	[46.8, 54.8]	45.9	[41.9, 49.8]	4.2	[3.1, 5.0]
2006	638	66.9	[63.1, 70.4]	58.8	[54.9, 62.5]	54.2	[50.3, 58.0]	50.6	[46.7, 54.4]	46.9	[42.9, 50.7]	4.1	[3.0, 5.2]
2007	691	67.3	[63.7, 70.7]	58.7	[55.0, 62.3]	54.8	[51.0, 58.5]	52.1	[48.3, 55.7]	49.6	[45.8, 53.3]	4.7	[3.4, 6.1]
2008	666	67.6	[63.9, 71.0]	59.3	[55.5, 62.9]	55.3	[51.4, 58.9]	50.6	[46.7, 54.3]	47.0	[43.2, 50.7]	4.1	[3.4, 5.2]
2009	691	70.0	[66.5, 73.3]	61.5	[57.7, 65.0]	55.8	[52.0, 59.4]	53.3	[49.5, 57.0]	50.8	[47.1, 54.5]	5.3	[3.9, 7.1]
2010	699	71.6	[68.1, 74.8]	63.2	[59.5, 66.6]	59.3	[55.6, 62.8]	55.3	[51.5, 58.9]	52.7	[48.9, 56.3]	5.9	[4.8, 7.2]
2011	720	69.1	[65.6, 72.4]	61.3	[57.7, 64.8]	56.8	[53.0, 60.3]	53.1	[49.4, 56.7]	49.5	[45.8, 53.1]	4.7	[3.8, 6.5]
2012	779	70.3	[67.0, 73.4]	62.8	[59.3, 66.1]	58.4	[54.9, 61.8]	55.4	[51.9, 58.9]	51.7	[48.1, 55.2]	5.7	[4.5, 7.1]
2013	806	70.7	[67.4, 73.7]	62.5	[59.1, 65.8]	58.7	[55.2, 62.0]	55.8	[52.3, 59.2]	53.0	[49.5, 56.3]	5.9	[4.9, .]
2014	806	68.1	[64.7, 71.2]	59.6	[56.2, 62.9]	56.3	[52.8, 59.6]	53.8	[50.3, 57.2]	51.5	[48.0, 54.9]	>6	
2015	777	71.2	[67.8, 74.2]	63.1	[59.6, 66.3]	56.6	[53.1, 60.0]	53.4	[49.8, 56.8]	51.6	[48.0, 55.2]	>5	
2016	748	70.3	[66.9, 73.4]	63.2	[59.6, 66.5]	58.3	[54.7, 61.8]	54.7	[50.8, 58.3]	no FU	—	>4	
2017	753	72.8	[69.4, 75.8]	65.2	[61.7, 68.5]	62.6	[58.9, 66.1]	no FU	—	no FU	—	>3	



Table 110 – Diffuse Large B-cell Lymphoma (2004-2017), time trend relative survival with incidence year

Unadjusted relative survival, %											
Characteristic	N at risk	%	1 year	%	2 year	%	3 year	%	4 year	%	5 year
			95% CI		95% CI		95% CI		95% CI		95% CI
All											
2004	578	70.9	[66.7, 74.6]	64.9	[60.6, 69.0]	62.4	[57.9, 66.7]	59.1	[54.4, 63.5]	57.8	[53.0, 62.4]
2005	599	69.6	[65.4, 73.4]	62.3	[57.9, 66.5]	59.6	[55.1, 64.0]	57.5	[52.8, 62.0]	53.6	[48.8, 58.3]
2006	638	68.3	[64.3, 72.1]	62.1	[57.8, 66.2]	59.3	[54.9, 63.6]	57.3	[52.8, 61.8]	54.9	[50.2, 59.5]
2007	691	68.1	[64.2, 71.7]	61.2	[57.1, 65.1]	59.0	[54.7, 63.0]	57.9	[53.5, 62.1]	57.1	[52.6, 61.5]
2008	666	68.8	[64.8, 72.4]	62.3	[58.1, 66.3]	60.0	[55.7, 64.1]	56.9	[52.5, 61.3]	54.8	[50.2, 59.3]
2009	691	71.3	[67.5, 74.8]	64.5	[60.4, 68.4]	60.6	[56.3, 64.6]	59.9	[55.5, 64.1]	59.2	[54.7, 63.6]
2010	699	73.5	[69.7, 76.9]	66.8	[62.8, 70.6]	64.8	[60.6, 68.8]	62.5	[58.1, 66.7]	61.7	[57.1, 66.0]
2011	720	70.5	[66.7, 73.9]	64.5	[60.5, 68.3]	61.7	[57.5, 65.6]	59.7	[55.4, 63.9]	57.6	[53.2, 61.9]
2012	779	72.0	[68.5, 75.3]	66.3	[62.5, 69.9]	63.7	[59.7, 67.4]	62.4	[58.3, 66.4]	60.3	[56.0, 64.4]
2013	806	72.2	[68.7, 75.4]	66.0	[62.2, 69.5]	63.9	[60.0, 67.6]	62.9	[58.8, 66.7]	61.7	[57.5, 65.7]
2014	806	69.6	[66.1, 72.9]	62.8	[59.1, 66.4]	61.3	[57.4, 65.1]	60.7	[56.6, 64.6]	60.3	[56.1, 64.3]
2015	777	72.6	[69.0, 75.9]	66.5	[62.7, 70.2]	61.9	[57.9, 65.8]	60.7	[56.5, 64.7]	60.4	[55.9, 64.7]
2016	748	71.6	[68.0, 75.0]	66.5	[62.6, 70.2]	63.4	[59.3, 67.3]	60.6	[56.1, 64.9]	no FU	—
2017	753	74.8	[71.2, 78.0]	69.3	[65.4, 72.9]	68.6	[64.5, 72.6]	no FU	—	no FU	—



Appendix 8.1.1.9. Mantle cell lymphoma, exploration

Table 111 – Mantle cell lymphoma (2004-2017): Frequency table of patient and tumour characteristics

Characteristic	Total	Incidence period		
		2004-2008	2009-2013	2014-2017
Overall	1,755	552	634	569
Gender				
Male	1,230 (70.1)	391 (70.8)	436 (68.8)	403 (70.8)
Female	525 (29.9)	161 (29.2)	198 (31.2)	166 (29.2)
Age at diagnosis (year)				
<50 years	100 (5.7)	35 (6.3)	38 (6.0)	27 (4.7)
50-59 years	245 (14.0)	79 (14.3)	90 (14.2)	76 (13.4)
60-69 years	473 (27.0)	171 (31.0)	167 (26.3)	135 (23.7)
70-79 years	591 (33.7)	194 (35.1)	217 (34.2)	180 (31.6)
80+ years	346 (19.7)	73 (13.2)	122 (19.2)	151 (26.5)
WHO - Performance Status				
0 – Asymptomatic	374 (21.3)	98 (17.8)	138 (21.8)	138 (24.3)
1 – Symptomatic but completely ambulatory	805 (45.9)	186 (33.7)	313 (49.4)	306 (53.8)
2 – Symptomatic, <50% in bed during the day	110 (6.3)	41 (7.4)	40 (6.3)	29 (5.1)
3 – Symptomatic, >50% in bed, but not bedbound	38 (2.2)	7 (1.3)	15 (2.4)	16 (2.8)
4 – Bedbound	14 (0.8)	3 (0.5)	4 (0.6)	7 (1.2)
Not reported	414 (23.6)	217 (39.3)	124 (19.6)	73 (12.8)

Note: the values between parentheses are column percentages.



Appendix 8.1.1.10. Mantle cell lymphoma, Observed and Relative Survival graphs

Mantle cell lymphoma (2004-2017)

Figure 202 – Mantle cell lymphoma (2004-2017), Kaplan-Meier graphs observed survival by incidence period

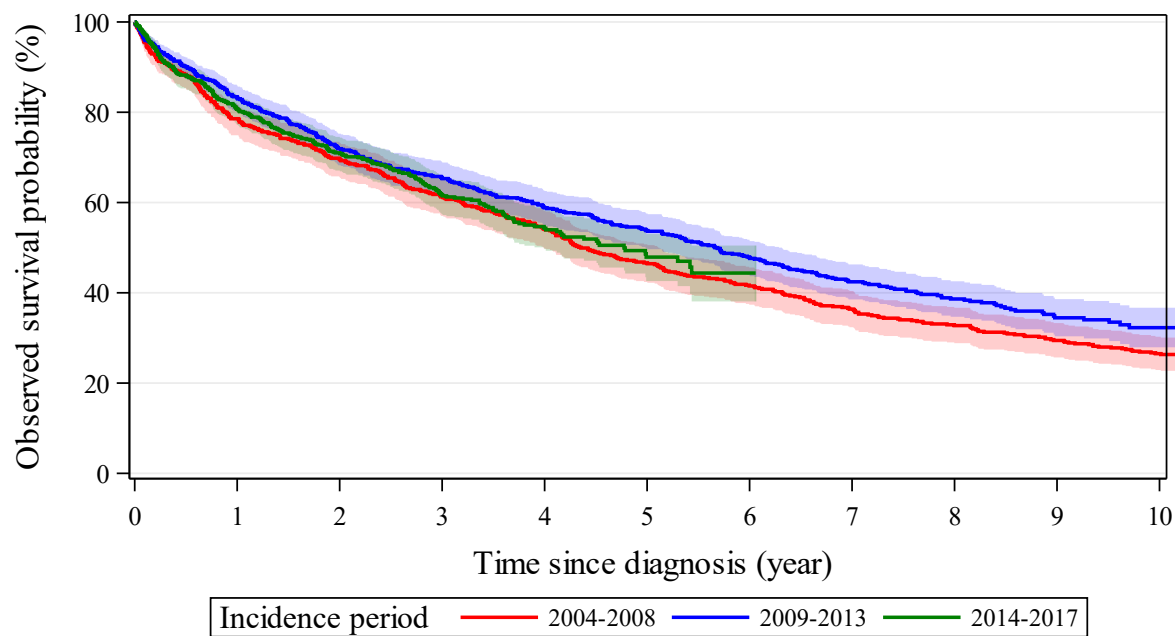
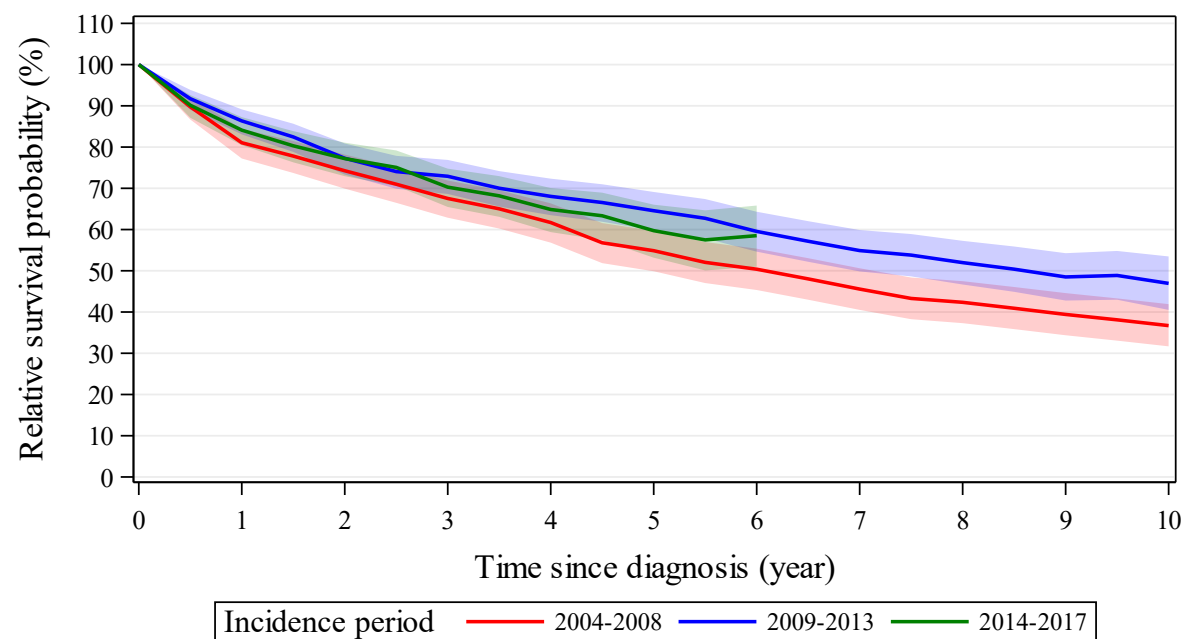


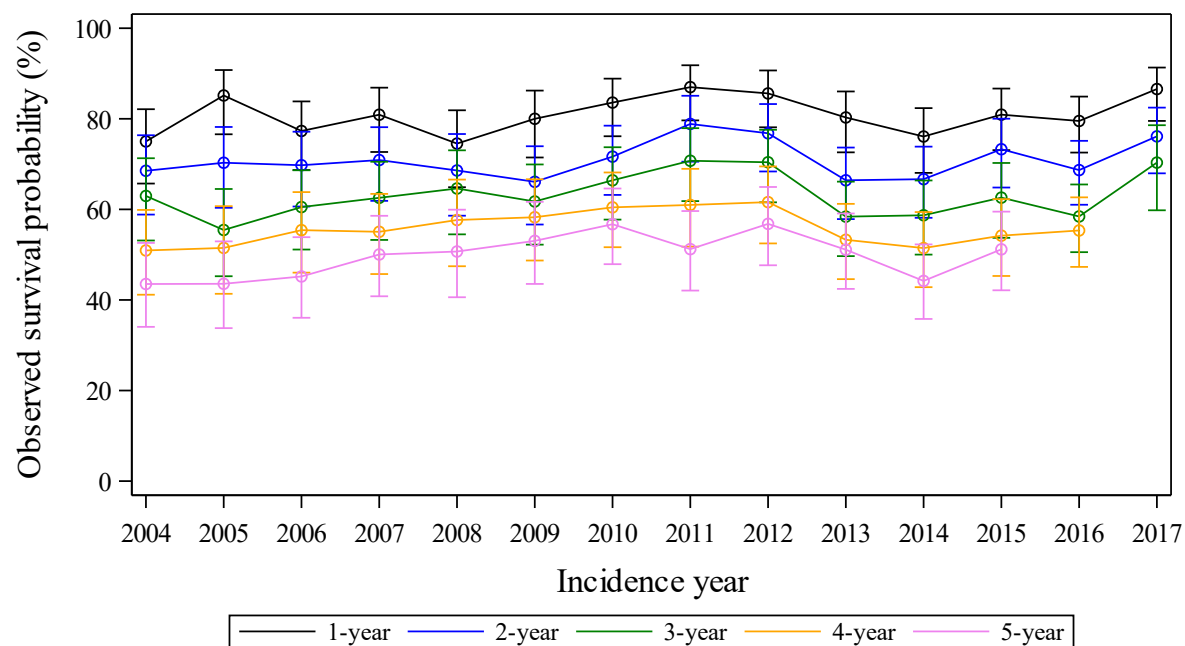
**Figure 203 – Mantle cell lymphoma (2004-2017), relative survival graphs by incidence period**



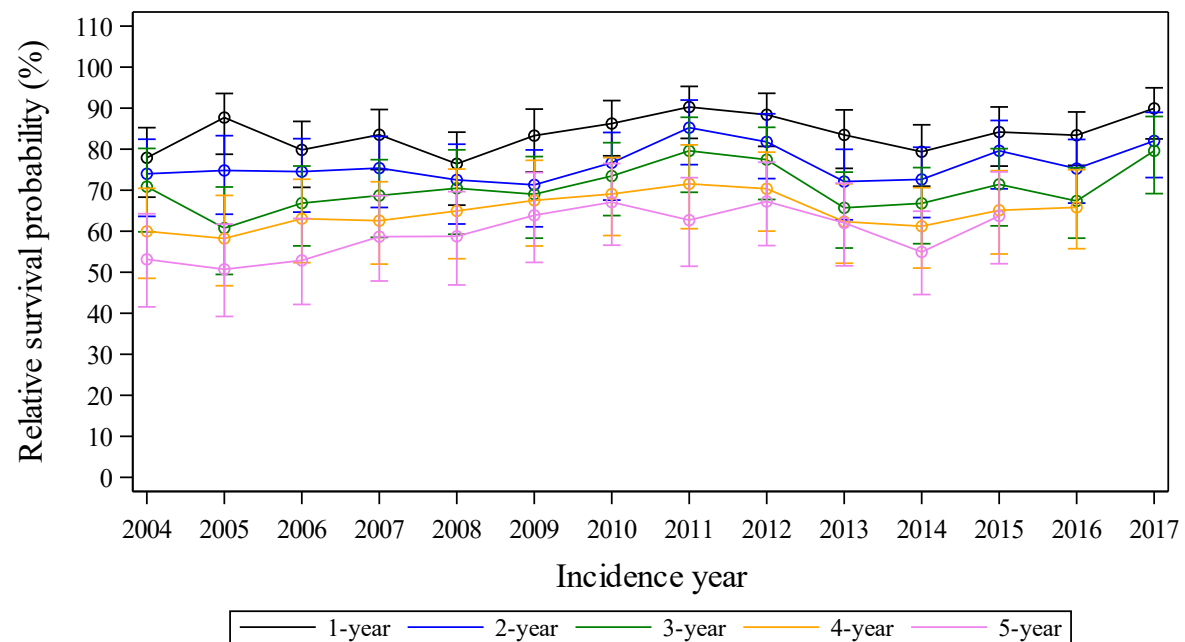
Appendix 8.1.1.11. Mantle cell lymphoma, time trend Observed and Relative Survival

Mantle cell lymphoma (2004-2017)

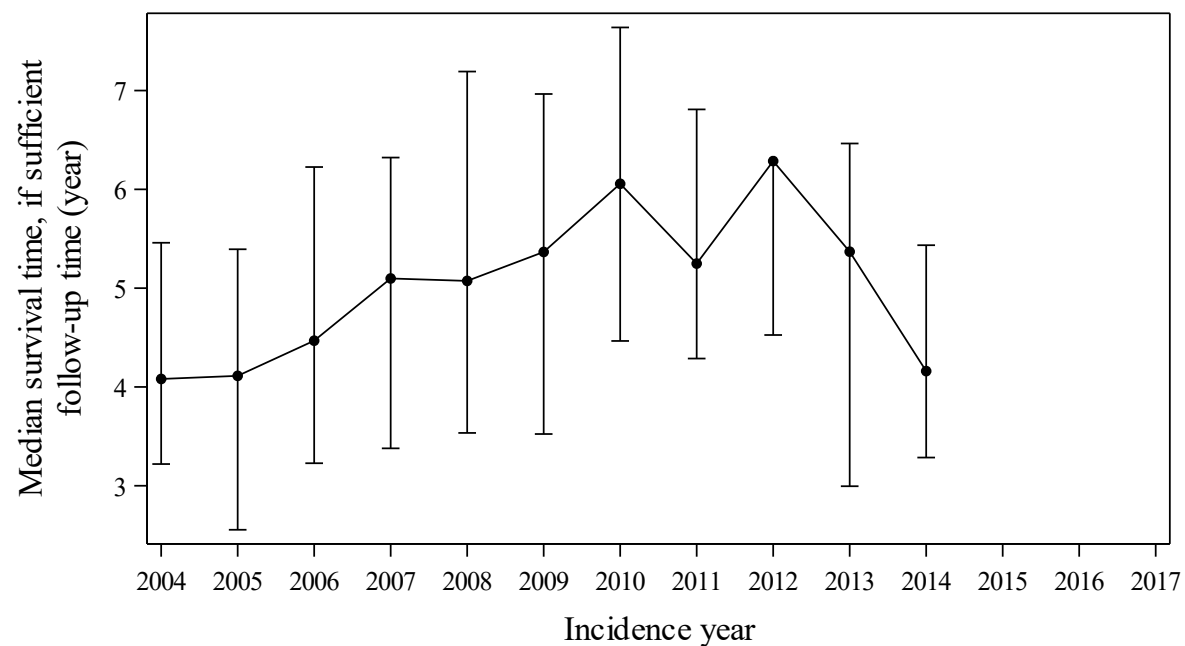
Figure 204 – Mantle cell lymphoma (2004-2017), time trend observed survival with incidence year



Note: the error bars represent the 95% CI.

**Figure 205 – Mantle cell lymphoma (2004-2017), time trend relative survival with incidence year**

Note: the error bars represent the 95% CI.

**Figure 206 – Mantle cell lymphoma (2004-2017), Median time observed survival**

Note: the error bars represent the 95% CI. When the upper error is not plotted, the upper limit could not be determined with the follow-up available.



Appendix 8.1.1.12. Mantle cell lymphoma, time trend tables Observed and Relative Survival

Table 112 – Mantle cell lymphoma (2004-2017), time trend observed survival with incidence year

Unadjusted observed survival, %													
Characteristic	N at risk	1 year		2 year		3 year		4 year		5 year		Median survival time (year)	
		%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI	T	95% CI
All													
2004	108	75.0	[65.7, 82.1]	68.5	[58.9, 76.4]	63.0	[53.1, 71.3]	50.9	[41.2, 59.9]	43.5	[34.1, 52.6]	4.1	[3.2, 5.5]
2005	101	85.1	[76.6, 90.8]	70.3	[60.4, 78.2]	55.4	[45.2, 64.5]	51.5	[41.4, 60.7]	43.6	[33.8, 52.9]	4.1	[2.6, 5.4]
2006	119	77.3	[68.7, 83.8]	69.7	[60.6, 77.1]	60.5	[51.1, 68.6]	55.4	[46.0, 63.8]	45.2	[36.1, 53.9]	4.5	[3.2, 6.2]
2007	121	80.9	[72.7, 86.9]	70.9	[61.9, 78.1]	62.6	[53.3, 70.5]	55.0	[45.7, 63.4]	50.0	[40.8, 58.6]	5.1	[3.4, 6.3]
2008	103	74.5	[64.9, 81.9]	68.6	[58.6, 76.6]	64.6	[54.5, 73.0]	57.7	[47.4, 66.6]	50.7	[40.6, 59.9]	5.1	[3.5, 7.2]
2009	115	80.0	[71.5, 86.2]	66.1	[56.7, 73.9]	61.7	[52.2, 69.9]	58.3	[48.7, 66.6]	53.0	[43.5, 61.7]	5.4	[3.5, 7.0]
2010	134	83.6	[76.1, 88.9]	71.6	[63.2, 78.5]	66.4	[57.7, 73.7]	60.4	[51.6, 68.1]	56.7	[47.9, 64.6]	6.1	[4.5, 7.6]
2011	123	87.0	[79.6, 91.8]	78.9	[70.5, 85.1]	70.7	[61.8, 77.9]	61.0	[51.8, 69.0]	51.2	[42.1, 59.6]	5.2	[4.3, 6.8]
2012	125	85.6	[78.1, 90.7]	76.8	[68.4, 83.3]	70.4	[61.6, 77.6]	61.6	[52.5, 69.5]	56.8	[47.7, 64.9]	6.3	[4.5, .]
2013	137	80.3	[72.6, 86.0]	66.4	[57.9, 73.7]	58.4	[49.7, 66.1]	53.3	[44.6, 61.2]	51.1	[42.4, 59.1]	5.4	[3.0, 6.5]
2014	138	76.1	[68.1, 82.4]	66.7	[58.1, 73.9]	58.7	[50.0, 66.4]	51.4	[42.8, 59.4]	44.2	[35.8, 52.3]	4.2	[3.3, 5.4]
2015	131	80.9	[73.1, 86.7]	73.3	[64.8, 80.0]	62.6	[53.7, 70.2]	54.2	[45.3, 62.3]	51.2	[42.1, 59.5]	>5	
2016	166	79.5	[72.5, 84.9]	68.7	[61.0, 75.1]	58.4	[50.6, 65.5]	55.3	[47.3, 62.7]	no FU	—	>4	
2017	134	86.6	[79.5, 91.3]	76.1	[68.0, 82.5]	70.3	[59.8, 78.6]	no FU	—	no FU	—	>3	



Table 113 – Mantle cell lymphoma (2004-2017), time trend relative survival with incidence year

Unadjusted relative survival, %											
Characteristic	N at risk	%	1 year	%	2 year	%	3 year	%	4 year	%	5 year
			95% CI		95% CI		95% CI		95% CI		95% CI
All											
2004	108	77.9	[68.3, 85.3]	74.0	[63.6, 82.4]	70.9	[59.9, 80.2]	60.0	[48.5, 70.5]	53.1	[41.6, 64.3]
2005	101	87.7	[78.8, 93.6]	74.8	[64.1, 83.3]	60.8	[49.5, 70.8]	58.2	[46.7, 68.7]	50.7	[39.2, 61.7]
2006	119	79.8	[70.7, 86.8]	74.5	[64.7, 82.6]	66.8	[56.4, 75.9]	63.1	[52.3, 72.7]	52.9	[42.1, 63.1]
2007	121	83.5	[75.0, 89.7]	75.4	[65.8, 83.1]	68.7	[58.5, 77.4]	62.6	[52.0, 72.1]	58.7	[47.9, 68.7]
2008	103	76.4	[66.4, 84.2]	72.5	[61.8, 81.2]	70.5	[59.3, 79.8]	64.9	[53.3, 75.2]	58.8	[46.9, 69.7]
2009	115	83.3	[74.4, 89.8]	71.3	[61.1, 79.8]	69.0	[58.3, 78.2]	67.5	[56.4, 77.3]	63.9	[52.4, 74.3]
2010	134	86.3	[78.4, 91.9]	76.7	[67.6, 84.1]	73.5	[63.8, 81.6]	69.1	[59.0, 77.9]	67.1	[56.6, 76.5]
2011	123	90.3	[82.6, 95.3]	85.2	[76.2, 92.0]	79.6	[69.5, 87.8]	71.5	[60.6, 81.0]	62.7	[51.5, 73.1]
2012	125	88.4	[80.7, 93.6]	81.8	[72.8, 88.6]	77.5	[67.7, 85.3]	70.4	[60.0, 79.3]	67.3	[56.5, 76.8]
2013	137	83.5	[75.3, 89.6]	72.1	[62.8, 80.0]	65.7	[55.9, 74.4]	62.3	[52.2, 71.6]	62.0	[51.6, 71.7]
2014	138	79.4	[71.0, 86.0]	72.6	[63.3, 80.5]	66.8	[57.0, 75.5]	61.2	[51.0, 70.6]	54.9	[44.6, 64.9]
2015	131	84.2	[75.9, 90.3]	79.6	[70.3, 87.0]	71.4	[61.3, 80.1]	65.1	[54.4, 74.8]	63.7	[52.1, 74.5]
2016	166	83.4	[76.1, 89.1]	75.3	[66.9, 82.4]	67.4	[58.3, 75.5]	65.8	[55.7, 75.0]	no FU	—
2017	134	89.9	[82.5, 95.0]	82.0	[73.1, 89.0]	79.6	[69.2, 88.0]	no FU	—	no FU	—



Appendix 8.1.2. Uptake of selected drugs

Table 114 – CLL/SLL: proportion of patients who received at least one dose during 5-year period after diagnosis

Drug/incidence year (n)	2004 (661)	2005 (635)	2006 (626)	2007 (664)	2008 (722)	2009 (765)	2010 (797)	2011 (807)	2012 (852)	2013 (876)	2014 (942)	2015 (968)	2016 (826)	2017 (791)
Rituximab	10.3%	9.3%	18.2%	19.9%	18.8%	26.1%	28.4%	25.0%	22.8%	25.3%	22.5%	20.0%	13.6%	12.3%
Ibrutinib							1.9%	3.6%	3.4%	5.3%	7.1%	5.2%	4.0%	4.0%
Obinutuzumab							0.3%	1.5%	1.6%	2.4%	3.7%	5.1%	5.7%	3.8%

* Number in yellow indicates the first calendar year of reimbursement. For example, rituximab was first reimbursed in 2009. The columns in this table indicate the incidence year. For example, for incidence year 2010, 28.4% of patients received reimbursed rituximab during the 5 years after diagnosis. Source: BCR-IMA. Remark: IMA data were only available up to the second trimester of 2019. Five-year follow-up data are thus not complete for the last years in this table.

Table 115 – DLBCL: proportion of patients who received at least one dose during 5-year period after diagnosis

Drug/incidence year (n)	2004 (579)	2005 (600)	2006 (640)	2007 (693)	2008 (668)	2009 (694)	2010 (701)	2011 (727)	2012 (780)	2013 (812)	2014 (808)	2015 (782)	2016 (749)	2017 (756)
Rituximab*	68.7%	75.0%	72.2%	75.3%	75.9%	78.8%	78.7%	74.4%	77.3%	76.5%	77.1%	76.7%	80.8%	82.7%

* Rituximab is reimbursed for DLBCL since 2002. Source: BCR-IMA.

Table 116 – Mantle cell lymphoma: proportion of patients who received at least one dose during 5-year period after diagnosis

Drug/incidence year (n)	2004 (108)	2005 (102)	2006 (119)	2007 (121)	2008 (103)	2009 (115)	2010 (134)	2011 (123)	2012 (125)	2013 (137)	2014 (138)	2015 (131)	2016 (166)	2017 (134)
Rituximab	50.9%	63.7%	64.7%	67.8%	61.2%	73.0%	75.4%	71.5%	77.6%	68.6%	72.5%	80.9%	71.1%	76.1%
Ibrutinib							8.2%	7.3%	24.8%	19.7%	26.8%	26.0%	24.7%	8.2%

* Number in yellow indicates the first calendar year of reimbursement. Ibrutinib was first reimbursed in 2015. The columns in this table indicate the incidence year. For example, for incidence year 2016, 24.7.9% of patients received reimbursed ibrutinib during the 5 years after diagnosis. Source: BCR-IMA. Remark: IMA data were only available up to the second trimester of 2019. Five-year follow-up data are thus not complete for the last years in this table.



Appendix 8.2. reimbursement criteria for selected drugs

Table 117 – Targeted therapy in non-Hodgkin lymphoma: reimbursement criteria in Belgium

Drug	Trade name	Date start reimbursement	Indication NL	Indication Fr
Rituximab	MabThera	1/8/2000 recurrent follicular NHL 1/12/2002 DLBCL 1/10/2009 CLL 1/5/2010 maintenance 1/11/2017 current reimbursement criteria	ernstige aandoening die de levensprognose aantast en voor dewelke de arts-specialist verantwoordelijk voor de behandeling zich baseert op wetenschappelijk valide data die een brede erkenning genieten en die de werkzaamheid en veiligheid van rituximab in de desbetreffende indicatie aantonen. De bedoelde wetenschappelijke data zijn bovendien terug te vinden in internationale aanbevelingen van wetenschappelijke verenigingen die expliciet het gebruik van rituximab in de bedoelde indicatie aanvaarden. De behandelde patiënt dient te lijden aan: - hetzij een hemato-oncologische aandoening, - hetzij een ernstige immuunziekte, - hetzij hemofilie, - hetzij is de patiënt getransplanteerd.	une affection grave, engageant le pronostic vital et pour laquelle le médecin spécialiste responsable du traitement se base sur des données scientifiquement valides et largement reconnues et qui démontrent l'efficacité et la sécurité de rituximab dans l'indication en question. Les données scientifiques précitées se trouvent, en outre, dans des recommandations internationales des sociétés savantes acceptant explicitement l'utilisation de rituximab dans l'indication en question. Le patient traité par rituximab doit être atteint : - soit par une maladie hémato-oncologique, - soit par une maladie immunitaire grave, - soit par une hémophilie, - soit le patient est greffé.
Ibrutinib	Imbruvica	1/8/2015	gerecidiveerd of refractair mantelcellymfoom (MCL), na minstens één eerdere behandeling in overeenstemming met de richtlijnen van de Belgian Hematology Society voor de behandeling van MCL versie 2018.	lymphome à cellule du manteau (LCM) récidivant ou réfractaire, après au moins un traitement préalable conformément aux directives de la Belgian Hematology Society en matière de traitement du LCM version 2018.
		1/8/2015	behandeling van volwassen patiënten met chronische lymfatische leukemie (CLL). De vergoeding is toegestaan voor zover de patiënt in aanmerking komt voor behandeling volgens de meest recente criteria van de internationale werkgroep voor CLL (IWCLL) in geval van aangetoonde aanwezigheid van de 17p-deletie of TP53-mutatie.	traitement des patients adultes atteints de leucémie lymphatique chronique (LLC). Le remboursement est accordé pour autant que le patient a besoin d'un traitement selon les critères les plus récents du groupe de travail international pour la LLC (IWCLL) dans le cas de présence établie de la délétion 17p ou de la mutation de TP53.
		1/8/2015	behandeling van volwassen patiënten met chronische lymfatische leukemie (CLL). De vergoeding is toegestaan voor zover de patiënt in aanmerking komt voor het starten van een behandeling volgens de meest recente criteria van de internationale werkgroep voor CLL (IWCLL) na minstens één eerdere behandeling in overeenstemming met de richtlijnen van de Belgian	patient adulte atteint de leucémie lymphatique chronique (LLC). Le remboursement est accordé pour autant que le patient a besoin de commencer un traitement selon les critères les plus récents du groupe de travail international pour la LLC (IWCLL) après au moins un traitement préalable conformément aux directives de la Belgian Hematology Society version 2018 en matière de traitement de la LLC.



			Hematology Society versie 2018 voor de behandeling van CLL.	
		1/5/2017	behandeling van volwassen patiënten met nog niet eerder behandelde chronische lymfatische leukemie en met co-morbiditeiten waardoor zij niet in aanmerking komen voor een behandeling op basis van fludarabine. De vergoeding is toegestaan voor zover de patiënt in aanmerking komt voor het starten van een behandeling volgens de criteria van de internationale werkgroep voor CLL (IWCLL versie 2018).	traitement des patients adultes atteints de leucémie lymphoïde chronique non précédemment traités et présentant des comorbidités les rendant inéligibles à un traitement à base de fludarabine. Le remboursement est accordé pour autant que le patient a besoin de commencer un traitement selon les critères du groupe de travail international pour la LLC (IWCLL version 2018).
Obinutuzumab	Gazyvaro	1/11/2015	<p>vergoeding voor een periode van maximaal 6 cycli in combinatie met chlorambucil voor de behandeling van volwassen patiënten met nog niet eerder behandelde chronische lymfatische leukemie in afwezigheid van deletie 17p of een mutatie van TP53 en met co-morbiditeiten waardoor zij niet in aanmerking komen voor een behandeling op basis van een volledige dosis fludarabine met een:</p> <ul style="list-style-type: none"> - Rai-stadium III/IV (Binet-stadium C), - of Rai-stadium 0/I/II (Binet-stadium A/B) wanneer de patiënt zich in 1 van volgende situaties bevindt: aanwezigheid van ziektegerelateerde symptomen (gewichtsverlies, extreme vermoeidheid, nachtelijk zweten of koorts), progressieve afname van de beenmergreserve, massieve of progressieve hepatosplenomegalie of lymfadenopathie, meer dan 50 % verhoging van de perifere bloedlymfocyten over een periode van 2 maanden of een geanticipeerde verdubbeling van deze cellen in minder dan 6 maanden. 	<p>remboursement pour une période de maximum 6 cycles en association avec le chlorambucil pour le traitement des patients adultes atteints de leucémie lymphoïde chronique non précédemment traités en absence établie de la délétion 17p ou de la mutation de TP53 et présentant des comorbidités les rendant inéligibles à un traitement à base de fludarabine à pleine dose, avec un :</p> <ul style="list-style-type: none"> - stade Rai III/IV (stade Binet C), - Ou stade Rai 0/I/II (stade Binet A/B), si le patient se trouve dans 1 des situations suivantes : présence de symptômes liés à la maladie (perte de poids, fatigue extrême, sueurs nocturnes ou fièvre), insuffisance progressive de la moëlle, hépato-splénomégalie ou lymphadénopathie massive ou progressive, augmentation des lymphocytes sanguins périphériques de plus de 50 % sur une période de 2 mois ou un temps de redoublement anticipé de ces cellules de moins de 6 mois.



Appendix 8.3. Medical literature: search for evidence

Appendix 8.3.1. Search medical literature (systematic reviews)

The search for systematic reviews in MEDLINE, PreMedline and the Cochrane library of systematic reviews (inception to search date) specifically developed for this research question, yielded 439 records and 2 SRs from another source were added (Figure 324). After de-duplication, 451 (2020-2010) reviews of the 451 remaining reviews were screened based on title and abstract, of which 381 were excluded. In total 70 full text articles were assessed for eligibility. Based on full text evaluation, 59 reviews were excluded (Figure 325).

(All databases were searched in April 2020 without publication date or language restrictions. These searches were later updated at the end of January 2021 with the addition of new keywords related to CLL, Mantle cell lymphoma and diffuse large cell lymphoma.)

Figure 207 – Non-Hodgkin lymphoma – Selection of SRs - Study flow

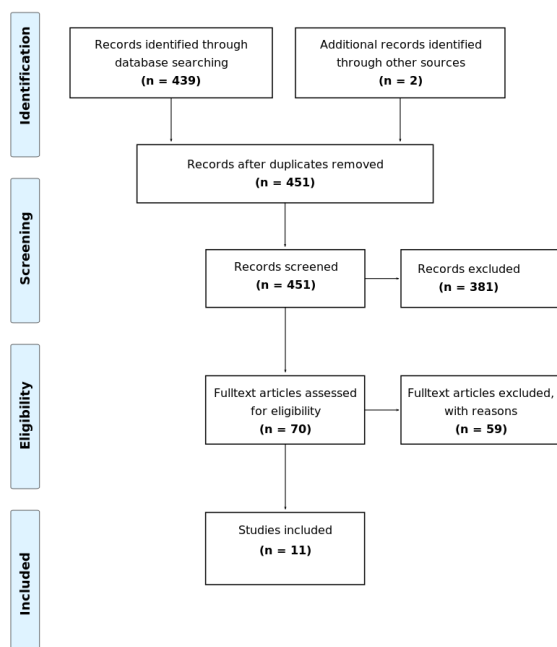



Table 118 – Non-Hodgkin lymphoma: excluded reviews and reason for exclusion

	Year	Publication	Reason for exclusion
1	2020	Zhu, J. Yang, Y. Tao, J. et al. Association of progression-free or event-free survival with overall survival in diffuse large B-cell lymphoma after immunochemotherapy: a systematic review. <i>Leukemia</i> 2020;34(10):2576-2591	Wrong research question
2	2020	Wang, J. Huang, J. Zeng, Q. Network meta-analysis of targeted therapies for diffuse large B cell lymphoma. <i>BMC Cancer</i> 2020;20(1):1218	Included
3	2020	Thuresson, P. O. Vander Velde, N.Gupta, P.Talbot, J. A Systematic Review of the Clinical Efficacy of Treatments in Relapsed or Refractory Diffuse Large B Cell Lymphoma. <i>Adv Ther</i> 2020;37(12):4877-4893	Wrong research question
4	2020	Sheng, Z. Song, S. Yu, M. et al. Comparison of acalabrutinib plus obinutuzumab, ibrutinib plus obinutuzumab and venetoclax plus obinutuzumab for untreated CLL: a network meta-analysis. <i>Leuk Lymphoma</i> 2020;61(14):3432-3439	Full text could not be obtained
5	2020	Molica, S. Giannarelli, D. Montserrat, E. Comparison Between Venetoclax-based and Bruton Tyrosine Kinase Inhibitor-based Therapy as Upfront Treatment of Chronic Lymphocytic Leukemia (CLL): A Systematic Review and Network Meta-analysis. <i>Clin Lymphoma Myeloma Leuk</i> 2020;29:29	Wrong research question
6	2020	Amitai, I. Gafter-Gvili, A. Shargian-Alon, L. et al. Obinutuzumab-related adverse events: A systematic review and meta-analysis. <i>Hematol Oncol</i> 2020;30:30	Included for search (see above)
7	2020	Molica, S. Giannarelli, D. Shanafelt, T. D. Comparison of venetoclax plus rituximab with B-cell receptor inhibitors in patients with relapsed/refractory chronic lymphocytic leukemia: a systematic review and network Meta-analysis. <i>Leuk Lymphoma</i> 2020; 61(4):955-958	Searched only 1 database, no critical appraisal
8	2020	Molica, S. Giannarelli, D. Baumann, T. Montserrat, E. Ibrutinib as initial therapy in chronic lymphocytic leukemia: A systematic review and meta-analysis. <i>Eur J Haematol</i> 2020; 104(5): 512-515	Included (searched only 1 database but no other recent SR found)
9	2020	Ma, S. Y. Tian, X. P. Cai, J. et al. Upfront autologous stem cell transplantation for untreated diffuse large B cell lymphoma patients in rituximab era: a systematic review and meta-analysis. <i>Ann Hematol</i> 2020; 13:13	wrong research question
10	2020	Linschoten, M. Kamphuis, J. A. M. van Rhenen, A. et al. Cardiovascular adverse events in patients with non-Hodgkin lymphoma treated with first-line cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or CHOP with rituximab (R-CHOP): a systematic review and meta-analysis. <i>Lancet Haematol</i> 2020; 7(4):e295-e308	Wrong outcome
11	2020	Lee, C. H. Chen, P. H. Lin, C. et al. A network meta-analysis of maintenance therapy in chronic lymphocytic leukemia. 2020; 15(1): e0226879	Included
12	2020	Farooqui, A. A. Ashraf, A. Farooq, T. B. et al. Novel Targeted Therapies for Chronic Lymphocytic Leukemia in Elderly Patients: A Systematic Review. <i>Clin Lymphoma Myeloma Leuk</i> 2020; 27:27	no critical appraisal, narrative review of results
13	2020	Ball, S. Das, A. Vutthikraivit, W. et al. Risk of Infection Associated With Ibrutinib in Patients With B-Cell Malignancies: A Systematic Review and Meta-analysis of Randomized Controlled Trials. <i>Clin Lymphoma Myeloma Leuk</i> 2020; 2:87-97	wrong outcome
14	2019	Harkins, R. A. Patel, S. P. Flowers, C. R. Cost-effectiveness of New Targeted Agents in the Treatment of Chronic Lymphocytic Leukemia. <i>Cancer J</i> 2020;25(6):418-427	Wrong research question



	Year	Publication	Reason for exclusion
15	2019	Zhou, Y. Lu, H. Yang, M. Xu, C. Adverse drug events associated with ibrutinib for the treatment of elderly patients with chronic lymphocytic leukemia: A systematic review and meta-analysis of randomized trials. <i>Medicine (Baltimore)</i> 2019; 98(33):e16915	wrong outcome
16	2019	Tappenden, P. Simpson, E. Hamilton, J. et al. Ibrutinib for Treating Relapsed or Refractory Mantle Cell Lymphoma: An Evidence Review Group Perspective of a NICE Single Technology Appraisal. <i>Pharmacoeconomics</i>	Included (not a systematic review, see above)
17	2019	Schmitt, A. M. Herbrand, A. K. Fox, C. P. Rituximab in primary central nervous system lymphoma-A systematic review and meta-analysis. <i>Hematol Oncol</i> 2019; 16:16	excluded
18	2019	Sardar, M. Malik, S. U. Khan, A. et al. Efficacy of Ibrutinib-Based Regimen in Chronic Lymphocytic Leukemia: A Systematic Review. <i>J Hematol (Brossard)</i> 2019; 8(1):1-10	single arm studies included, no meta-analysis
19	2019	Rozental, A. Gafter-Gvili, A. Vidal, L. et al. The role of maintenance therapy in patients with diffuse large B cell lymphoma: A systematic review and meta-analysis. <i>Hematol Oncol</i> 2019; 37(1):27-34	Included
20	2019	Pokrovsky, V. S. Vinnikov, D. Defining the toxicity of current regimens for extranodal NK/T cell lymphoma: a systematic review and metapropotion. <i>Expert Rev Anticancer Ther</i> 2019;19(1):93-104	selected drugs not included
21	2019	Molica, S. Giannarelli, D. Mirabelli, R. et al. The magnitude of improvement in progression-free survival with targeted therapy in relapsed/refractory chronic lymphocytic leukemia based on prognostic risk category: a systematic review and meta-analysis. <i>Leuk Lymphoma</i> 2019; 60(7):1644-1649	not specific for ibrutinib
22	2019	Kunacheewa, C. Thongthang, P. Ungprasert, P. et al. A systematic review and meta-analysis of the efficacy and adverse events of azacitidine-plus-lenalidomide treatment for patients with acute myeloid leukemia, myelodysplastic syndromes and chronic myelomonocytic leukemia 1. <i>Hematol</i> 2019; 24(1):498-506	Cohort studies only, wrong population
23	2019	Epperla, N. Hamadani, M. Reljic, T. et al. Upfront autologous hematopoietic stem cell transplantation consolidation for patients with aggressive B-cell lymphomas in first remission in the rituximab era: A systematic review and meta-analysis. <i>Cancer</i> 2019; 125(24): 4417-4425	wrong comparison
24	2019	Chen, P. H. Ho, C. L. Lin, C. Treatment Outcomes of Novel Targeted Agents in Relapse/Refractory Chronic Lymphocytic Leukemia: A Systematic Review and Network Meta-Analysis <i>J Clin Med</i> , 2019 May 23;8(5):737	Included
25	2019	Caldeira, D. Alves, D. Costa, J. et al. Ibrutinib increases the risk of hypertension and atrial fibrillation: Systematic review and meta-analysis. <i>PLoS ONE</i> 2019; 14(2): e0211228	wrong outcome
26	2018	Yamshon, S. Christos, P. J. Demetres, M. et al. Venous thromboembolism in patients with B-cell non-Hodgkin lymphoma treated with lenalidomide: a systematic review and meta-analysis. <i>Blood Adv</i> 2018;2(12):1429-1438	wrong outcome
27	2018	Xu, Y. Fahrbach, K. Dorman, E. et al. Front-line treatment of patients with chronic lymphocytic leukemia: a systematic review and network meta-analysis. <i>J. Comp. Eff. Res.</i> (2018) 7(5), 421–441	No pairwise meta-analysis, no additional information
28	2018	Vidal, L. Gafter-Gvili, A. Dreyling, M. et al. Maintenance Treatment for Patients With Mantle Cell Lymphoma: A Systematic Review and Meta-analysis of Randomized Trials. <i>HemaSphere</i> 2018;2(4):e136	Included



	Year	Publication	Reason for exclusion
29	2018	Tillman, B. F. Pauff, J. M. Satyanarayana, G. et al. Systematic review of infectious events with the Bruton tyrosine kinase inhibitor ibrutinib in the treatment of hematologic malignancies. <i>Eur J Haematol</i> 2018;100(4):325-334	wrong outcome
30	2018	Sorigue, M. Orna, E. Sancho, J. M. Venous thromboembolism in patients with non-Hodgkin lymphoma or chronic lymphocytic leukemia treated with lenalidomide: a systematic review. <i>Leuk Lymphoma</i> 2018;59(11):2602-2611	wrong outcome
31	2018	Pula, A. Stawiski, K. Braun, M. et al. Efficacy and safety of B-cell receptor signaling pathway inhibitors in relapsed/refractory chronic lymphocytic leukemia: a systematic review and meta-analysis of randomized clinical trials. <i>Leuk Lymphoma</i> 2018; 59(5):1084-1094	Not specific for ibrutinib
32	2018	Lin, Z. Chen, X. Li, Z. et al. The role of bortezomib in newly diagnosed diffuse large B cell lymphoma: a meta-analysis. <i>Ann Hematol</i> 2018; 97(11):2137-2144	Drug not selected
33	2018	Laribi, K. Alani, M. Truong, C. de Materre, A. B. Evolving Strategies for the Treatment of T-Cell Lymphoma: A Systematic Review and Recent Patents. <i>Recent Patents Anticancer Drug Discov</i> 2018; 13(3):308-340	Selected drugs not included
34	2018	Iacoboni, G. Zucca, E. Ghielmini, M. Stathis, A. Methodology of clinical trials evaluating the incorporation of new drugs in the first-line treatment of patients with diffuse large B-cell lymphoma (DLBCL): a critical review. <i>Ann Oncol</i> 29(5):1120-1129	not a systematic review
35	2018	Hilal, T. Wang, Z. Almader-Douglas, D. et al. Rituximab maintenance therapy for mantle cell lymphoma: A systematic review and meta-analysis. <i>Am J Hematol</i> 2018; 93(10):1220-1226	Observational studies included
36	2018	Andrasiak, I. Rybka, J. Wrobel, T. Response to the Therapy in Hairy Cell Leukemia: Systematic Review and Meta-Analysis. <i>Clin Lymphoma Myeloma Leuk</i> 2018; 18(6):392-399e3	wrong population
37	2018	Galaznik, A. Huelin, R. Stokes, M. et al. Systematic review of therapy used in relapsed or refractory diffuse large B-cell lymphoma and follicular lymphoma. <i>Future Sci OA</i> 2018; 4(7):FSO322	observational studies
38	2018	Beygi, S. Sadashiv, S. Reilly, J. B. et al. Frontline treatment of diffuse large B-cell lymphoma in elderly: a systematic review of clinical trials in post-rituximab era. <i>Leuk Lymphoma</i> 2018; 59(12):2847-2861	wrong comparisons
39	2017	Zhou, X. Ma, T. Zhang, Y. et al. Rituximab maintenance therapy for patients with diffuse large B-cell lymphoma: A meta-analysis. <i>PLoS ONE</i> 2017; 12(3):e0174648	Included
40	2017	Vidal, L. Gafter-Gvili, A. Salles, G. et al. Rituximab maintenance improves overall survival of patients with follicular lymphoma-Individual patient data meta-analysis. <i>Eur J Cancer</i> 2017; 76: 216-225	Wrong population
41	2017	Sorensen, S. Wildgust, M. Sengupta, N. et al. Indirect Treatment Comparisons of Ibrutinib Versus Physician's Choice and Idelalisib Plus Ofatumumab in Patients With Previously Treated Chronic Lymphocytic Leukemia. <i>Clin Ther</i> 2017 39(1): 178-189;e5	No additional information
42	2017	Song, Y. Wen, Y. Xue, W. et al. Effect of rituximab on primary central nervous system lymphoma: a meta-analysis. <i>Int J Hematol</i> 2017; 106(5):612-621	No additional information, inclusion of observational studies
43	2017	Rule, S. Dreyling, M. Goy, A. et al. Outcomes in 370 patients with mantle cell lymphoma treated with ibrutinib: a pooled analysis from three open-label studies. <i>Br J Haematol</i> 2017; 179(3):430-438	Not a systematic review



	Year	Publication	Reason for exclusion
44	2017	Andrasiak, I. Rybka, J. Knopinska-Posluszny, W. et al. Efficacy and Safety of Bendamustine and Ibrutinib in Previously Untreated Patients With Chronic Lymphocytic Leukemia: Indirect Comparison. 2017; 17(5):268-273	no additional information
45	2016	Yang, Y. T. Tai, C. J. Chen, C. et al. Highly Diverse Efficacy of Salvage Treatment Regimens for Relapsed or Refractory Peripheral T-Cell Lymphoma: A Systematic Review PLoS ONE 2016;11(10): e0161811	Reported results not within reimbursement criteria
46	2016	Taverna, J. A. Yun, S. Jonnadula, J. et al. Role of Maintenance Therapy after High-Dose Chemotherapy and Autologous Hematopoietic Cell Transplantation in Aggressive Lymphomas: A Systematic Review Biol Blood Marrow Transplant 2016; 22(7):1182-1196	No additional information
47	2016	Stadler, N. Shang, A. Bosch, F. et al. A Systematic Review and Network Meta-Analysis to Evaluate the Comparative Efficacy of Interventions for Unfit Patients with Chronic Lymphocytic Leukemia Adv Ther 2016;33(10):1814-1830	No additional information
48	2016	Nie, M. Wang, Y. Bi, X. W. et al. Effect of rituximab on adult Burkitt's lymphoma: a systematic review and meta-analysis. Ann Hematol 2016; 95(1):19-26	Observational studies included
49	2016	Liang, L. Zhao, M. Zhu, Y. C. et al. Efficacy of lenalidomide in relapsed/refractory chronic lymphocytic leukemia patient: a systematic review and meta-analysis. Ann Hematol 2016;95(9): 1473-82	Not within reimbursement criteria
50	2016	Leong, D. P. Caron, F. Hillis, C. et al. The risk of atrial fibrillation with ibrutinib use: a systematic review and meta-analysis Blood 2016; 128(1):138-140	letter to the editor
51	2016	Blommestein, H. M. Armstrong, N. Ryder, S. et al. Lenalidomide for the Treatment of Low- or Intermediate-1-Risk Myelodysplastic Syndromes Associated with Deletion 5q Cytogenetic Abnormality: An Evidence Review of the NICE Submission from Celgene. Pharmacoeconomics 2016;34(1):23-31	Not a systematic review, wrong population
52	2016	Lian XY, Zhang ZH, Deng ZQ et al. Efficacy and Safety of Lenalidomide for Treatment of Low-/Intermediate-1-Risk Myelodysplastic Syndromes With or Without 5q Deletion: A Systematic Review and Meta-Analysis PLoS One. 2016 Nov 8;11(11):e0165948	Wrong population
53	2015	Saret, C. J. Winn, A. N. Shah, G. et al. Value of innovation in hematologic malignancies: a systematic review of published cost-effectiveness analyses Blood 2015; 125(12):1866-9	Wrong research question
54	2015	Ren, Y. R. Jin, Y. D. Zhang, Z. H. et al. Rituximab treatment strategy for patients with diffuse large B-cell lymphoma after first-line therapy: a systematic review and meta-analysis Chin Med J 2015;128(3):378-83	Included
55	2015	Nannya, Y. Goto, N. Shimizu, M. et al. Efficacy of rituximab maintenance therapy for aggressive B-cell lymphoma depends on use of rituximab in induction therapy: a meta-analysis of randomized controlled trials. Haematologica 2015;100(12):e519-20	No additional information
56	2015	Messori, A. Fadda, V. Maratea, D. Trippoli, S. First-line treatments for chronic lymphocytic leukaemia: interpreting efficacy data by network meta-analysis. Ann Hematol 2015;94(6):1003-9	No additional information, searched only 1 database
57	2015	Messori, A. Fadda, V. Maratea, D. Trippoli, S. Comparative effectiveness of treatments for newly diagnosed follicular non-Hodgkin lymphoma Leuk Lymphoma 2015; 56(9):277-28-30	searched only 1 database, no critical appraisal, no additional information



	Year	Publication	Reason for exclusion
58	2015	Meng, F. Zhong, D. Zhang, L. et al. Efficacy and safety of rituximab combined with chemotherapy in the treatment of diffuse large B-cell lymphoma: a meta-analysis. <i>Int J Clin Exp Med</i> 2015; 8(10):17515-22	No critical appraisal
59	2015	Ladyszynski, P. Molik, M. Foltynski, P. A network meta-analysis of progression free survival and overall survival in first-line treatment of chronic lymphocytic leukemia. <i>Cancer Treat Rev</i> 2015; 41(2): 77-93	No additional information
60	2015	Hua, Q. Zhu, Y. Liu, H. Severe and fatal adverse events risk associated with rituximab addition to B-cell non-Hodgkin's lymphoma (B-NHL) chemotherapy: a meta-analysis. <i>J Chemother</i> 2015;27(6): 365-70	No additional information
61	2015	He, G. Wang, C. Tan, H. He, S. Rituximab after autologous stem cell transplantation enhances survival of B-cell lymphoma patients: a meta-analysis and systematic review. <i>Transplant Proc</i> 2015; 47(2)	No additional information
62	2015	Ghose, A. Elias, H. K. Guha, G. et al. Influence of Rituximab on Central Nervous System Relapse in Diffuse Large B-Cell Lymphoma and Role of Prophylaxis--A Systematic Review of Prospective Studies. <i>Clin Lymphoma Myeloma Leuk</i> 2015; 15(8):451-7	No additional information
63	2015	Fang, C. Zhu, D. Dong, H. et al. Lenalidomide alone or in combination with chemotherapy treatment for subtypes of diffuse large B cell lymphoma: a systematic review and meta-analysis <i>Int J Clin Exp Med</i> 2015;8(7):10705-13	wrong comparison
64	2014	Nabhan, C. Ollberding, N. J. Villines, D. et al. A systematic review of comparative schedule-related toxicities with maintenance rituximab in follicular and mantle cell lymphomas. <i>Leuk Lymphoma</i> 2014; 55(6):1288-94	wrong comparison
65	2014	Geynisman, D. M. Chien, C. R. Smieliauskas, F. et al. Economic evaluation of therapeutic cancer vaccines and immunotherapy: a systematic review <i>Hum Vaccin Immunother</i> 2014; 10(11):3415-24	Wrong research question
66	2014	Colosia, A. Njue, A. Trask, P. C. et al. Clinical efficacy and safety in relapsed/refractory diffuse large B-cell lymphoma: a systematic literature review <i>Clin Lymphoma Myeloma Leuk</i> 2014; 14(5):343-355.e6	No additional information
67	2013	Terasawa, T. Trikalinos, N. A. Djulbegovic, B. Trikalinos, T. A. Comparative efficacy of first-line therapies for advanced-stage chronic lymphocytic leukemia: a multiple-treatment meta-analysis <i>Cancer Treat Rev</i> 2013;39(4):340-9	no additional information
68	2013	Nardone, B. Wu, S. Garden, B. C. et al. Risk of rash associated with lenalidomide in cancer patients: a systematic review of the literature and meta-analysis <i>Clin Lymphoma Myeloma Leuk</i> 2013; 13(4):424-9	Wrong outcomes
69	2013	Leitch, H. A. Buckstein, R. Shamy, A. Storrington, J. M. The immunomodulatory agents lenalidomide and thalidomide for treatment of the myelodysplastic syndromes: a clinical practice guideline <i>Crit Rev Oncol Hematol</i> 2013; 85(2):162-92	No additional information
70	2007	Schulz h, Bohlius J, Skoetz N et al. Chemotherapy plus Rituximab versus chemotherapy alone for B-cell non-Hodgkin's lymphoma. <i>Cochrane Database Syst Rev</i> . 2007 Oct 17;(4):CD003805	Included



Appendix 8.3.2. Critical appraisal systematic reviews

	Schulz 2007 ¹⁷⁰		Schmitt 2019 ¹⁷¹	
	Score	Rationale/comment	score	Rationale/comment
1. PICO	Y		Y	
2. A priori study design	N		Y	
3. Inclusion study designs	Y		Y	
4. Comprehensive literature search	Y		partial Y	No search of references, no consultation of content experts
5. Duplicate study selection	Y		Y	
6. Duplicate data extraction	Y		Y	
7. List of excluded studies and rationale	Y		N	
8. Characteristics of included studies provided	Y		Y	
9. Assessment of risk of bias	Y		Y	
10. Sources of funding reported	Y		N	
11. Appropriate methods to combine findings	Y		Y	
12. Assessment of impact RoB in included studies on results MA	Y		N	
13. RoB assessment used in interpretation of results and in conclusions	Y		Y	
14. Explanation for and discussion of any observed heterogeneity	Y		N	
15. Adequate investigation of publication bias and its impact on the results	Y		N	
16. Potential sources of conflict of interest reported	Y		Y	



	Rozenal 2019 ¹⁷²		Vidal 2018 ¹⁷³	
	Score	Rationale/comment	score	Rationale/comment
1. PICO	Y		Y	
2. A priori study design	N		N	
3. Inclusion study designs	Y		Y	
4. Comprehensive literature search	partial Y	no search of trial registers, no content experts consulted	Y	(authors are content experts themselves)
5. Duplicate study selection	N	unclear	N	unclear
6. Duplicate data extraction	Y		Y	
7. List of excluded studies and rationale	N	aggregated data only	Partial Y	Rationale not reported
8. Characteristics of included studies provided	Y		Y	
9. Assessment of risk of bias	Y		Y	
10. Sources of funding reported	N	Funding of included studies not reported	N	Funding of included studies not reported
11. Appropriate methods to combine findings	Y		Y	
12. Assessment of impact RoB in included studies on results MA	N		N	
13. RoB assessment used in interpretation of results and in conclusions	N		Y	
14. Explanation for and discussion of any observed heterogeneity	Y		Y	
15. Adequate investigation of publication bias and its impact on the results	N		Y	
16. Potential sources of conflict of interest reported	Y		Y	



	Zhou 2017 ¹⁷⁴		Vidal 2017 ¹⁷⁵	
	Score	Rationale/comment	score	Rationale/comment
1. PICO	Y		Y	
2. A priori study design	N		N	
3. Inclusion study designs	Y		Y	
4. Comprehensive literature search	Partial Y	No search of references, no search of trial registries, no consultation of content experts	Partial Y	
5. Duplicate study selection	Y		Y	
6. Duplicate data extraction	Y		Y	
7. List of excluded studies and rationale	N	aggregated data only	N	
8. Characteristics of included studies provided	partial Y		Y	
9. Assessment of risk of bias	Y		Y	
10. Sources of funding reported	N	Funding of included studies not reported	N	Funding of included studies not reported. MA funded by Roche
11. Appropriate methods to combine findings	Y		Y	
12. Assessment of impact RoB in included studies on results MA	N		N	
13. RoB assessment used in interpretation of results and in conclusions	N		N	
14. Explanation for and discussion of any observed heterogeneity	Y		Y	
15. Adequate investigation of publication bias and its impact on the results	N		N	
16. Potential sources of conflict of interest reported	Y		Y	



	Colosia 2014 ¹⁷⁶		Lian 2016 ¹⁷⁷	
	Score	Rationale/comment	score	Rationale/comment
1. PICO	Y			
2. A priori study design	N			
3. Inclusion study designs	Y			
4. Comprehensive literature search	Y			
5. Duplicate study selection	Y		?	Unclear, a third reviewer is mentioned
6. Duplicate data extraction	Y		Y	
7. List of excluded studies and rationale	N		N	
8. Characteristics of included studies provided	Y		Y	
9. Assessment of risk of bias	Y		Y/N	Risk of bias assessment of non-randomised studies unclear
10. Sources of funding reported	N	SR funded by Sanofi. Funding of included studies not reported.	N	Funding of included studies not reported
11. Appropriate methods to combine findings	Y	Unclear, but no MA performed with reasons	Y	
12. Assessment of impact RoB in included studies on results MA	Y		N	
13. RoB assessment used in interpretation of results and in conclusions	Y		N	
14. Explanation for and discussion of any observed heterogeneity	Y		N	
15. Adequate investigation of publication bias and its impact on the results	N	(low number of RCTs)	Y	
16. Potential sources of conflict of interest reported	Y		N	



	Ball 2020 ¹⁷⁸		Leong 2016 ¹⁷⁹	
	Score	Rationale/comment	score	Rationale/comment
1. PICO	Y		Y	
2. A priori study design	N		N	
3. Inclusion study designs	Y		Y	
4. Comprehensive literature search	partial Y	No search of reference lists, no search of trial registries,	partial Y	No search of reference lists, no search of trial registries,
5. Duplicate study selection	Y		Y	
6. Duplicate data extraction	N	unclear	N	
7. List of excluded studies and rationale	N		N	aggregated data only
8. Characteristics of included studies provided	Y		Y	
9. Assessment of risk of bias	Y		N	
10. Sources of funding reported	N		N	funding of included studies not reported
11. Appropriate methods to combine findings	Y		Y	
12. Assessment of impact RoB in included studies on results MA	N		N	
13. RoB assessment used in interpretation of results and in conclusions	N		N	
14. Explanation for and discussion of any observed heterogeneity	Y		N	
15. Adequate investigation of publication bias and its impact on the results	Y		N	
16. Potential sources of conflict of interest reported	Y		Y	



	Chen 2019 ¹⁸⁰		Lee 2020 ¹⁸¹	
	Score	Rationale/comment	score	Rationale/comment
1. PICO	Y		Y	
2. A priori study design	Y		Y	
3. Inclusion study designs	Y		Y	
4. Comprehensive literature search	Y		partial Y	No search of reference lists of included studies, no search of trial registries
5. Duplicate study selection	N		Y	
6. Duplicate data extraction	Y		Y	
7. List of excluded studies and rationale	N		Y	
8. Characteristics of included studies provided	Y		Y	
9. Assessment of risk of bias	Y		Y	
10. Sources of funding reported	N	Funding sources of included studies not reported	N	Funding sources of included studies not reported
11. Appropriate methods to combine findings	Y		Y	
12. Assessment of impact RoB in included studies on results MA	Y		Y	
13. RoB assessment used in interpretation of results and in conclusions	N		Y	
14. Explanation for and discussion of any observed heterogeneity	N		N	
15. Adequate investigation of publication bias and its impact on the results	N		Y	
16. Potential sources of conflict of interest reported	Y		Y	



	Molica 2020 ¹⁸²		Ren 2015 ¹⁸³	
	Score	Rationale/comment	score	Rationale/comment
1. PICO	Y		Y	
2. A priori study design	N		N	
3. Inclusion study designs	Y		Y	
4. Comprehensive literature search	N	searched only 1 database, no search of references, no search of trial databases	N	no search of trial databases
5. Duplicate study selection	Y		Y	
6. Duplicate data extraction	N		Y	
7. List of excluded studies and rationale	N		N	
8. Characteristics of included studies provided	partial Y		Y	
9. Assessment of risk of bias	Y		partial Y	no assessment of selective reporting
10. Sources of funding reported	N		N	Funding of included studies not reported
11. Appropriate methods to combine findings	Y		Y	
12. Assessment of impact RoB in included studies on results MA	Y		Y	
13. RoB assessment used in interpretation of results and in conclusions	N		N	
14. Explanation for and discussion of any observed heterogeneity	Y		Y	
15. Adequate investigation of publication bias and its impact on the results	Y		N	
16. Potential sources of conflict of interest reported	Y		Y	



	Wang 2020 ¹⁸⁴		Amitai 2020 ¹⁸⁵	
	Score	Rationale/comment	score	Rationale/comment
1. PICO	Y		Y	
2. A priori study design	N		N	
3. Inclusion study designs	Y		Y	
4. Comprehensive literature search	Partial Y	No search of trial registries, no consultation of content experts	Yes	
5. Duplicate study selection	Y		Y	
6. Duplicate data extraction	Y		Y	
7. List of excluded studies and rationale	N		N	
8. Characteristics of included studies provided	Y		Y	
9. Assessment of risk of bias	Partial Y	No assessment of selective outcome reporting	Y	
10. Sources of funding reported	Y		N	
11. Appropriate methods to combine findings	Y		Y	
12. Assessment of impact RoB in included studies on results MA	N		N	
13. RoB assessment used in interpretation of results and in conclusions	N		N	
14. Explanation for and discussion of any observed heterogeneity	N		N	
15. Adequate investigation of publication bias and its impact on the results	Y		N	
16. Potential sources of conflict of interest reported	Y		Y	



Appendix 8.3.3. Search strategy

Appendix 8.3.3.1. Non-hodgkin lymphoma

Cochrane library of systematic reviews

Date	23/06/2020 20:18:20	
Database	Cochrane@Wiley.com	
Search strategy		
#1	[mh "Lymphoma"]	3164
#2	lymphoma*:ab,ti	9045
#3	nonhodgkin:ab,ti	2632
#4	"non-hodgkin":ab,ti	2871
#5	NHL*:ab,ti	2019
#6	((hematol* or haematol*) NEAR/3 malign*):ab,ti	1949
#7	germinoblastoma*:ab,ti	0
#8	reticulolymphosarcoma*:ab,ti	0
#9	(lymphatic NEAR/3 sarcoma?):ab,ti	0
#10	lymphosarcom*:ab,ti	23
#11	reticulosarcom*:ab,ti	4
#12	("reticulum cell sarcoma" or "reticulum cell sarcoma"):ab,ti	5
#13	(burkitt? NEAR/3 (leucemia? or leukemia? or leucaemia? or leukaemia? or tumor? or tumour?)):ab,ti	21
#14	lymphomatoid NEAR/3 granulomatos*:ab,ti	4
#15	"brill symmers disease":ab,ti	0
#16	immunoblastoma?:ab,ti	0
#17	(immunoblastic NEAR/3 sarcom*):ab,ti	1
#18	"granulomatous slack skin":ab,ti	0
#19	lymphomatoid NEAR/3 papulos*:ab,ti	2
#20	"mycosis fungoides":ab,ti	177
#21	pagetoid NEAR/3 reticulos*:ab,ti	0
#22	"ketron goodman disease":ab,ti	0
#23	"woringer kolopp disease":ab,ti	0
#24	"sezary erythroderma":ab,ti	0
#25	"sezary syndrome":ab,ti	58
#26	lymphoma:so	921
#27	#2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26	11770



#28	#1 or #27	12461
#29	[mh ^"Leukemia, Lymphocytic, Chronic, B-Cell"]	459
#30	(leu??emia? NEAR/3 lymphocytic NEAR/5 chronic):ab,ti	2
#31	(leu??emia? NEAR/3 lymphoblastic NEAR/5 chronic):ab,ti	0
#32	lymphocytic lymphoma?:ab,ti	565
#33	(chronic NEAR/3 leu??emia? NEAR/3 B-cell):ab,ti	1
#34	(small-cell NEAR/3 lymphoma?):ab,ti	0
#35	#30 OR #31 OR #32 OR #33 OR #34	567
#36	#29 or #35	923
#37	[mh "Myelodysplastic syndromes"]	685
#38	(myelodysplastic NEAR/3 syndrome?):ab,ti,so	1609
#39	(dysmyelopoietic NEAR/3 syndrome?):ab,ti	0
#40	(Hematopoietic NEAR/3 Myelodysplasia?):ab,ti	0
#41	(anemia? NEAR/3 refractory):ab,ti,so	189
#42	(anemia? NEAR/3 sideroblastic):ab,ti,so	12
#43	(Paroxysmal NEAR/3 Hemoglobinuria?):ab,ti,so	115
#44	(Marchiafava-Micheli NEAR/2 Syndrome):ab,ti	0
#45	#38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44	1824
#46	#37 or #45	2054
#47	#28 or #36 or #46	14461
#48	[mh ^"lenalidomide"]	373
#49	lenalidomide:ab,ti	1787
#50	Revlimid:ab,ti	167
#51	Revimid:ab,ti	0
#52	"IMiD3 Cpd":ab,ti	0
#53	"imid 3":ab,ti	3
#54	"CC 5013":ab,ti	64
#55	CC5013:ab,ti	1
#56	F0P408N6V4:ab,ti	0
#57	"SYP-1512":ab,ti	1
#58	SYP1512:ab,ti	0
#59	"CDC-501":ab,ti	4
#60	CDC501:ab,ti	0
#61	cdc5013:ab,ti	0
#62	"cdc 5013":ab,ti	2
#63	"enmd 0997":ab,ti	0
#64	enmd0997:ab,ti	0
#65	"191732-72-6":ab,ti	69



#66	#49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65	1821
#67	#48 or #66	1832
#68	ibrutinib:ab,ti	465
#69	IMBRUVICA:ab,ti	23
#70	1X70OSD4VX:ab,ti	0
#71	"CRA 032765":ab,ti	0
#72	CRA032765:ab,ti	0
#73	"PCI-32765":ab,ti	28
#74	PCI32765:ab,ti	0
#75	"PC 32765":ab,ti	0
#76	PC32765:ab,ti	0
#77	"936563-96-1":ab,ti	34
#78	#68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77	469
#79	[mh ^"rituximab"]	1222
#80	RITUXIMAB:ab,ti	4340
#81	Mabthera:ab,ti	352
#82	Rituxan:ab,ti	106
#83	TUXELLA:ab,ti	0
#84	TRUXIMA:ab,ti	4
#85	RITEMVIA:ab,ti	0
#86	BLITZIMA:ab,ti	0
#87	RUXIENCE:ab,ti	0
#88	"IDEC-C2B8":ab,ti	19
#89	GP2013:ab,ti	26
#90	4F4X42SYQ6:ab,ti	0
#91	"RG-105":ab,ti	0
#92	"IDEC-102":ab,ti	0
#93	"PF-05280586":ab,ti	15
#94	"CT-P10":ab,ti	48
#95	ABP798:ab,ti	2
#96	"ABP-798":ab,ti	5
#97	SAIT101:ab,ti	8
#98	"SAIT-101":ab,ti	0
#99	RHCACD20MA:ab,ti	1
#100	HS006:ab,ti	1
#101	"HS-006":ab,ti	0
#102	"BI-695500":ab,ti	8



#103	RG105:ab,ti	0
#104	IDEC102:ab,ti	0
#105	PF05280586:ab,ti	0
#106	BI695500:ab,ti	1
#107	#80 OR #81 OR #82 OR #83 OR #84 OR #85 OR #86 OR #87 OR #88 OR #89 OR #90 OR #91 OR #92 OR #93 OR #94 OR #95 OR #96 OR #97 OR #98 OR #99 OR #100 OR #101 OR #102 OR #103 OR #104 OR #105 OR #106	4391
#108	#79 or #107	4494
#109	#67 or #78 or #108	6372
#110	#47 and #109	3032
#111	[mh "angiogenesis inhibitors"]	1093
#112	[mh ^"Ikars Transcription Factor"/AI]	0
#113	[mh ^"Protein Kinase Inhibitors"]	762
#114	[mh "Protein-Tyrosine Kinases"/AI]	640
#115	[mh "immunologic factors"]	8153
#116	[mh ^"Chemokine CXCL12"/AI]	0
#117	[mh ^"Chemokine CXCL13"/AI]	0
#118	#111 OR #112 OR #113 OR #114 OR #115 OR #116 OR #117	10294
#119	(angiogenesis NEAR/5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)):ab,ti	668
#120	(ikars NEAR/5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)):ab,ti	9
#121	(ikzf* NEAR/5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)):ab,ti	3
#122	(CD20 NEAR/5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)):ab,ti	617
#123	((CXCL12 or cxcl 12) NEAR/5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)):ab,ti	10799
#124	((cxcl13 or cxcl 13) NEAR/5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)):ab,ti	3540
#125	immunomodulator?.ti,kf.	83
#126	(BTK NEAR/5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)):ab,ti	186
#127	#119 OR #120 OR #121 OR #122 OR #123 OR #124 OR #125 OR #126	15553
#128	#118 or #127	25537
#129	#47 and #128	683
#130	((new class* or innovative or target*) NEAR/3 (drug? or therapy or therapies or therapeutic* or treatment? or chemotherap*)):ab,ti	34196
#131	[mh "Antibodies, Monoclonal"]	12727
#132	(kinase NEAR/5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)):ab,ti	4316
#133	(monoclonal NEAR/3 antibod*):ab,ti	8824
#134	#130 or #131 or #132 or #133	55615
#135	#47 and #134	2232
#136	#110 or #129 or #135	4263
#137	#136 in Cochrane Reviews	27
Comments		



Update

Date	28/01/2021 07:03:02	
Database	Cochrane@Wiley.com	
Search strategy		
#1	[mh "Lymphoma"]	3246
#2	lymphoma*:ab,ti	9374
#3	nonhodgkin:ab,ti	2690
#4	"non-hodgkin":ab,ti	2936
#5	NHL*:ab,ti	2066
#6	((hematol* or haematol*) NEAR/3 malign*):ab,ti	2024
#7	germinoblastoma*:ab,ti	0
#8	reticulolymphosarcoma*:ab,ti	0
#9	(lymphatic NEAR/3 sarcoma?):ab,ti	0
#10	lymphosarcom*:ab,ti	23
#11	reticulosarcom*:ab,ti	4
#12	("reticulum cell sarcoma" or "reticulum cell sarcoma"):ab,ti	5
#13	(burkitt? NEAR/3 (leucemia? or leukemia? or leucaemia? or leukaemia? or tumor? or tumour?)):ab,ti	21
#14	lymphomatoid NEAR/3 granulomatos*:ab,ti	4
#15	"brill symmers disease":ab,ti	0
#16	immunoblastoma?:ab,ti	0
#17	(immunoblastic NEAR/3 sarcom*):ab,ti	1
#18	"granulomatous slack skin":ab,ti	0
#19	lymphomatoid NEAR/3 papulos*:ab,ti	2
#20	"mycosis fungoides":ab,ti	186
#21	pagetoid NEAR/3 reticulos*:ab,ti	0
#22	"ketron goodman disease":ab,ti	0
#23	"woringer kolopp disease":ab,ti	0
#24	"sezary erythroderma":ab,ti	0
#25	"sezary syndrome":ab,ti	65
#26	lymphoma:so	961
#27	#2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26	12206
#28	#1 or #27	12906
#29	[mh ^"Leukemia, Lymphocytic, Chronic, B-Cell"]	481
#30	(leu??emia? NEAR/3 lymphocytic NEAR/5 chronic):ab,ti	2
#31	(leu??emia? NEAR/3 lymphoblastic NEAR/5 chronic):ab,ti	0
#32	lymphocytic lymphoma?:ab,ti	591



#33	(chronic NEAR/3 leu??emia? NEAR/3 B-cell):ab,ti	1
#34	(small-cell NEAR/3 lymphomia?):ab,ti	0
#35	#30 OR #31 OR #32 OR #33 OR #34	593
#36	#29 or #35	969
#37	[mh "Myelodysplastic syndromes"]	700
#38	(myelodysplastic NEAR/3 syndrome?):ab,ti,so	1660
#39	(dysmyelopoietic NEAR/3 syndrome?):ab,ti	0
#40	(Hematopoietic NEAR/3 Myelodysplasia?):ab,ti	0
#41	(anemia? NEAR/3 refractory):ab,ti,so	190
#42	(anemia? NEAR/3 sideroblastic):ab,ti,so	12
#43	(Paroxysmal NEAR/3 Hemoglobinuria?):ab,ti,so	132
#44	(Marchiafava-Micheli NEAR/2 Syndrome):ab,ti	0
#45	#38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44	1892
#46	#37 or #45	2130
#47	#28 or #36 or #46	14991
#48	[mh ^"lenalidomide"]	395
#49	lenalidomide:ab,ti	1885
#50	Revlimid:ab,ti	173
#51	Revimid:ab,ti	0
#52	"IMiD3 Cpd":ab,ti	0
#53	"imid 3":ab,ti	3
#54	"CC 5013":ab,ti	64
#55	CC5013:ab,ti	1
#56	F0P408N6V4:ab,ti	0
#57	"SYP-1512":ab,ti	1
#58	SYP1512:ab,ti	0
#59	"CDC-501":ab,ti	4
#60	CDC501:ab,ti	0
#61	cdc5013:ab,ti	0
#62	"cdc 5013":ab,ti	2
#63	"enmd 0997":ab,ti	0
#64	enmd0997:ab,ti	0
#65	"191732-72-6":ab,ti	75
#66	#49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65	1920
#67	#48 or #66	1932
#68	ibrutinib:ab,ti	506
#69	IMBRUVICA:ab,ti	23



#70	1X70OSD4VX:ab,ti	0
#71	"CRA 032765":ab,ti	0
#72	CRA032765:ab,ti	0
#73	"PCI-32765":ab,ti	28
#74	PCI32765:ab,ti	0
#75	"PC 32765":ab,ti	0
#76	PC32765:ab,ti	0
#77	"936563-96-1":ab,ti	35
#78	#68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77	510
#79	[mh ^"rituximab"]	1277
#80	RITUXIMAB:ab,ti	4583
#81	Mabthera:ab,ti	361
#82	Rituxan:ab,ti	108
#83	TUXELLA:ab,ti	0
#84	TRUXIMA:ab,ti	6
#85	RITEMVIA:ab,ti	0
#86	BLITZIMA:ab,ti	0
#87	RUXIENCE:ab,ti	0
#88	"IDEC-C2B8":ab,ti	21
#89	GP2013:ab,ti	27
#90	4F4X42SYQ6:ab,ti	0
#91	"RG-105":ab,ti	0
#92	"IDEC-102":ab,ti	0
#93	"PF-05280586":ab,ti	15
#94	"CT-P10":ab,ti	50
#95	ABP798:ab,ti	2
#96	"ABP-798":ab,ti	12
#97	SAIT101:ab,ti	8
#98	"SAIT-101":ab,ti	0
#99	RHCACD20MA:ab,ti	1
#100	HS006:ab,ti	1
#101	"HS-006":ab,ti	0
#102	"BI-695500":ab,ti	8
#103	RG105:ab,ti	0
#104	IDEC102:ab,ti	0
#105	PF05280586:ab,ti	0
#106	BI695500:ab,ti	1



#107	#80 OR #81 OR #82 OR #83 OR #84 OR #85 OR #86 OR #87 OR #88 OR #89 OR #90 OR #91 OR #92 OR #93 OR #94 OR #95 OR #96 OR #97 OR #98 OR #99 OR #100 OR #101 OR #102 OR #103 OR #104 OR #105 OR #106	4637
#108	#79 or #107	4742
#109	#67 or #78 or #108	6732
#110	#47 and #109	3158
#111	[mh "angiogenesis inhibitors"]	1144
#112	[mh ^"Ikars Transcription Factor"/AI]	0
#113	[mh ^"Protein Kinase Inhibitors"]	822
#114	[mh "Protein-Tyrosine Kinases"/AI]	689
#115	[mh "immunologic factors"]	8313
#116	[mh ^"Chemokine CXCL12"/AI]	0
#117	[mh ^"Chemokine CXCL13"/AI]	0
#118	#111 OR #112 OR #113 OR #114 OR #115 OR #116 OR #117	10586
#119	(angiogenesis NEAR/5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)):ab,ti	703
#120	(ikaros NEAR/5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)):ab,ti	9
#121	(ikzf* NEAR/5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)):ab,ti	3
#122	(CD20 NEAR/5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)):ab,ti	662
#123	((CXCL12 or cxcl 12) NEAR/5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)):ab,ti	11332
#124	((cxcl13 or cxcl 13) NEAR/5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)):ab,ti	3727
#125	immunomodulator?:ti	615
#126	(BTK NEAR/5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)):ab,ti	215
#127	#119 OR #120 OR #121 OR #122 OR #123 OR #124 OR #125 OR #126	16881
#128	#118 or #127	27003
#129	#47 and #128	730
#130	((new class* or innovative or target*) NEAR/3 (drug? or therapy or therapies or therapeutic* or treatment? or chemotherap*)):ab,ti	36547
#131	[mh "Antibodies, Monoclonal"]	13410
#132	(kinase NEAR/5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)):ab,ti	4696
#133	(monoclonal NEAR/3 antibod*):ab,ti	9425
#134	#130 or #131 or #132 or #133	59362
#135	#47 and #134	2377
#136	#110 or #129 or #135	4477
#137	#136 with Cochrane Library publication date Between Jun 2020 and Jan 2021	202
Comments		



Medline + PreMedline

Date	June 22, 2020	
Database	Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946 to June 22, 2020>	
Search strategy		
1	exp Lymphoma/	171109
2	lymphoma*.ab,ti,kf.	179692
3	nonhodgkin?.ab,ti,kf.	131
4	non-hodgkin?.ab,ti,kf.	38233
5	NHL*.ab,ti,kf.	15675
6	(h?ematol* adj3 malign*).ab,ti,kf.	27728
7	germinoblastoma*.ab,ti,kf.	4
8	reticulolymphosarcoma*.ab,ti,kf.	14
9	(lymphatic adj3 sarcoma?).ab,ti,kf.	54
10	lymphosarcom*.ab,ti,kf.	5174
11	reticulosarcom*.ab,ti,kf.	1284
12	reticulum cell sarcoma?.ab,ti,kf.	1221
13	(burkitt? adj3 (leucemia? or leukemia? or leucaemia? or leukaemia? or tumor? or tumour?)).ab,ti,kf.	1014
14	lymphomatoid granulomatos*.ab,ti,kf.	735
15	brill symmers disease.ab,ti,kf.	216
16	immunoblastoma?.ab,ti,kf.	38
17	(immunoblastic adj3 sarcom*).ab,ti,kf.	214
18	granulomatous slack skin.ab,ti,kf.	90
19	lymphomatoid papulos*.ab,ti,kf.	883
20	mycosis fungoides.ab,ti,kf.	6278
21	pagetoid reticulos*.ab,ti,kf.	121
22	ketron goodman disease.ab,ti,kf.	6
23	woringer kolopp disease.ab,ti,kf.	65
24	sezary erythroderma.ab,ti,kf.	5
25	sezary syndrome.ab,ti,kf.	1961
26	lymphoma*.jw.	13815
27	2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26	224355
28	1 or 27	273112
29	Leukemia, Lymphocytic, Chronic, B-Cell/	16115
30	(leu#?emia? adj3 lymphocytic adj5 chronic).ab,ti,kf.	20576
31	(leu#?emia? adj3 lymphoblastic adj5 chronic).ab,ti,kf.	847
32	lymphocytic lymphoma?.ab,ti,kf.	2322



33	(chronic adj3 leu#?emia? adj3 B-cell).ab,ti,kf.	3415
34	(small-cell adj3 lymphomia?).ab,ti,kf.	0
35	30 or 31 or 32 or 33 or 34	22597
36	29 or 35	26099
37	exp Myelodysplastic syndromes/	20805
38	(myelodysplastic adj3 syndrome?).ab,ti,kf,jw.	17080
39	(dysmyelopoietic adj3 syndrome?).ab,ti,kf.	56
40	(Hematopoietic adj3 Myelodysplasia?).ab,ti,kf.	0
41	(anemia? adj3 refractory).ab,ti,kf,jw.	2681
42	(anemia? adj3 sideroblastic).ab,ti,kf,jw.	905
43	(Paroxysmal adj3 Hemoglobinuria?).ab,ti,kf,jw.	2828
44	(Marchiafava-Micheli adj2 Syndrome).ab,ti,kf.	38
45	38 or 39 or 40 or 41 or 42 or 43 or 44	21961
46	37 or 45	27799
47	28 or 36 or 46	312741
48	lenalidomide/	2613
49	lenalidomide.ab,ti,kf,rn.	4617
50	Revlimid.ab,ti,kf,rn.	131
51	Revimid.ab,ti,kf,rn.	9
52	IMiD3 Cpd.ab,ti,kf,rn.	0
53	imid 3.ab,ti,kf,rn.	6
54	CC 5013.ab,ti,kf,rn.	57
55	CC5013.ab,ti,kf,rn.	10
56	F0P408N6V4.ab,ti,kf,rn.	2613
57	SYP-1512.ab,ti,kf,rn.	0
58	SYP1512.ab,ti,kf,rn.	0
59	CDC-501.ab,ti,kf,rn.	1
60	CDC501.ab,ti,kf,rn.	0
61	cdc5013.ab,ti,kf,rn.	0
62	cdc 5013.ab,ti,kf,rn.	0
63	"enmd 0997".ab,ti,kf,rn.	2
64	enmd0997.ab,ti,kf,rn.	0
65	191732-72-6.ab,ti,kf,rn.	0
66	49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65	4650
67	48 or 66	4650
68	ibrutinib.ab,ti,kf,rn.	2007
69	IMBRUVICA.ab,ti,kf,rn.	34
70	1X70OSD4VX.ab,ti,kf,rn.	1



71	"CRA 032765".ab,ti,kf,rn.	1
72	CRA032765.ab,ti,kf,rn.	0
73	PCI-32765.ab,ti,kf,rn.	1100
74	PCI32765.ab,ti,kf,rn.	2
75	PC 32765.ab,ti,kf,rn.	1
76	PC32765.ab,ti,kf,rn.	0
77	936563-96-1.ab,ti,kf,rn.	1
78	68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77	2155
79	rituximab/	14538
80	RITUXIMAB.ab,ti,kf,rn.	23634
81	Mabthera.ab,ti,kf,rn.	185
82	Rituxan.ab,ti,kf,rn.	305
83	TUXELLA.ab,ti,kf,rn.	0
84	TRUXIMA.ab,ti,kf,rn.	11
85	RITEMVIA.ab,ti,kf,rn.	0
86	BLITZIMA.ab,ti,kf,rn.	0
87	RUXIENCE.ab,ti,kf,rn.	1
88	IDEC-C2B8.ab,ti,kf,rn.	53
89	GP2013.ab,ti,kf,rn.	10
90	4F4X42SYQ6.ab,ti,kf,rn.	14539
91	RG-105.ab,ti,kf,rn.	1
92	IDEC-102.ab,ti,kf,rn.	1
93	PF-05280586.ab,ti,kf,rn.	8
94	CT-P10.ab,ti,kf,rn.	30
95	ABP798.ab,ti,kf,rn.	0
96	ABP-798.ab,ti,kf,rn.	0
97	SAIT101.ab,ti,kf,rn.	0
98	SAIT-101.ab,ti,kf,rn.	0
99	RHCACD20MA.ab,ti,kf,rn.	0
100	HS006.ab,ti,kf,rn.	0
101	HS-006.ab,ti,kf,rn.	4
102	BI-695500.ab,ti,kf,rn.	0
103	RG105.ab,ti,kf,rn.	0
104	IDEC102.ab,ti,kf,rn.	0
105	PF05280586.ab,ti,kf,rn.	0
106	BI695500.ab,ti,kf,rn.	0
107	80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102 or 103 or 104 or 105 or 106	23703



108	79 or 107	23703
109	67 or 78 or 108	29710
110	47 and 109	14384
111	exp angiogenesis inhibitors/	57134
112	Ikaros Transcription Factor/ai	10
113	Protein Kinase Inhibitors/	45220
114	exp Protein-Tyrosine Kinases/ai [Antagonists & Inhibitors]	38027
115	exp immunologic factors/	1373981
116	Chemokine CXCL12/ai [Antagonists & Inhibitors]	208
117	Chemokine CXCL13/ai [Antagonists & Inhibitors]	9
118	111 or 112 or 113 or 114 or 115 or 116 or 117	1459001
119	(angiogenesis adj5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)).ab,ti,kf.	24149
120	(ikaros adj5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)).ab,ti,kf.	133
121	(ikzf* adj5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)).ab,ti,kf.	59
122	(CD20 adj5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)).ab,ti,kf.	5279
123	((CXCL12 or cxcl 12) adj5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)).ab,ti,kf.	1011
124	((cxcl13 or cxcl 13) adj5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)).ab,ti,kf.	133
125	immunomodulator?.ti,kf.	9326
126	(BTK adj5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)).ab,ti,kf.	1177
127	119 or 120 or 121 or 122 or 123 or 124 or 125 or 126	41092
128	118 or 127	1481038
129	47 and 128	61571
130	((new class* or innovative or target*) adj3 (drug? or therapy or therapies or therapeutic* or treatment? or chemotherap*)).ab,ti,kf.	330072
131	exp Antibodies, Monoclonal/	235214
132	(kinase adj5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)).ab,ti,kf.	141797
133	(monoclonal adj3 antibod*).ab,ti,kf.	196407
134	130 or 131 or 132 or 133	754827
135	47 and 134	34957
136	110 or 129 or 135	77889
137	((systematic review or systematic literature review or systematic scoping review or systematic narrative review or systematic qualitative review or systematic evidence review or systematic quantitative review or systematic meta-review or systematic critical review or systematic mixed studies review or systematic mapping review or systematic cochrane review or "systematic search and review" or systematic integrative review).ti. not comment.pt. not (protocol or protocols).ti. not medline.st.) or (Cochrane Database Syst Rev.ja. and review.pt.) or systematic review.pt.	159328
138	meta-analys*.ti.	108916
139	meta-analysis.pt.	116279
140	exp Technology Assessment, Biomedical/	11062



141	health technology assessment.ti,kf.	1917
142	HtA.ti,kf.	593
143	137 or 138 or 139 or 140 or 141 or 142	252947
144	136 and 143	485
Comments		

Update

Date	January 22, 2021	
Database	Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946 to January 22, 2021>	
Search strategy		
1	exp Lymphoma/	173499
2	lymphoma*.ab,ti,kf.	185533
3	nonhodgkin?.ab,ti,kf.	133
4	non-hodgkin?.ab,ti,kf.	39078
5	NHL*.ab,ti,kf.	16131
6	(h?ematol* adj3 malign*).ab,ti,kf.	29420
7	germinoblastoma*.ab,ti,kf.	4
8	reticulolymphosarcoma*.ab,ti,kf.	14
9	(lymphatic adj3 sarcoma?).ab,ti,kf.	54
10	lymphosarcom*.ab,ti,kf.	5205
11	reticulosarcom*.ab,ti,kf.	1297
12	reticulum cell sarcoma?.ab,ti,kf.	1226
13	(burkitt? adj3 (leucemia? or leukemia? or leucaemia? or leukaemia? or tumor? or tumour?)).ab,ti,kf.	1027
14	lymphomatoid granulomatos*.ab,ti,kf.	745
15	brill symmers disease.ab,ti,kf.	220
16	immunoblastoma?.ab,ti,kf.	38
17	(immunoblastic adj3 sarcom*).ab,ti,kf.	214
18	granulomatous slack skin.ab,ti,kf.	90
19	lymphomatoid papulos*.ab,ti,kf.	901
20	mycosis fungoides.ab,ti,kf.	6480
21	pagetoid reticulos*.ab,ti,kf.	121
22	ketron goodman disease.ab,ti,kf.	6
23	woringer kolopp disease.ab,ti,kf.	66
24	sezary erythroderma.ab,ti,kf.	5
25	sezary syndrome.ab,ti,kf.	2050
26	lymphoma*.jw.	14455



27	2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26	232272
28	1 or 27	281219
29	Leukemia, Lymphocytic, Chronic, B-Cell/	16511
30	(leu#?emia? adj3 lymphocytic adj5 chronic).ab,ti,kf.	21278
31	(leu#?emia? adj3 lymphoblastic adj5 chronic).ab,ti,kf.	867
32	lymphocytic lymphoma?.ab,ti,kf.	2378
33	(chronic adj3 leu#?emia? adj3 B-cell).ab,ti,kf.	3464
34	(small-cell adj3 lymphoma?).ab,ti,kf.	0
35	30 or 31 or 32 or 33 or 34	23327
36	29 or 35	26878
37	exp Myelodysplastic syndromes/	21238
38	(myelodysplastic adj3 syndrome?).ab,ti,kf,jw.	17711
39	(dysmyelopoietic adj3 syndrome?).ab,ti,kf.	56
40	(Hematopoietic adj3 Myelodysplasia?).ab,ti,kf.	0
41	(anemia? adj3 refractory).ab,ti,kf,jw.	2724
42	(anemia? adj3 sideroblastic).ab,ti,kf,jw.	921
43	(Paroxysmal adj3 Hemoglobinuria?).ab,ti,kf,jw.	2911
44	(Marchiafava-Micheli adj2 Syndrome).ab,ti,kf.	38
45	38 or 39 or 40 or 41 or 42 or 43 or 44	22707
46	37 or 45	28624
47	28 or 36 or 46	322024
48	lenalidomide/	2759
49	lenalidomide.ab,ti,kf,rn.	4950
50	Revlimid.ab,ti,kf,rn.	133
51	Revimid.ab,ti,kf,rn.	9
52	IMiD3 Cpd.ab,ti,kf,rn.	0
53	imid 3.ab,ti,kf,rn.	7
54	CC 5013.ab,ti,kf,rn.	57
55	CC5013.ab,ti,kf,rn.	10
56	F0P408N6V4.ab,ti,kf,rn.	2759
57	SYP-1512.ab,ti,kf,rn.	0
58	SYP1512.ab,ti,kf,rn.	0
59	CDC-501.ab,ti,kf,rn.	1
60	CDC501.ab,ti,kf,rn.	0
61	cdc5013.ab,ti,kf,rn.	0
62	cdc 5013.ab,ti,kf,rn.	0
63	"enmd 0997".ab,ti,kf,rn.	2



64	enmd0997.ab,ti,kf,rn.	0
65	191732-72-6.ab,ti,kf,rn.	0
66	49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65	4983
67	48 or 66	4983
68	ibrutinib.ab,ti,kf,rn.	2308
69	IMBRUVICA.ab,ti,kf,rn.	35
70	1X70OSD4VX.ab,ti,kf,rn.	27
71	"CRA 032765".ab,ti,kf,rn.	1
72	CRA032765.ab,ti,kf,rn.	0
73	PCI-32765.ab,ti,kf,rn.	1222
74	PCI32765.ab,ti,kf,rn.	2
75	PC 32765.ab,ti,kf,rn.	1
76	PC32765.ab,ti,kf,rn.	0
77	936563-96-1.ab,ti,kf,rn.	1
78	68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77	2467
79	rituximab/	15168
80	RITUXIMAB.ab,ti,kf,rn.	25131
81	Mabthera.ab,ti,kf,rn.	192
82	Rituxan.ab,ti,kf,rn.	312
83	TUXELLA.ab,ti,kf,rn.	0
84	TRUXIMA.ab,ti,kf,rn.	14
85	RITEMVIA.ab,ti,kf,rn.	0
86	BLITZIMA.ab,ti,kf,rn.	0
87	RUXIENCE.ab,ti,kf,rn.	2
88	IDEC-C2B8.ab,ti,kf,rn.	53
89	GP2013.ab,ti,kf,rn.	11
90	4F4X42SYQ6.ab,ti,kf,rn.	15169
91	RG-105.ab,ti,kf,rn.	1
92	IDEC-102.ab,ti,kf,rn.	1
93	PF-05280586.ab,ti,kf,rn.	9
94	CT-P10.ab,ti,kf,rn.	38
95	ABP798.ab,ti,kf,rn.	0
96	ABP-798.ab,ti,kf,rn.	8
97	SAIT101.ab,ti,kf,rn.	0
98	SAIT-101.ab,ti,kf,rn.	0
99	RHCACD20MA.ab,ti,kf,rn.	0
100	HS006.ab,ti,kf,rn.	0
101	HS-006.ab,ti,kf,rn.	4



102	BI-695500.ab,ti,kf,rn.	0
103	RG105.ab,ti,kf,rn.	0
104	IDEC102.ab,ti,kf,rn.	0
105	PF05280586.ab,ti,kf,rn.	0
106	BI695500.ab,ti,kf,rn.	0
107	80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102 or 103 or 104 or 105 or 106	25201
108	79 or 107	25201
109	67 or 78 or 108	31772
110	47 and 109	15216
111	exp angiogenesis inhibitors/	58656
112	Ikaros Transcription Factor/ai	12
113	Protein Kinase Inhibitors/	47531
114	exp Protein-Tyrosine Kinases/ai [Antagonists & Inhibitors]	39376
115	exp immunologic factors/	1394299
116	Chemokine CXCL12/ai [Antagonists & Inhibitors]	213
117	Chemokine CXCL13/ai [Antagonists & Inhibitors]	9
118	111 or 112 or 113 or 114 or 115 or 116 or 117	1482991
119	(angiogenesis adj5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)).ab,ti,kf.	25134
120	(ikaros adj5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)).ab,ti,kf.	140
121	(ikzf* adj5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)).ab,ti,kf.	72
122	(CD20 adj5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)).ab,ti,kf.	5552
123	((CXCL12 or cxcl 12) adj5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)).ab,ti,kf.	1052
124	((cxcl13 or cxcl 13) adj5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)).ab,ti,kf.	142
125	immunomodulator?.ti,kf.	10067
126	(BTK adj5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)).ab,ti,kf.	1339
127	119 or 120 or 121 or 122 or 123 or 124 or 125 or 126	43299
128	118 or 127	1506656
129	47 and 128	62902
130	((new class* or innovative or target*) adj3 (drug? or therapy or therapies or therapeutic* or treatment? or chemotherap*)).ab,ti,kf.	358023
131	exp Antibodies, Monoclonal/	241894
132	(kinase adj5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)).ab,ti,kf.	147278
133	(monoclonal adj3 antibod*).ab,ti,kf.	200253
134	130 or 131 or 132 or 133	795001
135	47 and 134	36608
136	110 or 129 or 135	80414



137	((systematic review or systematic literature review or systematic scoping review or systematic narrative review or systematic qualitative review or systematic evidence review or systematic quantitative review or systematic meta-review or systematic critical review or systematic mixed studies review or systematic mapping review or systematic cochrane review or "systematic search and review" or systematic integrative review).ti. not comment.pt. not (protocol or protocols).ti. not medline.st.) or (Cochrane Database Syst Rev.ja. and review.pt.) or systematic review.pt.	179754
138	meta-analys*.ti.	122451
139	meta-analysis.pt.	125413
140	exp Technology Assessment, Biomedical/	11285
141	health technology assessment.ti,kf.	2097
142	HtA.ti,kf.	645
143	137 or 138 or 139 or 140 or 141 or 142	278857
144	136 and 143	517
145	limit 144 to yr="2020-2021"	53
Comments		



Appendix 8.3.3.2. Chronic Lymphocytic Leukemia

Cochrane

Date	28/01/2021 16:13:06	
Database	Cochrane@Wiley.com	
Search strategy		
#1	[mh ^"lenalidomide"]	395
#2	lenalidomide:ab,ti	1885
#3	Revlimid:ab,ti	173
#4	Revimid:ab,ti	0
#5	"IMiD3 Cpd":ab,ti	0
#6	"imid 3":ab,ti	3
#7	"CC 5013":ab,ti	64
#8	CC5013:ab,ti	1
#9	F0P408N6V4:ab,ti	0
#10	"SYP-1512":ab,ti	1
#11	SYP1512:ab,ti	0
#12	"CDC-501":ab,ti	4
#13	CDC501:ab,ti	0
#14	cdc5013:ab,ti	0
#15	"cdc 5013":ab,ti	2
#16	"enmd 0997":ab,ti	0
#17	enmd0997:ab,ti	0
#18	"191732-72-6":ab,ti	75
#19	#2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18	1920
#20	#1 or #19	1932
#21	ibrutinib:ab,ti	506
#22	IMBRUVICA:ab,ti	23
#23	1X700SD4VX:ab,ti	0
#24	"CRA 032765":ab,ti	0
#25	CRA032765:ab,ti	0
#26	"PCI-32765":ab,ti	28
#27	PCI32765:ab,ti	0
#28	"PC 32765":ab,ti	0
#29	PC32765:ab,ti	0



#30	"936563-96-1":ab,ti	35
#31	#21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30	510
#32	[mh ^"rituximab"]	1277
#33	RITUXIMAB:ab,ti	4583
#34	Mabthera:ab,ti	361
#35	Rituxan:ab,ti	108
#36	TUXELLA:ab,ti	0
#37	TRUXIMA:ab,ti	6
#38	RITEMVIA:ab,ti	0
#39	BLITZIMA:ab,ti	0
#40	RUXIENCE:ab,ti	0
#41	"IDEC-C2B8":ab,ti	21
#42	GP2013:ab,ti	27
#43	4F4X42SYQ6:ab,ti	0
#44	"RG-105":ab,ti	0
#45	"IDEC-102":ab,ti	0
#46	"PF-05280586":ab,ti	15
#47	"CT-P10":ab,ti	50
#48	ABP798:ab,ti	2
#49	"ABP-798":ab,ti	12
#50	SAIT101:ab,ti	8
#51	"SAIT-101":ab,ti	0
#52	RHCACD20MA:ab,ti	1
#53	HS006:ab,ti	1
#54	"HS-006":ab,ti	0
#55	"BI-695500":ab,ti	8
#56	RG105:ab,ti	0
#57	IDEC102:ab,ti	0
#58	PF05280586:ab,ti	0
#59	BI695500:ab,ti	1
#60	#33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59	4637
#61	#32 or #60	4742
#62	#20 or #31 or #61	6732
#63	[mh "angiogenesis inhibitors"]	1144
#64	[mh ^"Ikaros Transcription Factor"/AI]	0
#65	[mh ^"Protein Kinase Inhibitors"]	822
#66	[mh "Protein-Tyrosine Kinases"/AI]	689



#67	[mh "immunologic factors"]	8313
#68	[mh ^"Chemokine CXCL12"/Al]	0
#69	[mh ^"Chemokine CXCL13"/Al]	0
#70	#63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69	10586
#71	(angiogenesis NEAR/5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)):ab,ti	703
#72	(ikaros NEAR/5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)):ab,ti	9
#73	(ikzf* NEAR/5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)):ab,ti	3
#74	(CD20 NEAR/5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)):ab,ti	662
#75	((CXCL12 or cxcl 12) NEAR/5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)):ab,ti	11332
#76	((cxcl13 or cxcl 13) NEAR/5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)):ab,ti	3727
#77	immunomodulator?:ti	615
#78	(BTK NEAR/5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)):ab,ti	215
#79	#71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77 OR #78	16881
#80	#70 or #79	27003
#81	((new class* or innovative or target*) NEAR/3 (drug? or therapy or therapies or therapeutic* or treatment? or chemotherap*)):ab,ti	36547
#82	[mh "Antibodies, Monoclonal"]	13410
#83	(kinase NEAR/5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)):ab,ti	4696
#84	(monoclonal NEAR/3 antibod*):ab,ti	9425
#85	#81 or #82 or #83 or #84	59362
#86	obinutuzumab:ab,ti	324
#87	afutuzumab:ab,ti	0
#88	gazyva:ab,ti	18
#89	"ga 101":ab,ti	11
#90	ga101:ab,ti	119
#91	hsdb8249:ab,ti	0
#92	"hsdb 8249":ab,ti	0
#93	humab:ab,ti	13
#94	humabcd20:ab,ti	0
#95	"ro 5072759":ab,ti	4
#96	ro5072759:ab,ti	23
#97	#86 OR #87 OR #88 OR #89 OR #90 OR #91 OR #92 OR #93 OR #94 OR #95 OR #96	357
#98	#62 or #80 or #85 or #97	85587
#99	[mh ^"Leukemia, Lymphocytic, Chronic, B-Cell"]	481
#100	"CLL lymphoplasmacytoid" NEAR/1 lymphoma?:ab,ti	0
#101	lymphocytic NEAR/1 lymphoma?:ab,ti	247
#102	("small cell" or "small-cells") NEAR/1 lymphoma?):ab,ti	7
#103	(disrupted NEAR/3 b-cell? NEAR/3 malignanc*):ab,ti	0



#104	(chronic NEAR/3 (b-cell or b-lymphocytic or lymphoblastic or lymphocytic or lymphoid or lymphatic) NEAR/3 leu*mia?):ab,ti	1508
#105	CLL:ti	662
#106	"hairy cell" NEAR/1 leu*mia?:ab,ti	103
#107	"large granular lymphocyte" NEAR/1 leu*mia?:ab,ti	1
#108	prolymphocytic NEAR/1 leu*mia?:ab,ti	18
#109	histiolympocytos*:ab,ti	0
#110	leu*mia? NEAR/1 reticulo?endotheliosis:ab,ti	0
#111	tricholeukocytary NEAR/1 leu*mia?:ab,ti	0
#112	#100 OR #101 OR #102 OR #103 OR #104 OR #105 OR #106 OR #107 OR #108 OR #109 OR #110 OR #111	1876
#113	#99 or #112	1939
#114	#98 and #113	1051
Comments		

Medline

Date	January 22, 2021	
Database	Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946 to January 22, 2021>	
Search strategy		
1	lenalidomide/	2759
2	lenalidomide.ab,ti,kf,rn.	4950
3	Revlimid.ab,ti,kf,rn.	133
4	Revimid.ab,ti,kf,rn.	9
5	IMiD3 Cpd.ab,ti,kf,rn.	0
6	imid 3.ab,ti,kf,rn.	7
7	CC 5013.ab,ti,kf,rn.	57
8	CC5013.ab,ti,kf,rn.	10
9	F0P408N6V4.ab,ti,kf,rn.	2759
10	SYP-1512.ab,ti,kf,rn.	0
11	SYP1512.ab,ti,kf,rn.	0
12	CDC-501.ab,ti,kf,rn.	1
13	CDC501.ab,ti,kf,rn.	0
14	cdc5013.ab,ti,kf,rn.	0
15	cdc 5013.ab,ti,kf,rn.	0
16	"enmd 0997".ab,ti,kf,rn.	2
17	enmd0997.ab,ti,kf,rn.	0
18	191732-72-6.ab,ti,kf,rn.	0
19	2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18	4983



20	1 or 19	4983
21	ibrutinib.ab,ti,kf,rn.	2308
22	IMBRUVICA.ab,ti,kf,rn.	35
23	1X70OSD4VX.ab,ti,kf,rn.	27
24	"CRA 032765".ab,ti,kf,rn.	1
25	CRA032765.ab,ti,kf,rn.	0
26	PCI-32765.ab,ti,kf,rn.	1222
27	PCI32765.ab,ti,kf,rn.	2
28	PC 32765.ab,ti,kf,rn.	1
29	PC32765.ab,ti,kf,rn.	0
30	936563-96-1.ab,ti,kf,rn.	1
31	21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30	2467
32	rituximab/	15168
33	RITUXIMAB.ab,ti,kf,rn.	25131
34	Mabthera.ab,ti,kf,rn.	192
35	Rituxan.ab,ti,kf,rn.	312
36	TUXELLA.ab,ti,kf,rn.	0
37	TRUXIMA.ab,ti,kf,rn.	14
38	RITEMVIA.ab,ti,kf,rn.	0
39	BLITZIMA.ab,ti,kf,rn.	0
40	RUXIENCE.ab,ti,kf,rn.	2
41	IDEC-C2B8.ab,ti,kf,rn.	53
42	GP2013.ab,ti,kf,rn.	11
43	4F4X42SYQ6.ab,ti,kf,rn.	15169
44	RG-105.ab,ti,kf,rn.	1
45	IDEC-102.ab,ti,kf,rn.	1
46	PF-05280586.ab,ti,kf,rn.	9
47	CT-P10.ab,ti,kf,rn.	38
48	ABP798.ab,ti,kf,rn.	0
49	ABP-798.ab,ti,kf,rn.	8
50	SAIT101.ab,ti,kf,rn.	0
51	SAIT-101.ab,ti,kf,rn.	0
52	RHCACD20MA.ab,ti,kf,rn.	0
53	HS006.ab,ti,kf,rn.	0
54	HS-006.ab,ti,kf,rn.	4
55	BI-695500.ab,ti,kf,rn.	0
56	RG105.ab,ti,kf,rn.	0
57	IDEC102.ab,ti,kf,rn.	0



58	PF05280586.ab,ti,kf,rn.	0
59	BI695500.ab,ti,kf,rn.	0
60	33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59	25201
61	32 or 60	25201
62	20 or 31 or 61	31772
63	exp angiogenesis inhibitors/	58656
64	Ikaros Transcription Factor/ai	12
65	Protein Kinase Inhibitors/	47531
66	exp Protein-Tyrosine Kinases/ai [Antagonists & Inhibitors]	39376
67	exp immunologic factors/	1394299
68	Chemokine CXCL12/ai [Antagonists & Inhibitors]	213
69	Chemokine CXCL13/ai [Antagonists & Inhibitors]	9
70	63 or 64 or 65 or 66 or 67 or 68 or 69	1482991
71	(angiogenesis adj5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)).ab,ti,kf.	25134
72	(ikaros adj5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)).ab,ti,kf.	140
73	(ikzf* adj5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)).ab,ti,kf.	72
74	(CD20 adj5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)).ab,ti,kf.	5552
75	((CXCL12 or cxcl 12) adj5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)).ab,ti,kf.	1052
76	((cxcl13 or cxcl 13) adj5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)).ab,ti,kf.	142
77	immunomodulator?.ti,kf.	10067
78	(BTK adj5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)).ab,ti,kf.	1339
79	71 or 72 or 73 or 74 or 75 or 76 or 77 or 78	43299
80	70 or 79	1506656
81	((new class* or innovative or target*) adj3 (drug? or therapy or therapies or therapeutic* or treatment? or chemotherap*)).ab,ti,kf.	358023
82	exp Antibodies, Monoclonal/	241894
83	(kinase adj5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)).ab,ti,kf.	147278
84	(monoclonal adj3 antibod*).ab,ti,kf.	200253
85	81 or 82 or 83 or 84	795001
86	obinutuzumab.ab,ti,kf,rn.	586
87	afutuzumab.ab,ti,kf,rn.	3
88	gazyva.ab,ti,kf,rn.	14
89	ga 101.ab,ti,kf,rn.	21
90	ga101.ab,ti,kf,rn.	90
91	hsdb8249.ab,ti,kf,rn.	0
92	hsdb 8249.ab,ti,kf,rn.	1
93	humab.ab,ti,kf,rn.	105



94	humabcd20.ab,ti,kf,rn.	1
95	ro 5072759.ab,ti,kf,rn.	1
96	ro5072759.ab,ti,kf,rn.	3
97	86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96	704
98	62 or 80 or 85 or 97	2000302
99	Leukemia, Lymphocytic, Chronic, B-Cell/	16511
100	"CLL lymphoplasmacytoid lymphoma?".ab,ti,kf.	2
101	lymphocytic lymphoma?.ab,ti,kf.	2378
102	small cell? lymphoma?.ab,ti,kf.	178
103	(disrupted adj3 b-cell? adj3 malignanc*).ab,ti,kf.	2
104	(chronic adj3 (b-cell or b-lymphocytic or lymphoblastic or lymphocytic or lymphoid or lymphatic) adj3 leu#?emia?).ab,ti,kf.	23522
105	CLL.ti,kw.	2790
106	hairy cell leu#?emia?.ab,ti,kf.	3924
107	large granular lymphocyte leu#?emia?.ab,ti,kf.	389
108	prolymphocytic leu#?emia?.ab,ti,kf.	1132
109	histiolympocytos*.ab,ti,kf.	2
110	leu#?mi#? reticulo?endotheliosis.ab,ti,kf.	132
111	tricholeukocytary leu#?emia?.ab,ti,kf.	0
112	100 or 101 or 102 or 103 or 104 or 105 or 106 or 107 or 108 or 109 or 110 or 111	29906
113	99 or 112	32361
114	98 and 113	12725
115	((systematic review or systematic literature review or systematic scoping review or systematic narrative review or systematic qualitative review or systematic evidence review or systematic quantitative review or systematic meta-review or systematic critical review or systematic mixed studies review or systematic mapping review or systematic cochrane review or "systematic search and review" or systematic integrative review).ti. not comment.pt. not (protocol or protocols).ti. not medline.st.) or (Cochrane Database Syst Rev.ja. and review.pt.) or systematic review.pt.	179754
116	meta-analys*.ti.	122451
117	meta-analysis.pt.	125413
118	exp Technology Assessment, Biomedical/	11285
119	health technology assessment.ti,kf.	2097
120	HtA.ti,kf.	645
121	115 or 116 or 117 or 118 or 119 or 120	278857
122	114 and 121	77
Comments		

*Appendix 8.3.3.3. Diffuse Large B-Cell Lymphoma***Medline**

Date	January 22, 2021	
Database	Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946 to January 22, 2021>	
Search strategy		
1	lenalidomide/	2759
2	lenalidomide.ab,ti,kf,rn.	4950
3	Revlimid.ab,ti,kf,rn.	133
4	Revimid.ab,ti,kf,rn.	9
5	IMiD3 Cpd.ab,ti,kf,rn.	0
6	imid 3.ab,ti,kf,rn.	7
7	CC 5013.ab,ti,kf,rn.	57
8	CC5013.ab,ti,kf,rn.	10
9	F0P408N6V4.ab,ti,kf,rn.	2759
10	SYP-1512.ab,ti,kf,rn.	0
11	SYP1512.ab,ti,kf,rn.	0
12	CDC-501.ab,ti,kf,rn.	1
13	CDC501.ab,ti,kf,rn.	0
14	cdc5013.ab,ti,kf,rn.	0
15	cdc 5013.ab,ti,kf,rn.	0
16	"enmd 0997".ab,ti,kf,rn.	2
17	enmd0997.ab,ti,kf,rn.	0
18	191732-72-6.ab,ti,kf,rn.	0
19	2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18	4983
20	1 or 19	4983
21	ibrutinib.ab,ti,kf,rn.	2308
22	IMBRUVICA.ab,ti,kf,rn.	35
23	1X70OSD4VX.ab,ti,kf,rn.	27
24	"CRA 032765".ab,ti,kf,rn.	1
25	CRA032765.ab,ti,kf,rn.	0
26	PCI-32765.ab,ti,kf,rn.	1222
27	PCI32765.ab,ti,kf,rn.	2
28	PC 32765.ab,ti,kf,rn.	1
29	PC32765.ab,ti,kf,rn.	0
30	936563-96-1.ab,ti,kf,rn.	1
31	21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30	2467



32	rituximab/	15168
33	RITUXIMAB.ab,ti,kf,rn.	25131
34	Mabthera.ab,ti,kf,rn.	192
35	Rituxan.ab,ti,kf,rn.	312
36	TUXELLA.ab,ti,kf,rn.	0
37	TRUXIMA.ab,ti,kf,rn.	14
38	RITEMVIA.ab,ti,kf,rn.	0
39	BLITZIMA.ab,ti,kf,rn.	0
40	RUXIENCE.ab,ti,kf,rn.	2
41	IDEC-C2B8.ab,ti,kf,rn.	53
42	GP2013.ab,ti,kf,rn.	11
43	4F4X42SYQ6.ab,ti,kf,rn.	15169
44	RG-105.ab,ti,kf,rn.	1
45	IDEC-102.ab,ti,kf,rn.	1
46	PF-05280586.ab,ti,kf,rn.	9
47	CT-P10.ab,ti,kf,rn.	38
48	ABP798.ab,ti,kf,rn.	0
49	ABP-798.ab,ti,kf,rn.	8
50	SAIT101.ab,ti,kf,rn.	0
51	SAIT-101.ab,ti,kf,rn.	0
52	RHCACD20MA.ab,ti,kf,rn.	0
53	HS006.ab,ti,kf,rn.	0
54	HS-006.ab,ti,kf,rn.	4
55	BI-695500.ab,ti,kf,rn.	0
56	RG105.ab,ti,kf,rn.	0
57	IDEC102.ab,ti,kf,rn.	0
58	PF05280586.ab,ti,kf,rn.	0
59	BI695500.ab,ti,kf,rn.	0
60	33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59	25201
61	32 or 60	25201
62	20 or 31 or 61	31772
63	exp angiogenesis inhibitors/	58656
64	Ikaros Transcription Factor/ai	12
65	Protein Kinase Inhibitors/	47531
66	exp Protein-Tyrosine Kinases/ai [Antagonists & Inhibitors]	39376
67	exp immunologic factors/	1394299
68	Chemokine CXCL12/ai [Antagonists & Inhibitors]	213



69	Chemokine CXCL13/ai [Antagonists & Inhibitors]	9
70	63 or 64 or 65 or 66 or 67 or 68 or 69	1482991
71	(angiogenesis adj5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)).ab,ti,kf.	25134
72	(ikaros adj5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)).ab,ti,kf.	140
73	(ikzf* adj5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)).ab,ti,kf.	72
74	(CD20 adj5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)).ab,ti,kf.	5552
75	((CXCL12 or cxcl 12) adj5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)).ab,ti,kf.	1052
76	((cxcl13 or cxcl 13) adj5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)).ab,ti,kf.	142
77	immunomodulator?.ti,kf.	10067
78	(BTK adj5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)).ab,ti,kf.	1339
79	71 or 72 or 73 or 74 or 75 or 76 or 77 or 78	43299
80	70 or 79	1506656
81	((new class* or innovative or target*) adj3 (drug? or therapy or therapies or therapeutic* or treatment? or chemotherap*)).ab,ti,kf.	358023
82	exp Antibodies, Monoclonal/	241894
83	(kinase adj5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)).ab,ti,kf.	147278
84	(monoclonal adj3 antibod*).ab,ti,kf.	200253
85	81 or 82 or 83 or 84	795001
86	((systematic review or systematic literature review or systematic scoping review or systematic narrative review or systematic qualitative review or systematic evidence review or systematic quantitative review or systematic meta-review or systematic critical review or systematic mixed studies review or systematic mapping review or systematic cochrane review or "systematic search and review" or systematic integrative review).ti. not comment.pt. not (protocol or protocols).ti. not medline.st.) or (Cochrane Database Syst Rev.ja. and review.pt.) or systematic review.pt.	179754
87	meta-analys*.ti.	122451
88	meta-analysis.pt.	125413
89	exp Technology Assessment, Biomedical/	11285
90	health technology assessment.ti,kf.	2097
91	HtA.ti,kf.	645
92	86 or 87 or 88 or 89 or 90 or 91	278857
93	Lymphoma, Large B-Cell, Diffuse/	19984
94	histiocytic lymphoma?.ab,ti,kf.	1164
95	(diffuse adj2 large b-cell? adj2 lymphoma?).ab,ti,kf.	14336
96	(diffuse adj2 large cell? adj2 lymphoma?).ab,ti,kf.	1303
97	dlbcl.ab,ti,kf.	7624
98	intravascular large b cell lymphoma?.ab,ti,kf.	540
99	("large lymphoid lymphoma?" adj2 diffuse).ab,ti,kf.	2
100	94 or 95 or 96 or 97 or 98 or 99	17602
101	93 or 100	28266



102	62 or 80 or 85	2000270
103	101 and 102	8680
104	92 and 103	76
Comments		

Cochrane

Date	28/01/2021 19:04:31	
Database	Cochrane@Wiley.com	
Search strategy		
#1	[mh ^"lenalidomide"]	395
#2	lenalidomide:ab,ti	1885
#3	Revlimid:ab,ti	173
#4	Revimid:ab,ti	0
#5	"IMiD3 Cpd":ab,ti	0
#6	"imid 3":ab,ti	3
#7	"CC 5013":ab,ti	64
#8	CC5013:ab,ti	1
#9	F0P408N6V4:ab,ti	0
#10	"SYP-1512":ab,ti	1
#11	SYP1512:ab,ti	0
#12	"CDC-501":ab,ti	4
#13	CDC501:ab,ti	0
#14	cdc5013:ab,ti	0
#15	"cdc 5013":ab,ti	2
#16	"enmd 0997":ab,ti	0
#17	enmd0997:ab,ti	0
#18	"191732-72-6":ab,ti	75
#19	#2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18	1920
#20	#1 or #19	1932
#21	ibrutinib:ab,ti	506
#22	IMBRUVICA:ab,ti	23
#23	1X700SD4VX:ab,ti	0
#24	"CRA 032765":ab,ti	0
#25	CRA032765:ab,ti	0
#26	"PCI-32765":ab,ti	28
#27	PCI32765:ab,ti	0



#28	"PC 32765":ab,ti	0
#29	PC32765:ab,ti	0
#30	"936563-96-1":ab,ti	35
#31	#21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30	510
#32	[mh ^"rituximab"]	1277
#33	RITUXIMAB:ab,ti	4583
#34	Mabthera:ab,ti	361
#35	Rituxan:ab,ti	108
#36	TUXELLA:ab,ti	0
#37	TRUXIMA:ab,ti	6
#38	RITEMVIA:ab,ti	0
#39	BLITZIMA:ab,ti	0
#40	RUXIENCE:ab,ti	0
#41	"IDEC-C2B8":ab,ti	21
#42	GP2013:ab,ti	27
#43	4F4X42SYQ6:ab,ti	0
#44	"RG-105":ab,ti	0
#45	"IDEC-102":ab,ti	0
#46	"PF-05280586":ab,ti	15
#47	"CT-P10":ab,ti	50
#48	ABP798:ab,ti	2
#49	"ABP-798":ab,ti	12
#50	SAIT101:ab,ti	8
#51	"SAIT-101":ab,ti	0
#52	RHCACD20MA:ab,ti	1
#53	HS006:ab,ti	1
#54	"HS-006":ab,ti	0
#55	"BI-695500":ab,ti	8
#56	RG105:ab,ti	0
#57	IDEC102:ab,ti	0
#58	PF05280586:ab,ti	0
#59	BI695500:ab,ti	1
#60	#33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59	4637
#61	#32 or #60	4742
#62	#20 or #31 or #61	6732
#63	[mh "angiogenesis inhibitors"]	1144
#64	[mh ^"Ikaros Transcription Factor"/AI]	0



#65	[mh ^"Protein Kinase Inhibitors"]	822
#66	[mh "Protein-Tyrosine Kinases"/AI]	689
#67	[mh "immunologic factors"]	8313
#68	[mh ^"Chemokine CXCL12"/AI]	0
#69	[mh ^"Chemokine CXCL13"/AI]	0
#70	#63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69	10586
#71	(angiogenesis NEAR/5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)):ab,ti	703
#72	(ikaros NEAR/5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)):ab,ti	9
#73	(ikzf* NEAR/5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)):ab,ti	3
#74	(CD20 NEAR/5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)):ab,ti	662
#75	((CXCL12 or cxcl 12) NEAR/5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)):ab,ti	11332
#76	((cxcl13 or cxcl 13) NEAR/5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)):ab,ti	3727
#77	immunomodulator?:ti	615
#78	(BTK NEAR/5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)):ab,ti	215
#79	#71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77 OR #78	16881
#80	#70 or #79	27003
#81	((new class* or innovative or target*) NEAR/3 (drug? or therapy or therapies or therapeutic* or treatment? or chemotherap*)):ab,ti	36547
#82	[mh "Antibodies, Monoclonal"]	13410
#83	(kinase NEAR/5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)):ab,ti	4696
#84	(monoclonal NEAR/3 antibod*):ab,ti	9425
#85	#81 or #82 or #83 or #84	59362
#86	#62 or #80 or #85	85534
#87	[mh ^"Lymphoma, Large B-Cell, Diffuse"]	409
#88	histiocytic NEAR/1 lymphoma?:ab,ti	36
#89	(diffuse NEAR/2 ("large b-cell" or "large b-cells") NEAR/2 lymphoma?):ab,ti	1107
#90	(diffuse NEAR/2 ("large cell" or "large cells") NEAR/2 lymphoma?):ab,ti	99
#91	dlbcl:ab,ti	960
#92	"intravascular large b cell" NEAR/2 lymphoma?:ab,ti	11
#93	((("large lymphoid lymphoma" or "large lymphoid lymphomas") NEAR/2 diffuse):ab,ti	0
#94	#88 OR #89 OR #90 OR #91 OR #92 OR #93	1399
#95	#87 or #94	1518
#96	#86 and #95	992
Comments		



Appendix 8.3.3.4. Mantle Cell Lymphoma

Medline

Date	January 22, 2021	
Database	Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946 to January 22, 2021>	
Search strategy		
1	lenalidomide/	2759
2	lenalidomide.ab,ti,kf,rn.	4950
3	Revlimid.ab,ti,kf,rn.	133
4	Revimid.ab,ti,kf,rn.	9
5	IMiD3 Cpd.ab,ti,kf,rn.	0
6	imid 3.ab,ti,kf,rn.	7
7	CC 5013.ab,ti,kf,rn.	57
8	CC5013.ab,ti,kf,rn.	10
9	F0P408N6V4.ab,ti,kf,rn.	2759
10	SYP-1512.ab,ti,kf,rn.	0
11	SYP1512.ab,ti,kf,rn.	0
12	CDC-501.ab,ti,kf,rn.	1
13	CDC501.ab,ti,kf,rn.	0
14	cdc5013.ab,ti,kf,rn.	0
15	cdc 5013.ab,ti,kf,rn.	0
16	"enmd 0997".ab,ti,kf,rn.	2
17	enmd0997.ab,ti,kf,rn.	0
18	191732-72-6.ab,ti,kf,rn.	0
19	2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18	4983
20	1 or 19	4983
21	ibrutinib.ab,ti,kf,rn.	2308
22	IMBRUVICA.ab,ti,kf,rn.	35
23	1X70OSD4VX.ab,ti,kf,rn.	27
24	"CRA 032765".ab,ti,kf,rn.	1
25	CRA032765.ab,ti,kf,rn.	0
26	PCI-32765.ab,ti,kf,rn.	1222
27	PCI32765.ab,ti,kf,rn.	2
28	PC 32765.ab,ti,kf,rn.	1
29	PC32765.ab,ti,kf,rn.	0
30	936563-96-1.ab,ti,kf,rn.	1
31	21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30	2467



32	rituximab/	15168
33	RITUXIMAB.ab,ti,kf,rn.	25131
34	Mabthera.ab,ti,kf,rn.	192
35	Rituxan.ab,ti,kf,rn.	312
36	TUXELLA.ab,ti,kf,rn.	0
37	TRUXIMA.ab,ti,kf,rn.	14
38	RITEMVIA.ab,ti,kf,rn.	0
39	BLITZIMA.ab,ti,kf,rn.	0
40	RUXIENCE.ab,ti,kf,rn.	2
41	IDEC-C2B8.ab,ti,kf,rn.	53
42	GP2013.ab,ti,kf,rn.	11
43	4F4X42SYQ6.ab,ti,kf,rn.	15169
44	RG-105.ab,ti,kf,rn.	1
45	IDEC-102.ab,ti,kf,rn.	1
46	PF-05280586.ab,ti,kf,rn.	9
47	CT-P10.ab,ti,kf,rn.	38
48	ABP798.ab,ti,kf,rn.	0
49	ABP-798.ab,ti,kf,rn.	8
50	SAIT101.ab,ti,kf,rn.	0
51	SAIT-101.ab,ti,kf,rn.	0
52	RHCACD20MA.ab,ti,kf,rn.	0
53	HS006.ab,ti,kf,rn.	0
54	HS-006.ab,ti,kf,rn.	4
55	BI-695500.ab,ti,kf,rn.	0
56	RG105.ab,ti,kf,rn.	0
57	IDEC102.ab,ti,kf,rn.	0
58	PF05280586.ab,ti,kf,rn.	0
59	BI695500.ab,ti,kf,rn.	0
60	33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59	25201
61	32 or 60	25201
62	20 or 31 or 61	31772
63	exp angiogenesis inhibitors/	58656
64	Ikaros Transcription Factor/ai	12
65	Protein Kinase Inhibitors/	47531
66	exp Protein-Tyrosine Kinases/ai [Antagonists & Inhibitors]	39376
67	exp immunologic factors/	1394299
68	Chemokine CXCL12/ai [Antagonists & Inhibitors]	213



69	Chemokine CXCL13/ai [Antagonists & Inhibitors]	9
70	63 or 64 or 65 or 66 or 67 or 68 or 69	1482991
71	(angiogenesis adj5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)).ab,ti,kf.	25134
72	(ikaros adj5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)).ab,ti,kf.	140
73	(ikzf* adj5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)).ab,ti,kf.	72
74	(CD20 adj5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)).ab,ti,kf.	5552
75	((CXCL12 or cxcl 12) adj5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)).ab,ti,kf.	1052
76	((cxcl13 or cxcl 13) adj5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)).ab,ti,kf.	142
77	immunomodulator?.ti,kf.	10067
78	(BTK adj5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)).ab,ti,kf.	1339
79	71 or 72 or 73 or 74 or 75 or 76 or 77 or 78	43299
80	70 or 79	1506656
81	((new class* or innovative or target*) adj3 (drug? or therapy or therapies or therapeutic* or treatment? or chemotherap*)).ab,ti,kf.	358023
82	exp Antibodies, Monoclonal/	241894
83	(kinase adj5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)).ab,ti,kf.	147278
84	(monoclonal adj3 antibod*).ab,ti,kf.	200253
85	81 or 82 or 83 or 84	795001
86	((systematic review or systematic literature review or systematic scoping review or systematic narrative review or systematic qualitative review or systematic evidence review or systematic quantitative review or systematic meta-review or systematic critical review or systematic mixed studies review or systematic mapping review or systematic cochrane review or "systematic search and review" or systematic integrative review).ti. not comment.pt. not (protocol or protocols).ti. not medline.st.) or (Cochrane Database Syst Rev.ja. and review.pt.) or systematic review.pt.	179754
87	meta-analys*.ti.	122451
88	meta-analysis.pt.	125413
89	exp Technology Assessment, Biomedical/	11285
90	health technology assessment.ti,kf.	2097
91	HtA.ti,kf.	645
92	86 or 87 or 88 or 89 or 90 or 91	278857
93	LYMPHOMA, MANTLE-CELL/	3163
94	(mantle cell adj2 lymphoma?).ab,ti,kf.	5126
95	(mantle-zone adj2 lymphoma?).ab,ti,kf.	110
96	(centrocytic adj2 small-cell adj2 lymphoma?).ab,ti,kf.	2
97	("poorly differentiated" adj3 "diffuse lymphocytic lymphoma?").ab,ti,kf.	6
98	(intermediate adj2 lymphocytic lymphoma).ab,ti,kf.	84
99	94 or 95 or 96 or 97 or 98	5287
100	93 or 99	5681
101	62 or 80 or 85	2000270



102	100 and 101	2442
103	92 and 102	21
Comments		

Cochrane

Date	28/01/2021 19:23:45	
Database	Cochrane@Wiley.com	
Search strategy		
#1	[mh ^"lenalidomide"]	395
#2	lenalidomide:ab,ti	1885
#3	Revlimid:ab,ti	173
#4	Revimid:ab,ti	0
#5	"IMiD3 Cpd":ab,ti	0
#6	"imid 3":ab,ti	3
#7	"CC 5013":ab,ti	64
#8	CC5013:ab,ti	1
#9	F0P408N6V4:ab,ti	0
#10	"SYP-1512":ab,ti	1
#11	SYP1512:ab,ti	0
#12	"CDC-501":ab,ti	4
#13	CDC501:ab,ti	0
#14	cdc5013:ab,ti	0
#15	"cdc 5013":ab,ti	2
#16	"enmd 0997":ab,ti	0
#17	enmd0997:ab,ti	0
#18	"191732-72-6":ab,ti	75
#19	#2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18	1920
#20	#1 or #19	1932
#21	ibrutinib:ab,ti	506
#22	IMBRUVICA:ab,ti	23
#23	1X700SD4VX:ab,ti	0
#24	"CRA 032765":ab,ti	0
#25	CRA032765:ab,ti	0
#26	"PCI-32765":ab,ti	28
#27	PCI32765:ab,ti	0
#28	"PC 32765":ab,ti	0



#29	PC32765:ab,ti	0
#30	"936563-96-1":ab,ti	35
#31	#21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30	510
#32	[mh ^"rituximab"]	1277
#33	RITUXIMAB:ab,ti	4583
#34	Mabthera:ab,ti	361
#35	Rituxan:ab,ti	108
#36	TUXELLA:ab,ti	0
#37	TRUXIMA:ab,ti	6
#38	RITEMVIA:ab,ti	0
#39	BLITZIMA:ab,ti	0
#40	RUXIENCE:ab,ti	0
#41	"IDEC-C2B8":ab,ti	21
#42	GP2013:ab,ti	27
#43	4F4X42SYQ6:ab,ti	0
#44	"RG-105":ab,ti	0
#45	"IDEC-102":ab,ti	0
#46	"PF-05280586":ab,ti	15
#47	"CT-P10":ab,ti	50
#48	ABP798:ab,ti	2
#49	"ABP-798":ab,ti	12
#50	SAIT101:ab,ti	8
#51	"SAIT-101":ab,ti	0
#52	RHCACD20MA:ab,ti	1
#53	HS006:ab,ti	1
#54	"HS-006":ab,ti	0
#55	"BI-695500":ab,ti	8
#56	RG105:ab,ti	0
#57	IDEC102:ab,ti	0
#58	PF05280586:ab,ti	0
#59	BI695500:ab,ti	1
#60	#33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59	4637
#61	#32 or #60	4742
#62	#20 or #31 or #61	6732
#63	[mh "angiogenesis inhibitors"]	1144
#64	[mh ^"Ikaro Transcription Factor"/AI]	0
#65	[mh ^"Protein Kinase Inhibitors"]	822



#66	[mh "Protein-Tyrosine Kinases"/AI]	689
#67	[mh "immunologic factors"]	8313
#68	[mh ^"Chemokine CXCL12"/AI]	0
#69	[mh ^"Chemokine CXCL13"/AI]	0
#70	#63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69	10586
#71	(angiogenesis NEAR/5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)):ab,ti	703
#72	(ikaros NEAR/5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)):ab,ti	9
#73	(ikzf* NEAR/5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)):ab,ti	3
#74	(CD20 NEAR/5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)):ab,ti	662
#75	((CXCL12 or cxcl 12) NEAR/5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)):ab,ti	11332
#76	((cxcl13 or cxcl 13) NEAR/5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)):ab,ti	3727
#77	immunomodulator?:ti	615
#78	(BTK NEAR/5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)):ab,ti	215
#79	#71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77 OR #78	16881
#80	#70 or #79	27003
#81	((new class* or innovative or target*) NEAR/3 (drug? or therapy or therapies or therapeutic* or treatment? or chemotherap*)):ab,ti	36547
#82	[mh "Antibodies, Monoclonal"]	13410
#83	(kinase NEAR/5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)):ab,ti	4696
#84	(monoclonal NEAR/3 antibod*):ab,ti	9425
#85	#81 or #82 or #83 or #84	59362
#86	#62 or #80 or #85	85534
#87	[mh ^"LYMPHOMA, MANTLE-CELL"]	140
#88	(mantle cell NEAR/2 lymphoma?):ab,ti	566
#89	(mantle-zone NEAR/2 lymphoma?):ab,ti	1
#90	(centrocytic NEAR/2 small-cell NEAR/2 lymphoma?):ab,ti	0
#91	("poorly differentiated" NEAR/3 "diffuse lymphocytic" NEAR/1 lymphoma?):ab,ti	0
#92	(intermediate NEAR/2 lymphocytic NEAR/1 lymphoma?):ab,ti	0
#93	#88 OR #89 OR #90 OR #91 OR #92	566
#94	#87 or #93	596
#95	#86 and #94	421
Comments		



Appendix 8.4. Economic literature

Appendix 8.4.1. Search economic literature (HTA reports)

The search strategy in CRD's HTA database identified 83 references (Table 119). In a first round, 11 references were selected based on a review of title, keywords and abstract. The 72 remaining references were excluded for the following reasons: intervention (60), design (6), language (2), update available (3) or withdrawn guidance report because no longer relevant to clinical practice (1). In a second round, the full text of the 11 selected references was reviewed. Four references were excluded because of the study design. Seven references were retained. These references are indicated in Table 120 with an asterisk (*). These seven references were excluded later on because 1) the authors did not perform a de novo (base-case) economic evaluation and 2) after discussion with extern experts, only specific subtypes of Non-Hodgkin lymphoma were further elaborated.

Furthermore, in May 2020, the website of the National Institute for Health and Care Excellence (NICE) was searched. The following search terms were used: rituximab (79 hits, 13 relevant Technology Assessments (TAs), 11 not previously identified); and ibrutinib (22 hits, 4 relevant TAs, 4 not previously identified). Nine of the identified references for rituximab were excluded in a later stage because an updated report was available and/or the subtype was excluded in a later stage of the report. Also for ibrutinib, the reference related to Waldenstrom's macroglobulinaemia was excluded. Obinutuzumab was added later on to the selection of relevant drugs in B-cell chronic lymphocytic leukemia & small lymphocytic lymphoma (CLL/SLL). However, due to time restrictions and the large number of already identified reports for the twelve included indications, it was decided not to update the search for this drug.

For the other indications, the website of the National Institute for Health Research (NIHR) was also searched for relevant reports. However, due to the extra restrictions related to the included subtypes of NHL, most identified references could be excluded. Only the references related to included NICE reports were withheld. These references are indicated in Table 120 by adding superscript 'α' next to the reference.

An overview of the identified references is provided in Table 120.

Table 119 – Search strategy and results for CRD: HTA

Date			
Date covered	All		
Search Strategy	1	MeSH DESCRIPTOR Lymphoma, Non-Hodgkin EXPLODE ALL TREES	207
	2	* IN HTA	17351
	3	5 #1 AND #2	83 references
Note	/		

**Table 120 – Non-Hodgkin Lymphoma – Identified HTA reports for the selected drugs**

Selected reports	
Ibrutinib with rituximab (& bendamustine)	
•	NICE, TA437. March 2017. Ibrutinib with bendamustine and rituximab for treating relapsed or refractory chronic lymphocytic leukaemia after systemic therapy (terminated appraisal). ^{186 β}
Ibrutinib	
•	NICE, TA502. January 2018. Ibrutinib for treating relapsed or refractory mantle cell lymphoma. ^{187 β} <ul style="list-style-type: none"> ○ Tappenden P, Simpson E, Hamilton J, et al. Ibrutinib for Treating Relapsed or Refractory Mantle Cell Lymphoma: An Evidence Review Group Perspective of a NICE Single Technology Appraisal. <i>Pharmacoeconomics</i>. 2019; 37(3):333-43.^{188 α}
•	NICE, TA452. July 2017. Ibrutinib for untreated chronic lymphocytic leukaemia without a 17p deletion or TP53 mutation (terminated appraisal). ^{189 β}
•	NICE, TA429. January 2017. Ibrutinib for previously treated chronic lymphocytic leukaemia and untreated chronic lymphocytic leukaemia with 17p deletion or TP53 mutation. ^{190 β} <ul style="list-style-type: none"> ○ The following reference was found on NIHR's website: "Ibrutinib for treating chronic lymphocytic leukaemia [ID749]". However, following the link, no report could be downloaded (8 April 2021).
Rituximab (& venetoclax)	
•	NICE, TA561. February 2019. Venetoclax with rituximab for previously treated chronic lymphocytic leukaemia. ^{191 β} <ul style="list-style-type: none"> ○ The following reference was found on NIHR's website: "Venetoclax in combination with rituximab for treating relapsed or refractory chronic lymphocytic leukaemia [ID1097]". However, following the link, no report could be downloaded (8 April 2021).
Rituximab	
•	NICE, TA193. July 2010. Rituximab for the treatment of relapsed or refractory chronic lymphocytic leukaemia. ^{192 β} <ul style="list-style-type: none"> ○ The following reference was found on NIHR's website: Dretzke J, Barton P, Kaambwa B, Connock M, Uthman O. Rituximab for the treatment of relapsed/refractory chronic lymphocytic leukaemia, September 2009 ^α However, following the link, no report could be downloaded (8 April 2021).
•	NICE, TA174. July 2009. Rituximab for the first-line treatment of chronic lymphocytic leukaemia. ^{193 β} <ul style="list-style-type: none"> ○ The following reference was found on NIHR's website: Main C, Pitt M, Moxham T, Stein K. The clinical effectiveness and cost-effectiveness of rituximab for the first-line treatment of chronic lymphocytic leukaemia: an evidence review of the submission from Roche. However, following the link, no report could be downloaded (8 April 2021).
Excluded reports	
Lenalidomide & rituximab	
•	NICE, TA627. April 2020. Lenalidomide with rituximab for previously treated follicular lymphoma. ^{194 β}
Ibrutinib	
•	NICE, TA491. November 2017. Ibrutinib for treating Waldenstrom's macroglobulinaemia. ^{195 β}



- Waldenström's macroglobulinaemia was excluded from this overview.

Rituximab

- NICE, Evidence summary ESNM46. September 2014. Non-Hodgkin's lymphoma: rituximab subcutaneous injection.^{196 β}
 - This report does not present a systematic review of published economic evaluations and did not perform a de novo (base-case) economic evaluation.
- CADTH. Rituximab for Non-Hodgkin's Lymphoma: A Review of the Clinical and Cost-Effectiveness and Guidelines. January 2010.^{197 *}
 - This report presents a systematic review of published economic evaluations but did not perform a de novo (base-case) economic evaluation.
- NICE, TA243. January 2012. Rituximab for the first-line treatment of stage III-IV follicular lymphoma.^{198 β}
 - Dundar Y, Bagust A, Hounsborne J, McLeod C, Boland A, Davis H, et al. Rituximab for the first-line treatment of stage III-IV follicular non-Hodgkin's lymphoma. Health Technology Assessment. 2009; Vol. 13: Suppl. 1.^{199 * α}
 - Follicular NHL was excluded from this overview.
- NICE, TA226. June 2011. Rituximab for the first-line maintenance treatment of follicular non-Hodgkin's lymphoma.^{200 * β}
 - Follicular NHL was excluded from this overview.
- NICE, TA137. February 2008. Rituximab for the treatment of relapsed or refractory stage III or IV follicular non-Hodgkin's lymphoma.^{201 β}
 - Boland A, Bagust A, Hockenhull J, Davis H, Chu P, Dickson R. Rituximab for the treatment of relapsed or refractory stage III or IV follicular non-Hodgkin's lymphoma. Health Technology Assessment. 2009; Vol. 13: Suppl. 2.^{202 * α}
 - Bagust A, Boland A, Dickson R, Chu P, Hockenhull J, Davis H. Rituximab for the treatment of relapsed or refractory stage III or IV follicular non-Hodgkin's lymphoma. Liverpool Reviews and Implementation Group. 2007.^{203 α}
 - Follicular NHL was excluded from this overview.
- NICE, TA110. September 2006. Rituximab for the treatment of follicular lymphoma.^{204 β}
 - Papaioannou D, Rafia R, Rathbone J, Stevenson M, Buckley Woods H, Stevens J. Rituximab for the first-line treatment of stage III-IV follicular lymphoma (review of Technology Appraisal No. 110): a systematic review and economic evaluation. Health Technol Assess. 2012;16(37).^{205 * α}
 - This guidance has been updated and replaced by NICE technology appraisal guidance 243.¹⁹⁸
- NICE, TA65. September 2003. Rituximab for aggressive non-Hodgkin's lymphoma.^{206 β}
 - Knight C, Hind D, Brewer N, Abbott V. Rituximab (MabThera®) for aggressive non-Hodgkin's lymphoma: systematic review and economic evaluation. Health Technol Assess. 2004;8(37).^{207 * α}
 - After consultation the guidance has been withdrawn because it is no longer relevant to clinical practice. Rituximab is now routinely used outside its licensed indication.
- NICE, TA37. March 2002. The clinical effectiveness and cost effectiveness of rituximab for follicular lymphoma.^{208 β}
 - Wake B, Hyde C, Bryan S, Barton P, Song F, Fry-Smith A, et al. Rituximab as third-line treatment for refractory or recurrent Stage III or IV follicular non-Hodgkin's lymphoma: a systematic review and economic evaluation. Health Technol Assess. 2002;6(3).^{209 * α}
 - This guidance has been updated and replaced by NICE technology appraisal guidance 137.²⁰¹

Reports retrieved from search for systematic reviews

- Harkins RA, Patel SP, Flowers CR. Cost-effectiveness of New Targeted Agents in the Treatment of Chronic Lymphocytic Leukemia. Cancer J 2019;25(6):418-427.²¹⁰
 - This is a brief review of the economic literature on, among others, treatments against non-hodkin lymphoma. No primary economic evaluation is performed.



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- Saret CJ, Winn AN, Shah G, et al. Value of innovation in hematologic malignancies: a systematic review of published cost-effectiveness analyses. *Blood* 2015; 125(12):1866-9.²¹¹
 - This is a brief review of the economic literature on, among others, treatments against non-hodkin lymphoma. No primary economic evaluation is performed.
 - Geynisman DM, Chien CR, Smieliauskas F, et al. Economic evaluation of therapeutic cancer vaccines and immunotherapy: a systematic review. *Hum Vaccin Immunother* 2014; 10(11):3415-24.²¹²
 - This is a brief review of the economic literature on, among others, treatments against non-hodkin lymphoma. No primary economic evaluation is performed.
-

* These references were identified in CRD's HTA database. α References identified on NIHR's website. β References identified on NICE's website.

Appendix 8.4.2. Results economic literature (HTA reports)

Chronic lymphocytic leukaemia

Appendix 8.4.2.1. NICE, TA437 (2017): ibrutinib with rituximab and bendamustine (terminated appraisal)

- "NICE is unable to make a recommendation about the use in the NHS of ibrutinib with bendamustine and rituximab for treating relapsed or refractory chronic lymphocytic leukaemia after systemic therapy because no evidence submission was received from Janssen-Cilag for the technology."¹⁸⁶
- "Ibrutinib will only be used as monotherapy for the treatment of R/R CLL."¹⁸⁶

Appendix 8.4.2.2. NICE, TA452 (2017): ibrutinib (terminated appraisal)

- "NICE is unable to make a recommendation about the use in the NHS of ibrutinib for untreated chronic lymphocytic leukaemia without a 17p deletion or TP53 mutation because no evidence submission was received from Janssen-Cilag. The company has confirmed that it does not intend to make a submission."¹⁸⁹



Appendix 8.4.2.3. NICE, TA429 (2017): ibrutinib

- QoL:
 - “The committee noted that the company had collected EQ-5D data in RESONATE. The committee noted that the quality-of-life values collected at baseline before treatment did not differ much from those collected during treatment in both arms of RESONATE. (...) Having heard the positive experience of patients with ibrutinib, particularly with regard to energy levels and few side effects, the committee was concerned that benefits may not have been appropriately captured, noting that the EQ-5D does not directly measure fatigue.”¹⁹⁰
 - “The committee concluded that the EQ-5D may not have captured the experience of people with CLL, and the base case may have underestimated the quality-of-life benefit with ibrutinib.”¹⁹⁰
- Results:
 - “The committee considered the cost effectiveness of ibrutinib based on the evidence available. The committee reiterated that these ICERs were associated with uncertainty relating to efficacy estimates, utility values and long-term outcomes.”¹⁹⁰
 - “The committee considered that the true ICER was likely to fall between the results of the ERG scenarios that did or did not adjust for crossover in the RESONATE trial.”¹⁹⁰
 - “The committee considered the ICERs including the updated ibrutinib patient access scheme and the patient access scheme for idelalisib. It noted that the ERG scenario without adjusting for crossover in the RESONATE trial was around £50,000 per quality-adjusted life year (QALY) gained, and the scenario adjusting for crossover was below £50,000 per QALY gained.”¹⁹⁰
- Uncertainty and sensitivity:
 - “The committee was aware that no data were available for people with untreated CLL who have a 17p deletion or TP53 mutation. The committee agreed that, in the absence of any evidence, the data from the previously treated population could be taken into account, but recognised this was associated with uncertainty.”¹⁹⁰
 - “The committee noted that the scope included idelalisib plus rituximab as a comparator, but that the company presented results for idelalisib plus ofatumumab [*i.e. from the RESONATE trial*] rather than idelalisib plus rituximab. (...) The committee understood that the company considered that idelalisib plus ofatumumab was a proxy for idelalisib plus rituximab. (...) Therefore, it [*the Committee*] agreed there were uncertainties around the assumptions when comparing ibrutinib with idelalisib plus rituximab, but concluded that the company's assumption that idelalisib plus rituximab is equivalent to idelalisib plus ofatumumab was reasonable.”¹⁹⁰
 - “The committee noted that the company adjusted the trial results of RESONATE (which compared ibrutinib with ofatumumab) to account for crossover at disease progression. It agreed that this was appropriate, recognising that the unadjusted hazard ratio for death from the RESONATE trial would underestimate ibrutinib's effectiveness relative to ofatumumab.”¹⁹⁰
 - “The committee considered the clinical evidence that came from the randomised controlled RESONATE trial which compared ibrutinib with ofatumumab. The committee noted that after a positive interim analysis the trial terminated early, when the median time in the trial was 9.4 months. (...) It [The



Committee] was clear that the 'immaturity' of the data reflected the effectiveness of ibrutinib and viewed this positively. However, the committee was mindful that it did mean that a greater proportion of the modelled time horizon depended on extrapolations.”¹⁹⁰

- “The committee noted that data were immature (notably, median progression-free survival and overall survival had not been reached in the ibrutinib arm of RESONATE), which the committee acknowledged may reflect a successful treatment effect, but which led to uncertainty.”¹⁹⁰
- “The committee considered the company's extrapolations of data from RESONATE for progression-free survival and overall survival over the 20-year time horizon of the model. (...) The committee noted that the choice of model to extrapolate progression-free survival from RESONATE was a key driver of the cost-effectiveness results.”¹⁹⁰
- “The committee concluded that ibrutinib offered a more preferable toxicity profile, and was likely to offer progression-free and overall survival benefits compared with idelalisib plus rituximab, but was mindful that the extent of this benefit was uncertain.”¹⁹⁰
- Conclusions:
 - “The committee concluded that ibrutinib is an innovative treatment.”¹⁹⁰
 - “The committee concluded that both end-of-life criteria had been met for the populations in this appraisal.”¹⁹⁰
 - “The committee agreed that ibrutinib represented an important and effective treatment in CLL. It was satisfied that, in both populations of this appraisal, the incremental cost-effectiveness ratios (ICERs) for ibrutinib fell within the range normally considered as a cost-effective use of NHS resources for a treatment that fulfils the end-of-life criteria, when incorporating the confidential updated patient access scheme for ibrutinib and the existing patient access scheme for idelalisib.”¹⁹⁰
- (Confidential) price:
 - “The Department of Health and Janssen have agreed that ibrutinib will be available to the NHS with a patient access scheme which makes it available with a discount. The size of the discount is commercial in confidence.”¹⁹⁰
 - “The committee considered the ICERs including the updated ibrutinib patient access scheme and the patient access scheme for idelalisib.”¹⁹⁰



Reference Costs (list prices & remarks)	Population, Intervention & comparator IC, IE and ICERs	Remarks on use of generic utility instrument (e.g. EQ-5D) to measure impact on QoL in economic evaluations	Most uncertain variables or important variables in sensitivity analysis
Ibrutinib			
NICE TA429 (2017) ¹⁹⁰	<ul style="list-style-type: none"> - First-line treatment of CLL (patients with untreated CLL who have a 17p deletion or TP53 mutation and in whom chemo-immunotherapy is unsuitable) - Second-line treatment of CLL (patients with relapsed or refractory CLL who have had at least 1 prior therapy) Ibrutinib compared with idelalisib plus rituximab		
List price (confidential PAS): Ibrutinib £51.10 for a single 140-mg tablet BNF October 2016 Cost of a year's treatment course: £55 954.50	Decision-making ICER (based on the ERG results including PAS for ibrutinib and idelalisib): First-line treatment: <ul style="list-style-type: none"> - No evidence available. Results were extrapolated from the data for the second line treatment of CLL. Second line treatment: <ul style="list-style-type: none"> - Not adjusting for crossover: around £50 000 per QALY gained - Adjusting for crossover: below £50 000 per QALY gained Remark: ibrutinib meets the end-of-life criteria Conclusion: ibrutinib is a cost-effective use of NHS resources	EQ-5D data collected from the underlying RESONATE trial and modelled per health state. Progression-free state: not reported Post-progression state: not reported	Main uncertainties: <ul style="list-style-type: none"> - Proxy comparator in the underlying RESONATE trial - Magnitude of the benefit in OS - QoL benefit with ibrutinib likely underestimated - Long-term extrapolation method

CLL: chronic lymphocytic leukaemia, ERG: evidence review group, ICER: incremental cost-effectiveness ratio, OS: overall survival, QALY: quality-adjusted life-year, QoL: quality of life.



Appendix 8.4.2.4. NICE, TA561 (2019): rituximab (combined with venetoclax)

- QoL:
 - “It [The company] used utility values from previous NICE technology appraisal guidance for chronic lymphocytic leukaemia, including venetoclax monotherapy and idelalisib with rituximab.”¹⁹¹
- Results:
 - “The company's revised analyses submitted in response to consultation used results from the new MAIC analysis (see section 3.5) and the discounted price for venetoclax. The ERG's revised base-case analysis used results from the new network meta-analysis (see section 3.6) and the discounted prices for both venetoclax and ibrutinib.”¹⁹¹
 - “The committee noted that the company's cost-effectiveness estimates showed that venetoclax plus rituximab was cheaper and more effective than ibrutinib, but the ERG's base-case analysis showed venetoclax to be cheaper but less effective (the ICERs incorporated confidential discounts so cannot be reported here).”¹⁹¹
 - “The committee agreed that because of the lack of trial data directly comparing venetoclax plus rituximab with ibrutinib, and limitations in the MAIC and the network meta-analysis, it could not decide which analysis was more appropriate for decision making. It was therefore not able to determine the most plausible ICER.”¹⁹¹
 - “The committee concluded that even though the relative treatment effect of venetoclax plus rituximab compared with ibrutinib was uncertain, both sets of analyses produced ICERs within the range considered to be an acceptable use of NHS resources based on the cost per quality-adjusted life year (QALY) lost or gained.”¹⁹¹
- Uncertainty and sensitivity:
 - “There is no trial directly comparing venetoclax plus rituximab with ibrutinib. Indirect comparisons of venetoclax plus rituximab with ibrutinib have limitations, but can be used for decision making because there is no other evidence.”¹⁹¹
 - “Because the comparator in MURANO was bendamustine plus rituximab, a combination that is no longer standard care, the company did a matched-adjusted indirect comparison (MAIC) to indirectly compare progression-free survival and overall survival for venetoclax plus rituximab with ibrutinib.” (...) “The ERG noted that the results of the analysis were still clinically implausible, and the hazard-ratio estimate for progression-free survival (hazard ratio 0.797, 95% CI 0.505 to 1.258) was higher than the estimate for overall survival (hazard ratio 0.445, 95% CI 0.218 to 0.909). The ERG also highlighted that the effectiveness of ibrutinib was still underestimated in the analysis.”¹⁹¹
 - “The ERG did an alternative indirect comparison using a fixed-effect network meta-analysis to estimate the relative benefits of venetoclax plus rituximab compared with ibrutinib.”¹⁹¹
 - “The committee concluded that neither the company's MAIC nor the ERG's network meta-analysis were ideal but, because there were no other analyses, it agreed that they can be used for decision making.”¹⁹¹



- “The committee concluded that the company's new approach for extrapolating survival data was reasonable and noted that it had little effect on the incremental cost-effectiveness ratio (ICER).”¹⁹¹
- “The committee concluded that given the lack of evidence it was not possible to know how much venetoclax plus rituximab's treatment effect continues over time after treatment has stopped. But because there were no other data it agreed that the range of estimates could be used for decision making.”¹⁹¹
- Conclusions:
 - “It [The Committee] considered the new MAIC and network meta-analysis comparing venetoclax plus rituximab with ibrutinib (the appropriate comparator), but it could not decide which was more appropriate because of their limitations. However, because there were no other analyses it agreed to take them into account during decision making. It noted that the ICERs ranged from venetoclax plus rituximab being less costly and more effective than ibrutinib (company estimates) to venetoclax plus rituximab being less costly and less effective than ibrutinib (ERG estimates). However, both analyses produced ICERs showing that venetoclax was a cost-effective treatment. (...) The committee concluded that venetoclax with rituximab was a cost-effective use of NHS resources and could be recommended as an option for treating chronic lymphocytic leukaemia in adults after at least 1 previous treatment.”¹⁹¹
- (Confidential) price:
 - “The company has a commercial arrangement. This makes venetoclax with rituximab available to the NHS with a discount. The size of the discount is commercial in confidence.”¹⁹¹
 - “The ERG's revised base-case analysis used results from the new network meta-analysis and the discounted prices for both venetoclax and ibrutinib.”¹⁹¹



Reference Costs (list prices & remarks)	Population, Intervention & comparator IC, IE and ICERs	Remarks on use of generic utility instrument (e.g. EQ-5D) to measure impact on QoL in economic evaluations	Most uncertain variables or important variables in sensitivity analysis
Rituximab (& venetoclax)			
NICE, TA561 (2019) ¹⁹¹	Second-line treatment of CLL (adult patients with relapsed or refractory CLL who have had at least 1 previous therapy) Venetoclax plus rituximab compared with ibrutinib		
List price (confidential PAS): Venetoclax: £4789,47 for a 100-mg 112-tablet pack BNF September 2018 Rituximab: not reported	Company results (including PAS for venetoclax plus rituximab): - venetoclax plus rituximab dominates ibrutinib (it is cheaper and more effective) ERG results (including PAS for venetoclax plus rituximab and ibrutinib): - venetoclax plus rituximab is cheaper but less effective than ibrutinib - the ICER is within the range considered to be an acceptable use of NHS resources based on the cost per quality-adjusted life year (QALY) lost Conclusion: venetoclax plus rituximab is cost-effective	No underlying RCT. EQ-5D data obtained from NICE TA487 ²¹³ and NICE TA359. ²¹⁴ Estimates were not reported.	Main uncertainties: - Method used for indirect comparison - Relative treatment effect of venetoclax plus rituximab compared with ibrutinib - Duration of treatment effect

BNF: British national formulary, CLL: chronic lymphocytic leukaemia, ICER: incremental cost-effectiveness ratio, PAS: patient access scheme.



Appendix 8.4.2.5. NICE, TA193 (2010): rituximab

- QoL:
 - “Quality-of-life data were collected in the first year of the trial using the Functional Assessment of Cancer Therapy – General (FACT-G).”¹⁹²
 - “The utility values used in the manufacturer's submission were taken from a health technology assessment report that assessed the cost effectiveness of fludarabine as a first-line treatment for chronic lymphocytic leukaemia. A utility value of 0.8 was attached to the progression-free survival health state and 0.6 to the progressed health state. The estimates of utility were not preference based, and were estimated by the authors of the report from condition-specific health-related quality-of-life data.”¹⁹²
 - “The Committee discussed the utilities used in the economic model and noted that the evidence base for these estimates did not reflect the NICE reference case; in particular, preference-based methods were not used.”¹⁹²
- Results:
 - Population 1 (REACH trial population).
 - Company model: “The manufacturer provided a base-case estimate of incremental cost-effectiveness of rituximab plus fludarabine and cyclophosphamide compared with fludarabine and cyclophosphamide. The incremental quality-adjusted life year (QALY) gain was 0.585 at an incremental cost of £9128, giving an incremental cost-effectiveness ratio (ICER) of **£15,593 per QALY gained**.”¹⁹²
 - ERG model: “It [The Committee] noted that using an assumption of no overall survival advantage had the effect of increasing the cost-effectiveness estimates from £15,600 per QALY gained in the base case to £41,000 per QALY gained. (...) However, based on comments from the clinical specialists, the Committee was persuaded that it was appropriate to assume at least some gain in overall survival in the economic model. Overall, the Committee considered that the **most plausible ICER was likely to be at the upper end of the range of £20,000 to £30,000 per QALY gained**, which was higher than the ERG's corrected base case of **£16,600 per QALY gained**.”¹⁹²
 - Populations 2 (rituximab pre-treated population).
 - Company model: “During consultation on the appraisal consultation document, the manufacturer provided an estimate of the cost effectiveness of rituximab plus fludarabine and cyclophosphamide compared with fludarabine and cyclophosphamide, for the subgroup of people who had previously received rituximab. (...) This adjustment to the model resulted in a QALY gain of 0.406 at an incremental cost of £9134, giving an ICER of £22,519 per QALY gained.”¹⁹²
 - “It [The Committee] considered that in the rituximab-pretreated population, for which there was little research, the manufacturer's estimated ICER could not provide a basis for decision making.”¹⁹²
 - Population 3 (fludarabine-sensitive disease). “Therefore the Committee was persuaded that data from the REACH trial could apply to people who were sensitive to fludarabine combination therapy.”¹⁹²
 - Population 4 (fludarabine-refractory disease). “It [The Committee] also noted that the manufacturer had not provided an estimate of the cost effectiveness of rituximab plus fludarabine and cyclophosphamide in this population.”¹⁹²



- Uncertainty and sensitivity:
 - “The Committee noted that the clinical effectiveness evidence for this appraisal was based mainly on a single unpublished randomised controlled trial (the REACH trial). In this trial rituximab plus fludarabine and cyclophosphamide was compared with fludarabine and cyclophosphamide. (...) The Committee noted there was potential for bias in outcome assessment because of the open-label design of the trial.”¹⁹²
 - Population 1: “The Committee noted that in the REACH trial median overall survival had not been reached in the rituximab group, and that survival curves for patients in the two treatment groups hardly diverged until 30 months. The Committee heard from clinical specialists and patient experts that it is difficult for studies of chronic lymphocytic leukaemia to demonstrate an effect of treatment on overall survival because of the long natural history of the disease and because people with the disease often receive multiple treatments. It also heard that progression-free survival and response rates were often accepted as surrogates for overall survival.” (...) “On balance, the Committee was persuaded that the improvements observed in progression-free survival and response rates were likely to lead to at least some gain in overall survival, although this gain could not be quantified.”¹⁹²
 - Populations 2, 3 and 4: “The Committee discussed the exclusion from the REACH trial of people who were previously treated with fludarabine combination therapy, people who were previously treated with rituximab and people who had chronic lymphocytic leukaemia that was refractory to fludarabine. (...) The Committee considered the exclusion of these groups from the clinical trial was a limitation for decision making because it meant that the trial population did not reflect all the people with relapsed or refractory disease who would be eligible for rituximab plus fludarabine and cyclophosphamide in the NHS.”¹⁹²
 - Population 3 (fludarabine-sensitive disease): “The Committee discussed evidence from the REACH trial which included people whose disease was sensitive to fludarabine monotherapy. It noted that the REACH trial did not include people who had previously received fludarabine combination therapy. However, the Committee considered that the clinical effectiveness was likely to be similar for people who were sensitive to fludarabine monotherapy and for people who were sensitive to fludarabine combination therapy.”¹⁹²
 - Populations 2 (rituximab pre-treated population) and 4 (fludarabine-refractory disease):
 - “The Committee considered the evidence from uncontrolled phase II studies reporting the benefits of retreatment with rituximab and noted the methodological limitations of these studies. It discussed the MDACC data provided during consultation, reporting that there was a similar response rate and progression-free survival in people who have previously received rituximab compared with people who have not.”¹⁹²
 - The Committee considered that the results of the MDACC study indicated a lower response to treatment with rituximab plus fludarabine and cyclophosphamide in chronic lymphocytic leukaemia refractory to fludarabine than in disease that was sensitive to fludarabine. (...) However, it noted this study had limitations in its design (...).”¹⁹²
 - “It [The Committee] recognised that there was considerable uncertainty in the manufacturer's original base-case ICER because of the uncertainties in the gains in overall survival and the limitations in the health-related quality of life data available.”¹⁹²
 - “The Committee considered the lack of appropriate utility data contributed to uncertainty in the economic model.”¹⁹²
- Conclusions:



- Population 1 (REACH trial population) and population 3 (fludarabine-sensitive disease). “On balance, the Committee was persuaded that even taking into account the uncertainty about utility values and the uncertainty about a gain in overall survival from treatment with rituximab, the use of rituximab plus fludarabine and cyclophosphamide was a cost-effective use of NHS resources for the population represented in the REACH trial; that is, people who have not previously received rituximab or fludarabine combination therapy and those whose disease is not refractory to fludarabine monotherapy. Additionally, the Committee was persuaded that the cost effectiveness of rituximab plus fludarabine and cyclophosphamide could be generalised from people whose chronic lymphocytic leukaemia was sensitive to fludarabine monotherapy to those whose disease was sensitive to fludarabine combination therapy.”¹⁹²
- Populations 2 (rituximab pre-treated population). “The Committee concluded that rituximab plus fludarabine and cyclophosphamide could not be recommended as an appropriate use of NHS resources for everyone who had previously been treated with rituximab. However, because of the uncertainty about the benefits of retreatment with rituximab, the Committee concluded that rituximab plus fludarabine and cyclophosphamide should be recommended in the context of research for people with relapsed or refractory chronic lymphocytic leukaemia that has previously been treated with rituximab.”¹⁹²
- Population 4 (fludarabine-refractory disease). “On this basis the Committee considered that the use of rituximab plus fludarabine and cyclophosphamide for the treatment of people who had already had fludarabine could only be considered a cost-effective use of NHS resources when the chronic lymphocytic leukaemia remained fludarabine sensitive and not when it was fludarabine refractory.”¹⁹²
- (Confidential) price:
 - “The average undiscounted drug cost for rituximab was £9078 for all six cycles of treatment. The average undiscounted drug costs of fludarabine were £2569 for people in the rituximab plus fludarabine and cyclophosphamide group and £2510 for people in the fludarabine and cyclophosphamide group. The average undiscounted drug costs of cyclophosphamide were calculated as £21 and £20 for each group respectively.”¹⁹²



Reference Costs (list prices & remarks)	Population, Intervention & comparator IC, IE and ICERs	Remarks on use of generic utility instrument (e.g. EQ- 5D) to measure impact on QoL in economic evaluations	Most uncertain variables or important variables in sensitivity analysis
Rituximab (in combination with fludarabine and cyclophosphamide)			
NICE, TA193 (2010) ¹⁹²	<p>Second-line treatment of chronic lymphocytic leukaemia (adults with relapsed or refractory CLL)</p> <p>The sub-populations considered are:</p> <ol style="list-style-type: none"> 1. People who have not previously received rituximab or fludarabine combination therapy and those whose disease is not refractory to fludarabine monotherapy (population represented in the REACH trial). 2. People who have previously received treatment with rituximab (rituximab pre-treated population) 3. People who have previously received treatment with fludarabine and who are sensitive to fludarabine combination therapy (fludarabine-sensitive disease) 4. People who have previously received treatment with fludarabine and who are refractory to fludarabine combination therapy (fludarabine-refractory disease) <p>Rituximab plus fludarabine and cyclophosphamide (RFC) compared with fludarabine and cyclophosphamide</p>		
<p>List price:</p> <p>Rituximab: £174.63 for a 100-mg vial, and £873.15 for a 500-mg vial.</p> <p>The total cost of rituximab is £9954 per course.</p>	<p>Results for the sub-populations considered:</p> <ol style="list-style-type: none"> 1. Company ICER: £15 593 per QALY gained (IC: £9128, IE: 0.585) ERG base-case ICER: £16 600 per QALY gained Committee most plausible ICER: at the upper end of the range of £20 000 to £30 000 per QALY gained Conclusion: RFC is cost-effective for the population represented in the REACH trial 2. Company ICER: £22 519 per QALY gained (IC: £9134, IE: 0.406) ERG: no ICER was reported Committee: due to lack of evidence, a decision-making ICER is not available. Conclusion: RFC is not recommended for routine use, but only in the context of a clinical trial. 3. No ICER was derived. The Committee concluded that RFC is cost-effective, as results from population 1 could be generalised to population 3. 4. No ICER was derived The Committee concluded that RFC is not cost-effective. 	<p>Generic QoL measures were not collected from the underlying trial (REACH). QoL measures were obtained from the literature but with a non-preference based method.²¹⁵</p> <p>Progression-free state: 0.8 Post-progression state: 0.6</p>	<p>Uncertainties:</p> <ul style="list-style-type: none"> - gain in overall survival - health-related quality of life data available

CLL: chronic lymphocytic leukaemia, ERG: evidence review group, ICER: incremental cost-effectiveness ratio, IC: incremental cost, IE: incremental effect, RFC: rituximab plus fludarabine and cyclophosphamide.



Appendix 8.4.2.6. NICE, TA174 (2009): rituximab

- QoL:
 - “Quality-of-life data were collected in the trial using the Spitzer Quality of Life Index and the European Organisation for Research and Treatment of Cancer-Quality of Life Questionnaire Core 30 (EORTC-QLQC30).”¹⁹³
 - “The utility values used in the manufacturer’s submission were taken from a Health Technology Assessment report (Hancock et al. 2002²¹⁵) that assessed the cost effectiveness of fludarabine as a first-line treatment for chronic lymphocytic leukaemia. A utility of 0.8 was attached to the progression-free survival health state and 0.6 to the progressed health state. The estimates of utility were not preference based, and were estimated by the authors of the Health Technology Assessment report from condition-specific health-related quality-of-life data.”¹⁹³
 - “The Committee considered that the manufacturer may have been able to map the health-related quality-of-life data from the rituximab trial to a preference-based measure to derive utilities and that this may have provided an alternative to the utility data used. (...) The Committee considered the lack of appropriate utility data contributed to substantial uncertainty in the economic modelling.”¹⁹³
- Results:
 - “The manufacturer provided a base-case estimate of incremental cost effectiveness of rituximab in combination with fludarabine and cyclophosphamide in comparison with fludarabine and cyclophosphamide. The incremental quality-adjusted life year (QALY) gain was 0.88 at an incremental cost of £11,617, giving an incremental cost-effectiveness ratio (ICER) of £13,189 per QALY gained.”¹⁹³
 - “The ERG repeated the analysis completed by the manufacturer that removed the differences in overall survival between the two groups in the model. (...) A decrease in the probability of death in the fludarabine and cyclophosphamide group to 57% of the base-case level removed the difference in overall survival between the groups and resulted in a QALY gain of 0.24 at an incremental cost of £7228 and an ICER of £30,304 per QALY gained.”¹⁹³
 - “The Committee noted that when the overall survival benefit was removed from the model the ICER increased from £13,000 to £30,000 per QALY gained.”¹⁹³
 - “The ERG completed another exploratory analysis that assumed that the actual overall survival benefit from treatment with rituximab was somewhere between the manufacturer’s base case and the assumption of no overall survival benefit. (...) The results suggested that rituximab in combination with fludarabine and cyclophosphamide had a 72% probability of being cost effective compared with fludarabine and cyclophosphamide at £20,000 per QALY gained and 88% probability of being cost effective at £30,000 per QALY gained.”¹⁹³
- Uncertainty and sensitivity:
 - “This comparison was based on the CLL-8 trial, a phase III randomised controlled trial. The CLL-8 trial was a multicentre, open-label, parallel-group study in people with previously untreated chronic lymphocytic leukaemia.”¹⁹³
 - “A pre-planned interim analysis of the trial data after a median follow-up of 20.7 months showed a statistically significant difference in progression-free survival between the treatment groups. At this point the trial was halted and the interim analysis became the main analysis. (...) At this point median overall survival had not been reached (...).”¹⁹³



- “A sensitivity analysis was presented in the manufacturer's submission using different parametric models for the progression-free survival extrapolation. (...) The results were sensitive to the function used to extrapolate progression-free survival (exponential, Gompertz), and the highest ICER reported (using a Gompertz function) was £22,661 per QALY gained. (...) The ERG further considered that the sensitivity analyses presented by the manufacturer did not fully investigate the uncertainty associated with the extent to which gains in progression-free survival led to gains in overall survival.”¹⁹³
- “The Committee accepted that crossover and subsequent lines of treatment in the trial made the overall survival benefit difficult to prove. (...) On balance, the Committee was persuaded that the benefits observed in progression-free survival and response rate were likely to lead to a gain in overall survival, although currently this would be difficult to quantify.”¹⁹³
- “The Committee recognised therefore that the assumption about the amount of gain in overall survival from treatment with rituximab was an important assumption in the economic model and the use of different assumptions could have a large impact on the estimates of cost effectiveness.”¹⁹³
- Conclusions:
 - “The Committee noted that the probability, using the base-case utilities (that is, 0.80 for the progression-free survival health state and 0.60 for the progressed health state), of rituximab in combination with fludarabine and cyclophosphamide being cost effective at £20,000 per QALY gained was 71% and at £30,000 per QALY gained was 87%. On balance, the Committee was persuaded that even taking into account the additional uncertainty about the utility values, the economic analysis had demonstrated that rituximab in combination with fludarabine and cyclophosphamide for the first-line treatment of chronic lymphocytic leukaemia was a cost-effective use of NHS resources.”¹⁹³
- (Confidential) price:
 - “For six cycles of treatment the total drug cost of rituximab was £10,128. The total drug costs of fludarabine, cyclophosphamide and chlorambucil were calculated as £2790, £22 and £286, respectively.”¹⁹³



Reference Costs (list prices & remarks)	Population, Intervention & comparator IC, IE and ICERs	Remarks on use of generic utility instrument (e.g. EQ- 5D) to measure impact on QoL in economic evaluations	Most uncertain variables or important variables in sensitivity analysis
Rituximab (in combination with fludarabine and cyclophosphamide)			
NICE, TA174 (2009) ¹⁹³	First-line treatment of chronic lymphocytic leukaemia (people with previously untreated chronic lymphocytic leukaemia) Comparisons: Rituximab plus fludarabine and cyclophosphamide compared with fludarabine and cyclophosphamide		
List price: Rituximab: £174.63 for a 100-mg vial, and £873.15 for a 500-mg vial. The total cost of rituximab is £10 128 per course.	Decision-making ICER (based on the company's results including list prices for all drugs): - Company: £13 189 per QALY gained (IC: £11 617, IE: 0.88) - ERG (assuming no difference in OS between treatment groups): £30 304 per QALY gained (IC: £7228, IE: 0.24 QALY) - ERG (assuming OS benefit from treatment with rituximab is somewhere between the company's base case and the assumption of no OS benefit): o 72% probability of being cost-effective at £20 000 per QALY o 88% probability of being cost-effective at £30 000 per QALY Conclusion: rituximab in combination with fludarabine and cyclophosphamide is a cost-effective use of NHS resources.	Generic QoL measures were not collected from the underlying trial (CLL-8). QoL measures were obtained from a published study that collected QoL with a non- preference based method. ²¹⁵ Progression-free state: 0.8 Post-progression state: 0.6	Uncertainties: - method to extrapolate progression-free survival to OS - amount of gain in OS from treatment with rituximab - utility estimates

ERG: evidence review group, ICER: incremental cost-effectiveness ratio, IC: incremental cost, IE: incremental effect, OS: overall survival, QALY: quality-adjusted life-year.



Appendix 8.4.3. Mantel-cell lymphoma

Appendix 8.4.3.1. NICE, TA502 (2018): ibrutinib

- QoL:
 - “Health-utilities for the progression-free and post-progression states were derived from EQ-5D-5L data collected within the RAY and SPARK studies.”¹⁸⁸
 - QoL input data used in the model were not reported in NICE TA502¹⁸⁷ nor in the underlying report.¹⁸⁸
- Results:
 - “The committee re-examined the company's Markov approach, which it considered led to more plausible results (incremental QALYs for ibrutinib compared with R-chemo ranging from 0.82 to 1.87 depending on the scenario), although it acknowledged the considerable uncertainty associated with these estimates.”¹⁸⁷
 - **Overall R/R CML population:** “The committee noted that in the company's base-case analysis, incorporating the updated patient access scheme, the incremental cost-effectiveness ratio (ICER) for ibrutinib compared with R-chemo was £62,650 per QALY gained. It also noted that the company carried out a range of scenario analyses to test the assumptions in the model.” (...) “The committee also noted that the ICER was above £59,000 per QALY gained in all but 1 of the scenarios presented by the company.”¹⁸⁷
 - **Subgroup of R/R CML patients with only 1 previous treatment:** “The committee recalled its earlier conclusion that trial evidence and clinical experience suggest that ibrutinib is most effective in people who have had only 1 previous line of therapy. (...) It noted that the company's ICER of £49,849 per QALY gained may be a conservative estimate because updated trial data from RAY suggest that the model underestimates survival for this subgroup. The committee also noted that overall survival in RAY may have been confounded by the crossover of 39% of people from the temsirolimus arm to the ibrutinib arm. The committee concluded that the most plausible ICER in this group of patients is likely to be lower than the company's estimate of £49,848 per QALY gained.”¹⁸⁷
- Uncertainty and sensitivity:
 - “The committee noted that in the absence of any direct trial evidence for ibrutinib against a comparator reflective of current UK clinical practice, the company did an indirect treatment comparison using results from RAY and from the OPTIMAL study (Hess, 2009) that compared temsirolimus with clinician's choice of single-agent chemotherapy. The indirect treatment comparison compared ibrutinib against clinician's choice of single-agent chemotherapy in OPTIMAL, using temsirolimus as the common comparator. The committee noted that the company adjusted the treatment effect of chemotherapy, as estimated from the indirect comparison, to take into account the additional effect of adding rituximab (R-chemo).”¹⁸⁷
 - “The committee acknowledged the limitations of the indirect comparison that were highlighted by both the company and the evidence review group (ERG), such as differences in the patient populations in OPTIMAL and RAY.”¹⁸⁷
 - “The committee concluded that the overall-survival benefits from RAY were uncertain because of the crossover of many patients in the temsirolimus arm to the ibrutinib arm, and the use of further anticancer systemic therapies in both arms.”¹⁸⁷



- “The committee concluded that there is considerable uncertainty associated with the indirect comparisons and that the size of the benefit of ibrutinib compared with R-chemo is unclear, although it accepted that the available evidence and experience from clinical practice strongly suggest that ibrutinib is more effective.”¹⁸⁷
- Conclusions:
 - “It [The Committee] accepted that ibrutinib is indicated for people with a short life expectancy, noting that the estimates presented for people with relapsed or refractory mantle cell lymphoma ranged from 5.2 months to 9.7 months. It also accepted that there is enough evidence to indicate that ibrutinib offers an extension to life of at least an additional 3 months, compared with current NHS treatment. The committee concluded that ibrutinib met all the criteria to be considered a life-extending end-of-life treatment.”¹⁸⁷
 - “The committee concluded that the incremental cost-effectiveness ratios (ICERs) presented by the company for the whole population of people with relapsed or refractory mantle cell lymphoma, incorporating the updated confidential patient access scheme for ibrutinib, are above the range normally considered a cost-effective use of NHS resources (that is, £20,000 to £30,000 per quality-adjusted life year [QALY] gained). The committee noted that the evidence from trials and clinical experience suggest that ibrutinib is most effective in people who have had only 1 previous line of therapy. It concluded that ibrutinib is a cost-effective use of NHS resources for this subgroup.”¹⁸⁷
- (Confidential) price:
 - “The pricing arrangement considered during guidance development was a patient access scheme agreed with the Department of Health that applied to all indications for ibrutinib. The level of the discount increased during the appraisal and was commercial in confidence. The company subsequently agreed a commercial access agreement with NHS England that replaced the patient access scheme on equivalent terms. The financial terms of the agreement are commercial in confidence.”¹⁸⁷



Reference Costs (list prices & remarks)	Population, Intervention & comparator IC, IE and ICERs	Remarks on use of generic utility instrument (e.g. EQ- 5D) to measure impact on QoL in economic evaluations	Most uncertain variables or important variables in sensitivity analysis
Ibrutinib			
NICE, TA502 (2018) ¹⁸⁷ Tappenden et al. (2019) ¹⁸⁸	Second line treatment of mantle cell lymphoma (MCL) (adults with relapsed or refractory (R/R) MCL who have had only 1 previous line of therapy) Ibrutinib compared with rituximab plus chemotherapy (R-chemo)		
List price of ibrutinib (confidential PAS): £4 599 for 140-mg 90-capsule pack £6 132 for a 140-mg 120-capsule pack BNF June 2016	Decision-making ICER (based on the company's results including revised PAS): For the overall R/R MCL population: - above £59 000 per QALY gained - conclusion: ibrutinib is not cost-effective For the subgroup of R/R MCL patients with only 1 previous treatment: - below £49 848 per QALY gained - conclusion: ibrutinib is a cost-effective Remark: ibrutinib meets the end-of-life criteria	EQ-5D-5L data collected from the RAY trial (not the underlying RCT) and from the SPARK study. Quality of life modelled per health state QoL data not reported	Uncertain parameters: - size of the clinical benefit - Method used for indirect comparison

BNF: British national formulary, ICER: incremental cost-effectiveness ratio, PAS: patient access scheme, QALY: quality-adjusted life-year, R/R CML: relapsed or refractory mantle cell lymphoma.



APPENDIX 9. NON-SMALL CELL LUNG CANCER

Appendix 9.1. BCR data

Appendix 9.1.1. Descriptive statistics

Appendix 9.1.1.1. NSC Lung cancers, exploration

Table 121 – NSC Lung cancers (2004-2017): Frequency table of patient and tumour characteristics

Characteristic	Total	Incidence period		
		2004-2008	2009-2013	2014-2017
Overall	84,410	27,953	30,919	25,538
Gender				
Male	60,691 (71.9)	21,422 (76.6)	21,983 (71.1)	17,286 (67.7)
Female	23,719 (28.1)	6,531 (23.4)	8,936 (28.9)	8,252 (32.3)
Age at diagnosis (year)				
<50 years	4,215 (5.0)	1,686 (6.0)	1,512 (4.9)	1,017 (4.0)
50-59 years	15,432 (18.3)	5,308 (19.0)	5,865 (19.0)	4,259 (16.7)
60-69 years	26,691 (31.6)	8,150 (29.2)	9,700 (31.4)	8,841 (34.6)
70-79 years	26,980 (32.0)	9,510 (34.0)	9,682 (31.3)	7,788 (30.5)
80+ years	11,092 (13.1)	3,299 (11.8)	4,160 (13.5)	3,633 (14.2)
WHO - Performance Status				
0 – Asymptomatic	11,710 (13.9)	3,121 (11.2)	4,423 (14.3)	4,166 (16.3)
1 – Symptomatic but completely ambulatory	41,347 (49.0)	10,922 (39.1)	15,928 (51.5)	14,497 (56.8)
2 – Symptomatic, <50% in bed during the day	8,531 (10.1)	2,782 (10.0)	2,912 (9.4)	2,837 (11.1)
3 – Symptomatic, >50% in bed, but not bedbound	2,951 (3.5)	945 (3.4)	1,045 (3.4)	961 (3.8)
4 – Bedbound	820 (1.0)	276 (1.0)	304 (1.0)	240 (0.9)
Not reported	19,051 (22.6)	9,907 (35.4)	6,307 (20.4)	2,837 (11.1)
Combined stage				
0	38 (0.0)	2 (0.0)	9 (0.0)	27 (0.1)
is	3 (0.0)	0 (0.0)	0 (0.0)	3 (0.0)
I	14,682 (17.4)	4,334 (15.5)	5,369 (17.4)	4,979 (19.5)



II	6,589 (7.8)	1,734 (6.2)	2,627 (8.5)	2,228 (8.7)
III	16,958 (20.1)	5,595 (20.0)	6,300 (20.4)	5,063 (19.8)
IV	32,200 (38.1)	8,819 (31.5)	12,039 (38.9)	11,342 (44.4)
X/NA	13,940 (16.5)	7,469 (26.7)	4,575 (14.8)	1,896 (7.4)

Note: the values between parentheses are column percentages.

Table 122 – NSC Lung cancers (2004-2017), Combined stage I, Frequency table of patient and tumour characteristics

Characteristic	Total	Incidence period		
		2004-2008	2009-2013	2014-2017
Overall	14,682	4,334	5,369	4,979
Gender				
Male	10,069 (68.6)	3,272 (75.5)	3,651 (68.0)	3,146 (63.2)
Female	4,613 (31.4)	1,062 (24.5)	1,718 (32.0)	1,833 (36.8)
Age at diagnosis (year)				
<50 years	667 (4.5)	249 (5.7)	229 (4.3)	189 (3.8)
50-59 years	2,566 (17.5)	783 (18.1)	996 (18.6)	787 (15.8)
60-69 years	5,050 (34.4)	1,353 (31.2)	1,827 (34.0)	1,870 (37.6)
70-79 years	4,970 (33.9)	1,571 (36.2)	1,772 (33.0)	1,627 (32.7)
80+ years	1,429 (9.7)	378 (8.7)	545 (10.2)	506 (10.2)
WHO - Performance Status				
0 – Asymptomatic	4,370 (29.8)	1,084 (25.0)	1,582 (29.5)	1,704 (34.2)
1 – Symptomatic but completely ambulatory	6,961 (47.4)	1,869 (43.1)	2,549 (47.5)	2,543 (51.1)
2 – Symptomatic, <50% in bed during the day	673 (4.6)	265 (6.1)	205 (3.8)	203 (4.1)
3 – Symptomatic, >50% in bed, but not bedbound	146 (1.0)	49 (1.1)	52 (1.0)	45 (0.9)
4 – Bedbound	51 (0.3)	27 (0.6)	15 (0.3)	9 (0.2)
Not reported	2,481 (16.9)	1,040 (24.0)	966 (18.0)	475 (9.5)

Note: the values between parentheses are column percentages.



Table 123 – NSC Lung cancers (2004-2017), Combined stage II, Frequency table of patient and tumour characteristics

Characteristic	Total	Incidence period		
		2004-2008	2009-2013	2014-2017
Overall	6,589	1,734	2,627	2,228
Gender				
Male	4,974 (75.5)	1,407 (81.1)	1,961 (74.6)	1,606 (72.1)
Female	1,615 (24.5)	327 (18.9)	666 (25.4)	622 (27.9)
Age at diagnosis (year)				
<50 years	307 (4.7)	105 (6.1)	133 (5.1)	69 (3.1)
50-59 years	1,221 (18.5)	378 (21.8)	472 (18.0)	371 (16.7)
60-69 years	2,081 (31.6)	506 (29.2)	825 (31.4)	750 (33.7)
70-79 years	2,209 (33.5)	589 (34.0)	897 (34.1)	723 (32.5)
80+ years	771 (11.7)	156 (9.0)	300 (11.4)	315 (14.1)
WHO - Performance Status				
0 – Asymptomatic	1,379 (20.9)	320 (18.5)	513 (19.5)	546 (24.5)
1 – Symptomatic but completely ambulatory	3,690 (56.0)	874 (50.4)	1,525 (58.1)	1,291 (57.9)
2 – Symptomatic, <50% in bed during the day	431 (6.5)	133 (7.7)	144 (5.5)	154 (6.9)
3 – Symptomatic, >50% in bed, but not bedbound	129 (2.0)	35 (2.0)	50 (1.9)	44 (2.0)
4 – Bedbound	44 (0.7)	10 (0.6)	12 (0.5)	22 (1.0)
Not reported	916 (13.9)	362 (20.9)	383 (14.6)	171 (7.7)

Note: the values between parentheses are column percentages.



Table 124 – NSC Lung cancers (2004-2017), Combined stage III, Frequency table of patient and tumour characteristics

Characteristic	Total	Incidence period		
		2004-2008	2009-2013	2014-2017
Overall	16,958	5,595	6,300	5,063
Gender				
Male	12,744 (75.2)	4,435 (79.3)	4,710 (74.8)	3,599 (71.1)
Female	4,214 (24.8)	1,160 (20.7)	1,590 (25.2)	1,464 (28.9)
Age at diagnosis (year)				
<50 years	751 (4.4)	290 (5.2)	281 (4.5)	180 (3.6)
50-59 years	3,132 (18.5)	1,107 (19.8)	1,184 (18.8)	841 (16.6)
60-69 years	5,489 (32.4)	1,693 (30.3)	2,018 (32.0)	1,778 (35.1)
70-79 years	5,402 (31.9)	1,880 (33.6)	1,988 (31.6)	1,534 (30.3)
80+ years	2,184 (12.9)	625 (11.2)	829 (13.2)	730 (14.4)
WHO - Performance Status				
0 – Asymptomatic	2,702 (15.9)	830 (14.8)	1,000 (15.9)	872 (17.2)
1 – Symptomatic but completely ambulatory	10,161 (59.9)	3,051 (54.5)	3,874 (61.5)	3,236 (63.9)
2 – Symptomatic, <50% in bed during the day	1,749 (10.3)	674 (12.0)	591 (9.4)	484 (9.6)
3 – Symptomatic, >50% in bed, but not bedbound	535 (3.2)	212 (3.8)	178 (2.8)	145 (2.9)
4 – Bedbound	140 (0.8)	56 (1.0)	52 (0.8)	32 (0.6)
Not reported	1,671 (9.9)	772 (13.8)	605 (9.6)	294 (5.8)

Note: the values between parentheses are column percentages.



Table 125 – NSC Lung cancers (2004-2017), Combined stage IV, Frequency table of patient and tumour characteristics

Characteristic	Total	Incidence period		
		2004-2008	2009-2013	2014-2017
Overall	32,200	8,819	12,039	11,342
Gender				
Male	22,562 (70.1)	6,577 (74.6)	8,404 (69.8)	7,581 (66.8)
Female	9,638 (29.9)	2,242 (25.4)	3,635 (30.2)	3,761 (33.2)
Age at diagnosis (year)				
<50 years	1,829 (5.7)	632 (7.2)	687 (5.7)	510 (4.5)
50-59 years	6,257 (19.4)	1,803 (20.4)	2,456 (20.4)	1,998 (17.6)
60-69 years	10,284 (31.9)	2,655 (30.1)	3,748 (31.1)	3,881 (34.2)
70-79 years	9,702 (30.1)	2,801 (31.8)	3,581 (29.7)	3,320 (29.3)
80+ years	4,128 (12.8)	928 (10.5)	1,567 (13.0)	1,633 (14.4)
WHO - Performance Status				
0 – Asymptomatic	2,943 (9.1)	778 (8.8)	1,196 (9.9)	969 (8.5)
1 – Symptomatic but completely ambulatory	18,722 (58.1)	4,680 (53.1)	7,129 (59.2)	6,913 (61.0)
2 – Symptomatic, <50% in bed during the day	5,205 (16.2)	1,539 (17.5)	1,793 (14.9)	1,873 (16.5)
3 – Symptomatic, >50% in bed, but not bedbound	1,964 (6.1)	598 (6.8)	687 (5.7)	679 (6.0)
4 – Bedbound	509 (1.6)	167 (1.9)	188 (1.6)	154 (1.4)
Not reported	2,857 (8.9)	1,057 (12.0)	1,046 (8.7)	754 (6.6)

Note: the values between parentheses are column percentages.



Appendix 9.1.1.2. NSC Lung cancers, Observed and Relative Survival graphs

NSC Lung cancers (2004-2017)

Figure 208 – NSC Lung cancers (2004-2017), Kaplan-Meier graphs observed survival by incidence period

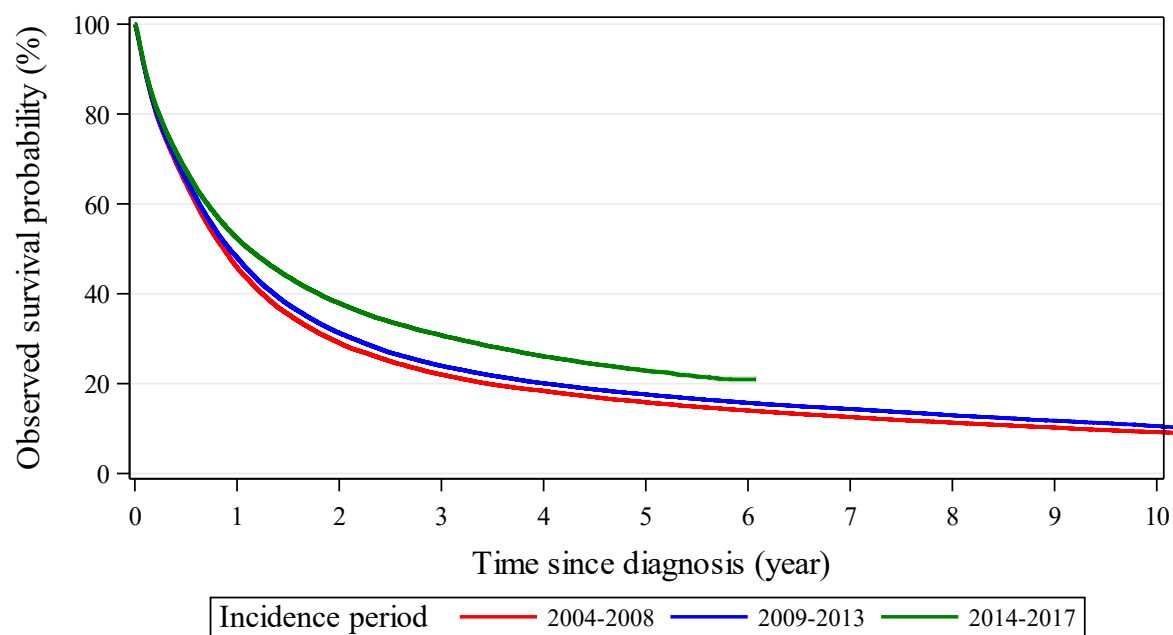
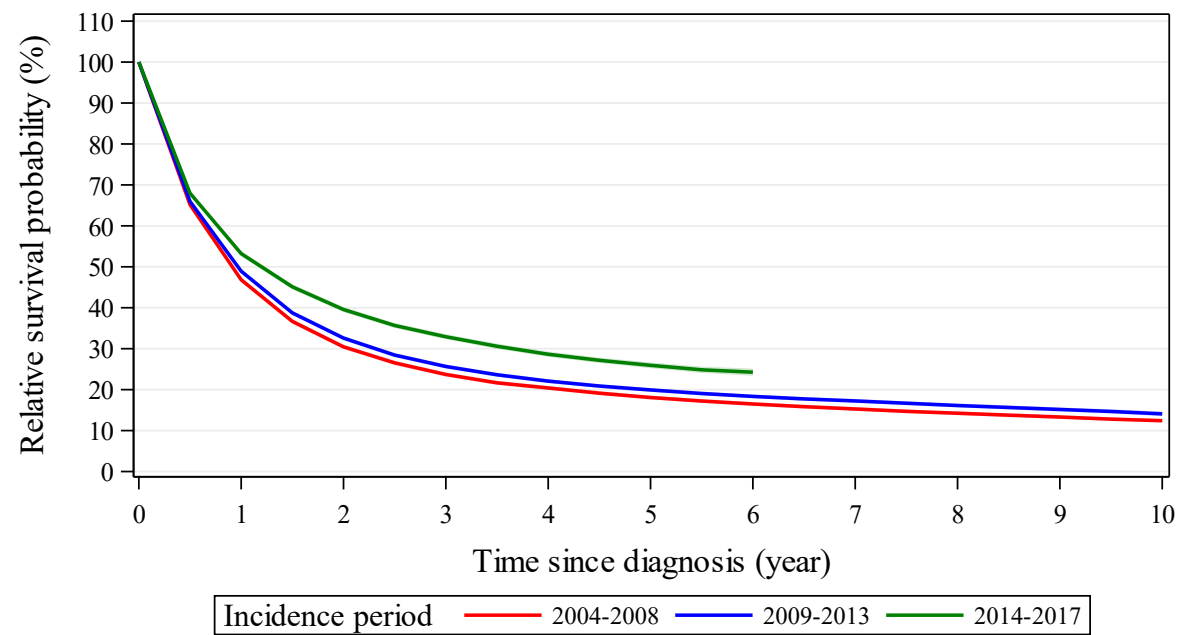




Figure 209 – NSC Lung cancers (2004-2017), relative survival graphs by incidence period



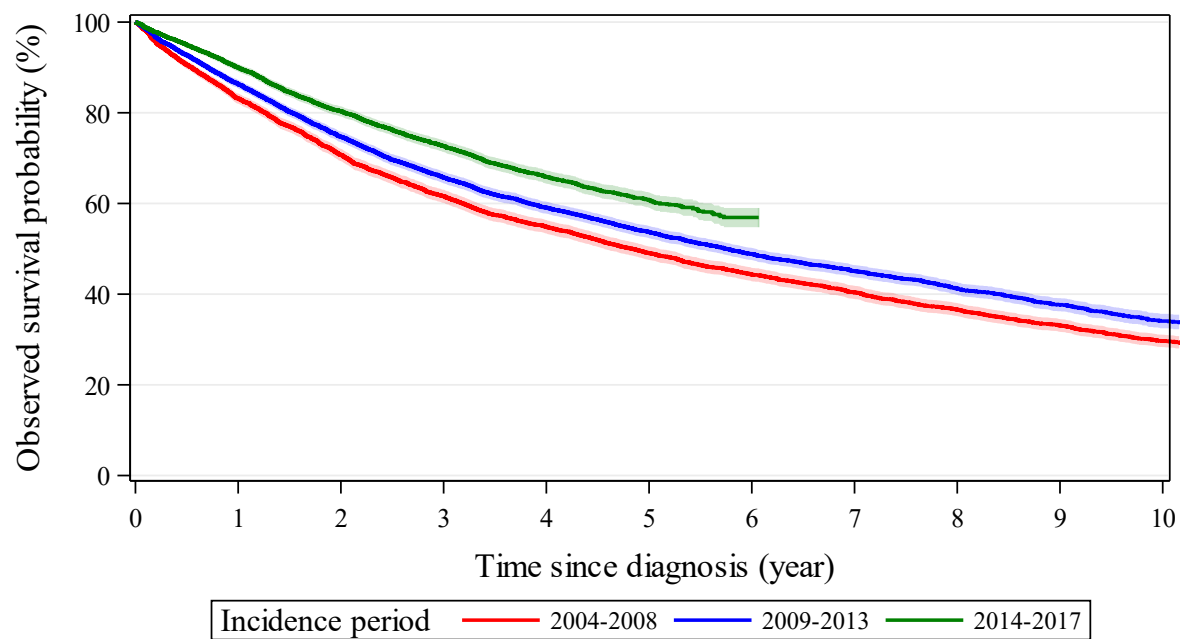
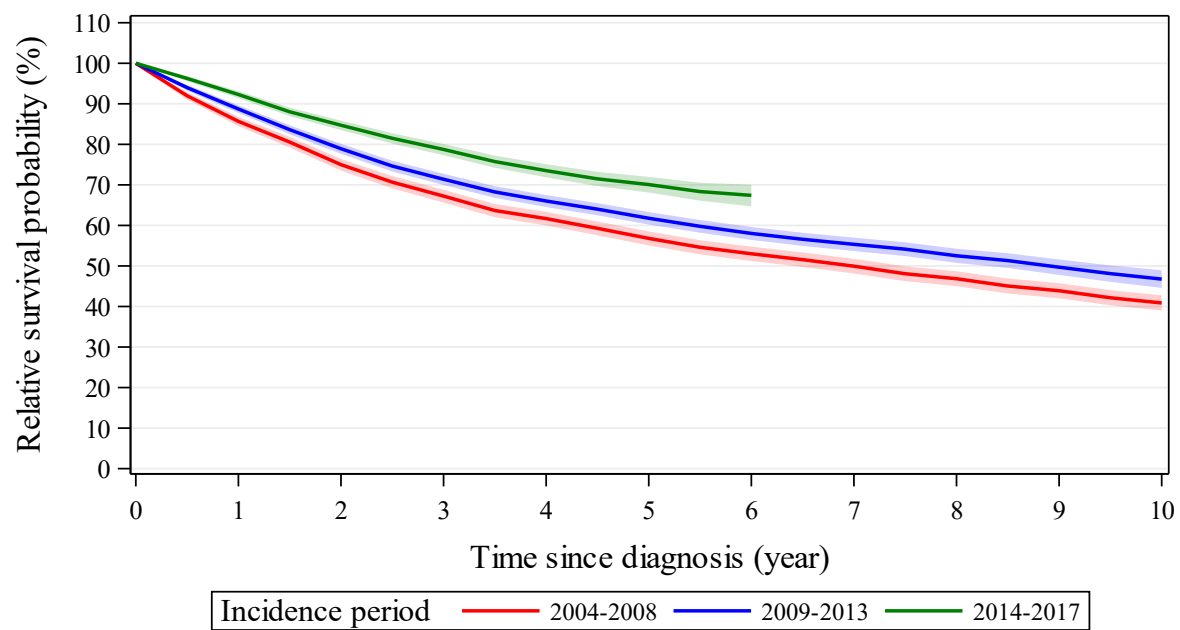
**NSC Lung cancers, combined stage I (2004-2017)****Figure 210 – NSC Lung cancers (2004-2017), combined stage I, Kaplan-Meier graphs observed survival by incidence period**



Figure 211 – NSC Lung cancers (2004-2017), combined stage I, relative survival graphs by incidence period



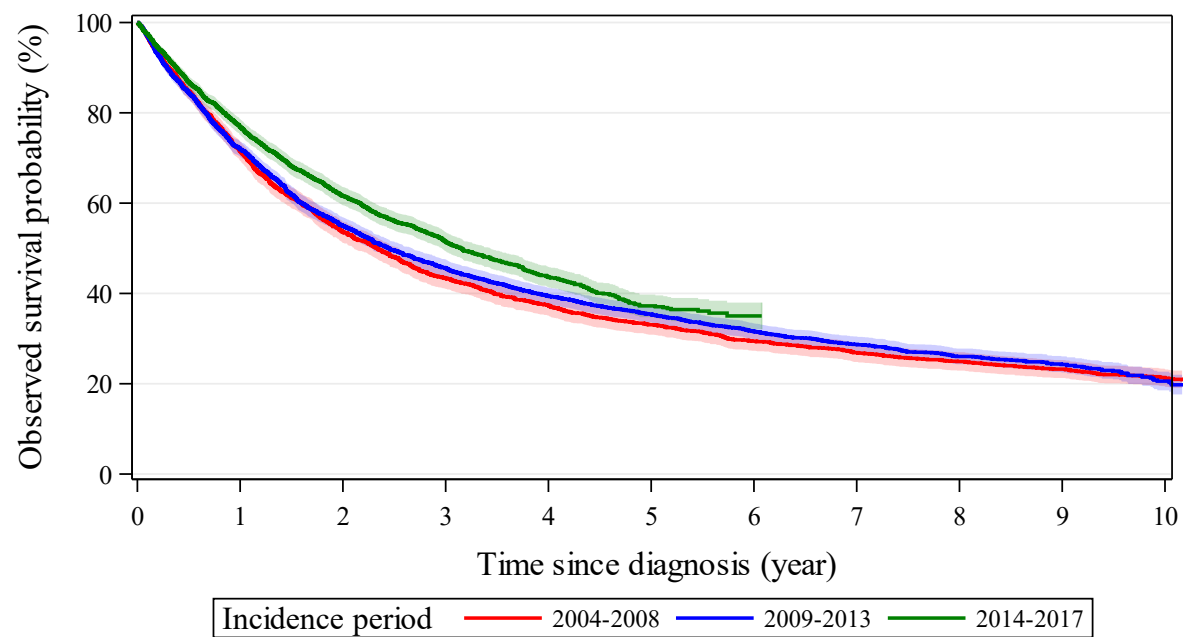
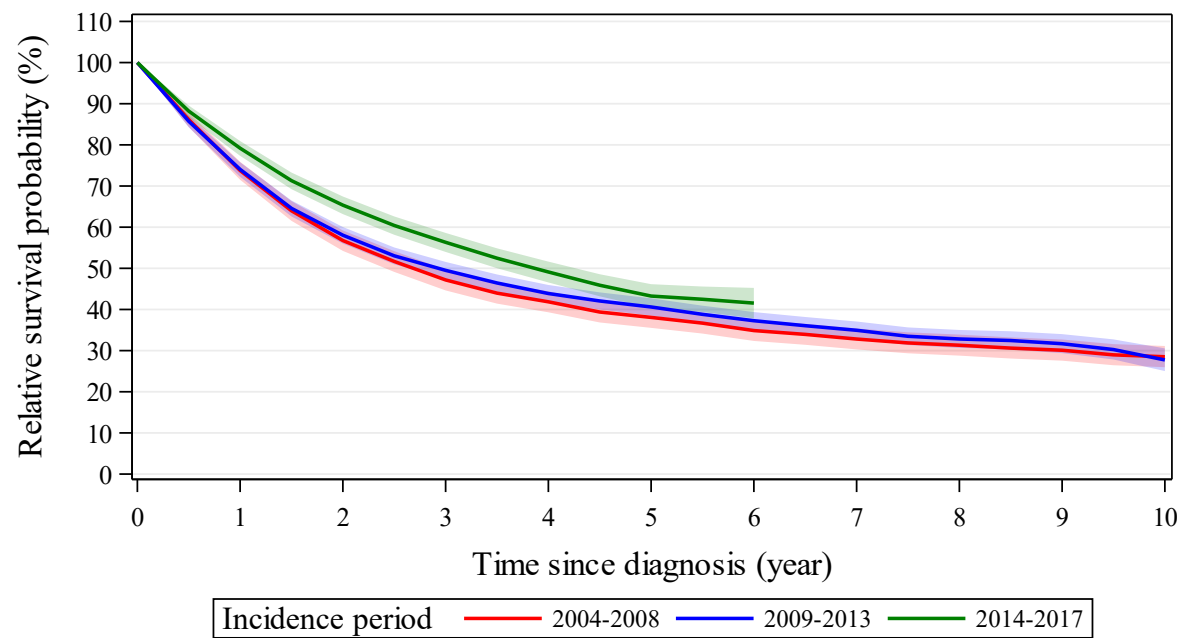
**NSC Lung cancers, combined stage II (2004-2017)****Figure 212 – NSC Lung cancers (2004-2017), combined stage II, Kaplan-Meier graphs observed survival by incidence period**



Figure 213 – NSC Lung cancers (2004-2017), combined stage II, relative survival graphs by incidence period



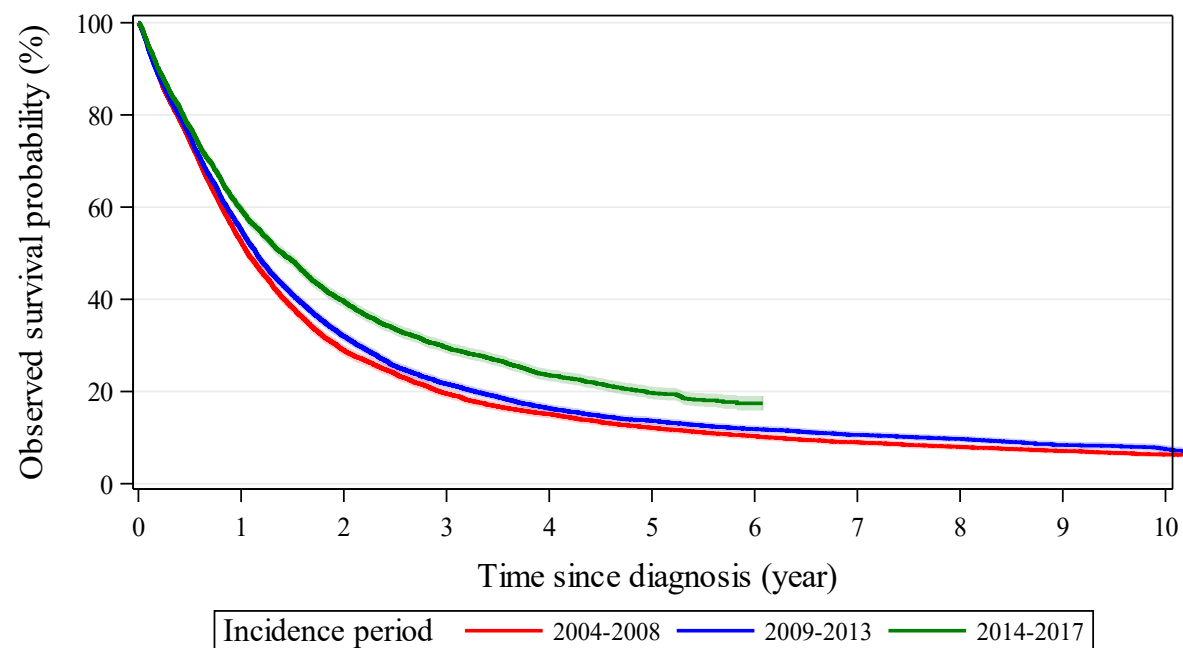
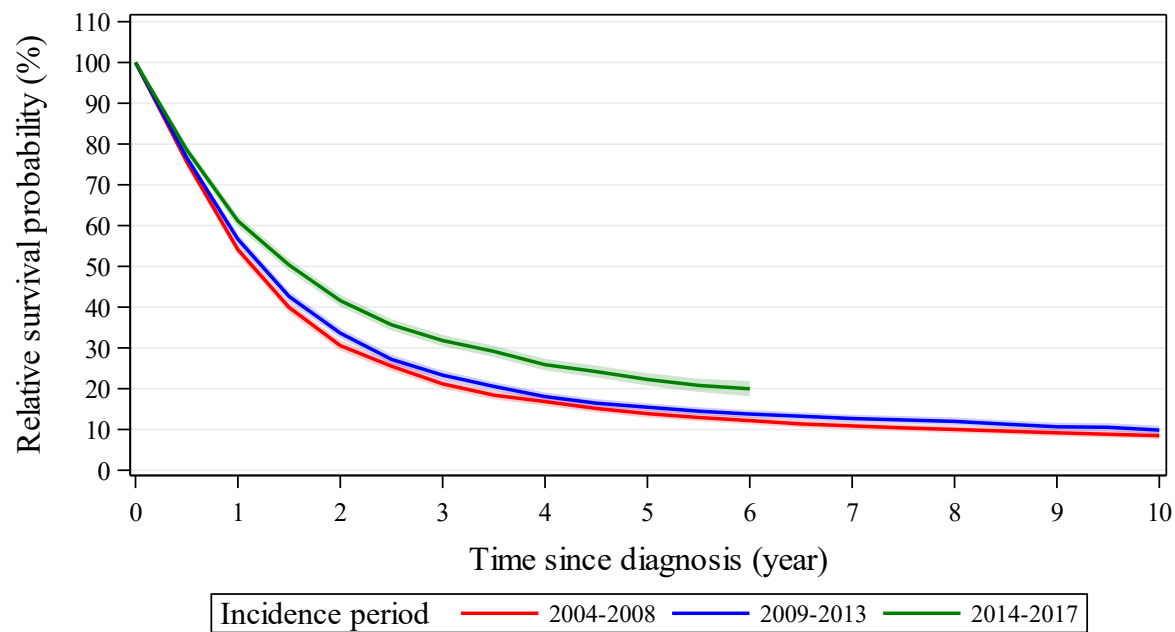
**NSC Lung cancers, combined stage III (2004-2017)****Figure 214 – NSC Lung cancers (2004-2017), combined stage III, Kaplan-Meier graphs observed survival by incidence period**



Figure 215 – NSC Lung cancers (2004-2017), combined stage III, relative survival graphs by incidence period



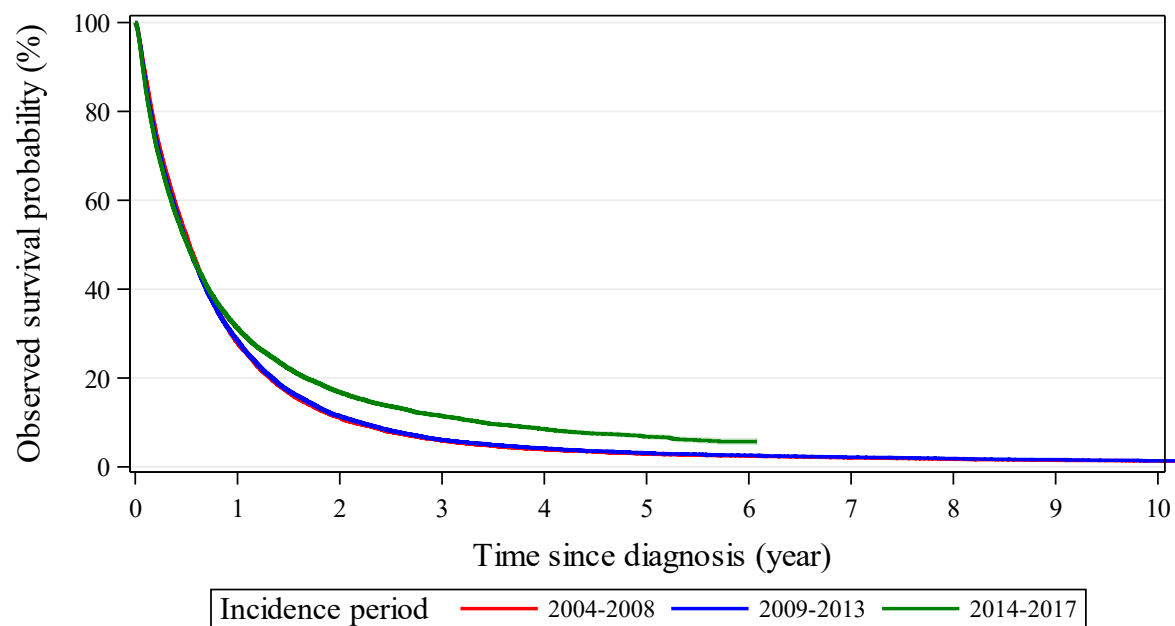
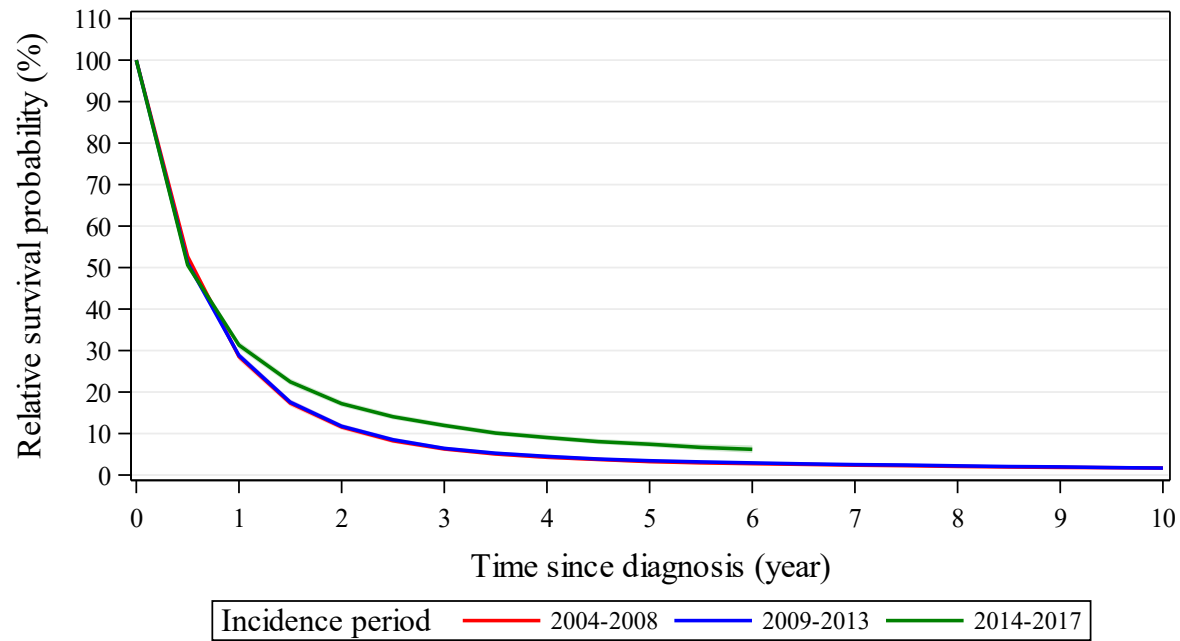
**NSC Lung cancers, combined stage IV (2004-2017)****Figure 216 – NSC Lung cancers (2004-2017), combined stage IV, Kaplan-Meier graphs observed survival by incidence period**



Figure 217 – NSC Lung cancers (2004-2017), combined stage IV, relative survival graphs by incidence period

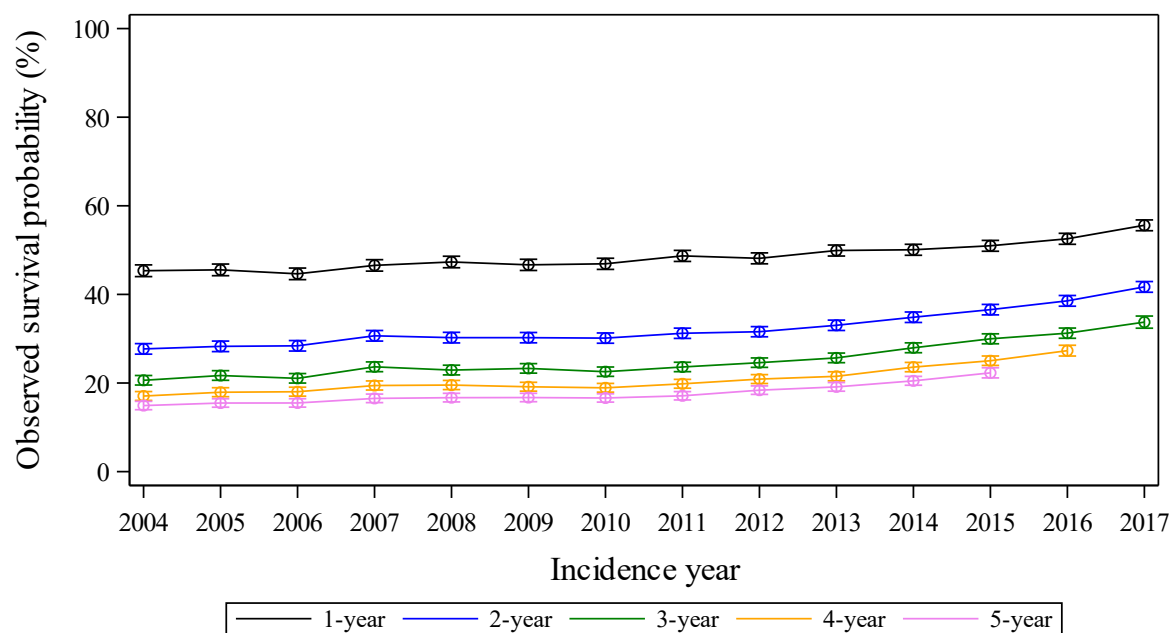




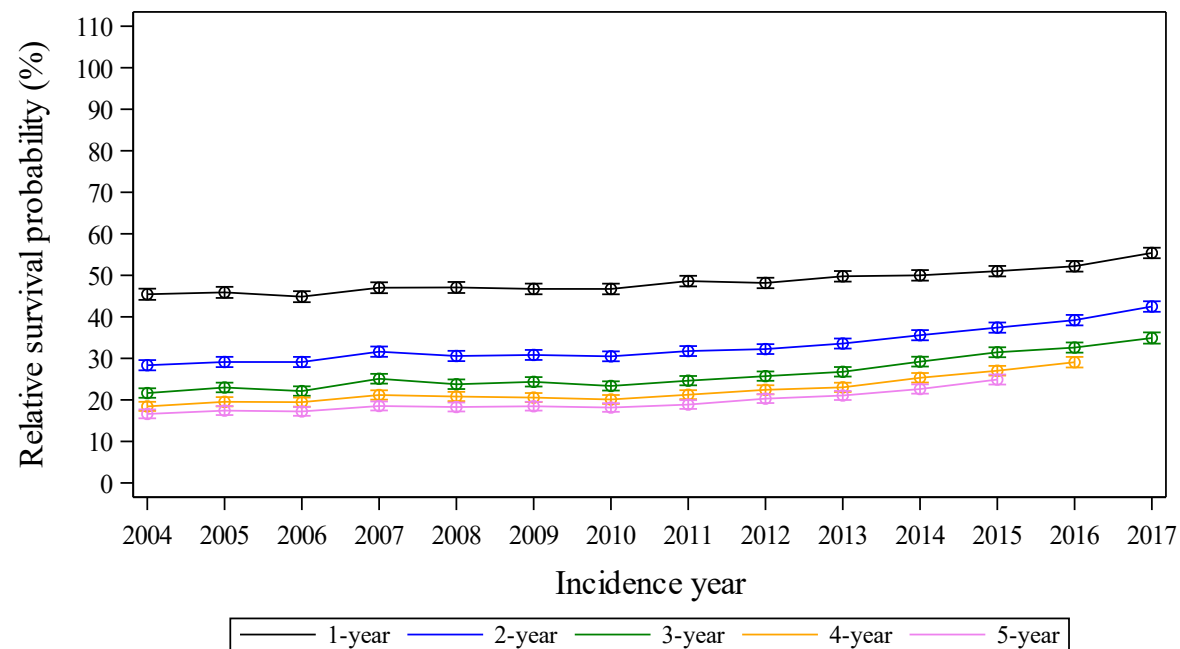
Appendix 9.1.1.3. NSC Lung cancers, time trend Observed and Relative Survival

NSC Lung cancers (2004-2017)

Figure 218 – NSC Lung cancers (2004-2017), time trend observed survival with incidence year

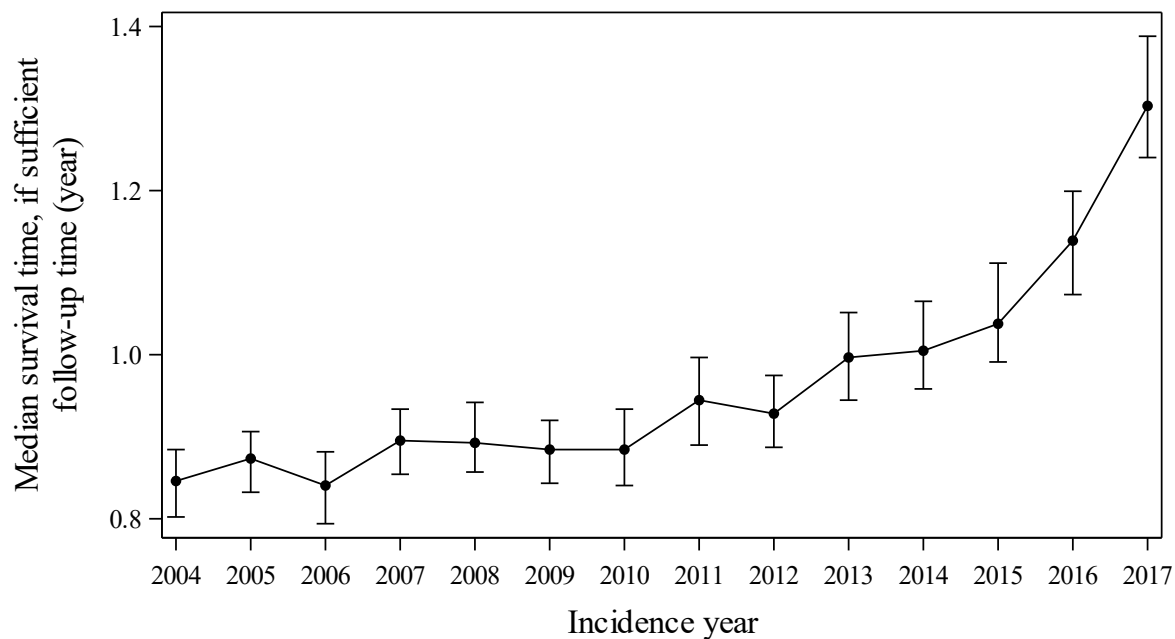


Note: the error bars represent the 95% CI.

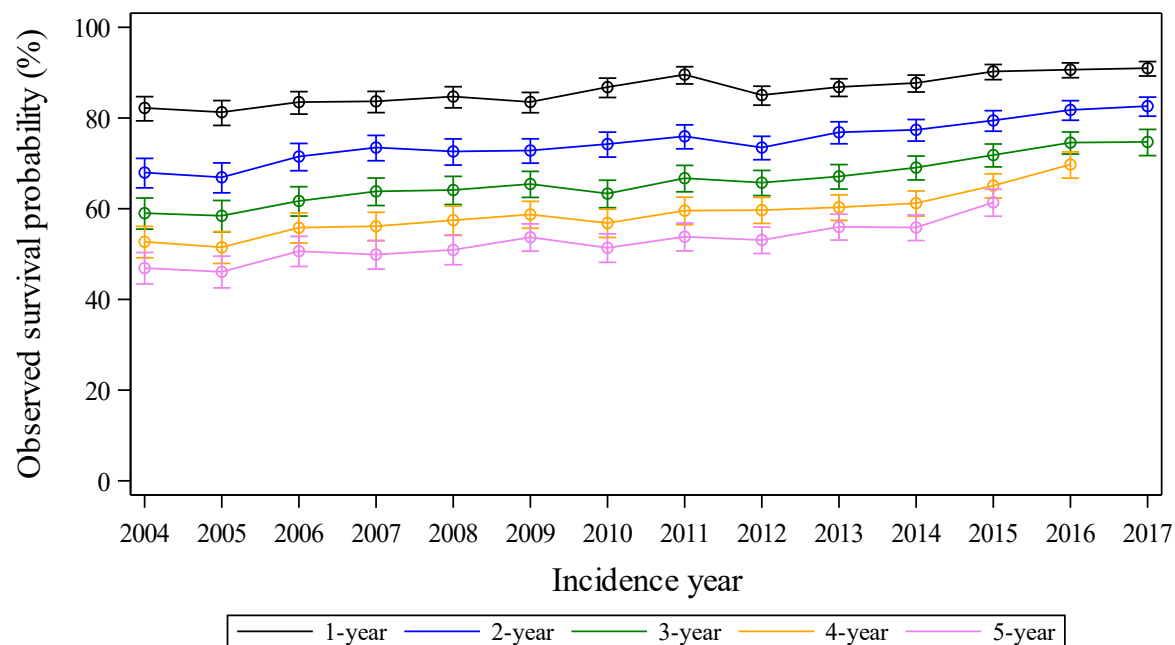
**Figure 219 – NSC Lung cancers (2004-2017), time trend relative survival with incidence year**

Note: the error bars represent the 95% CI.

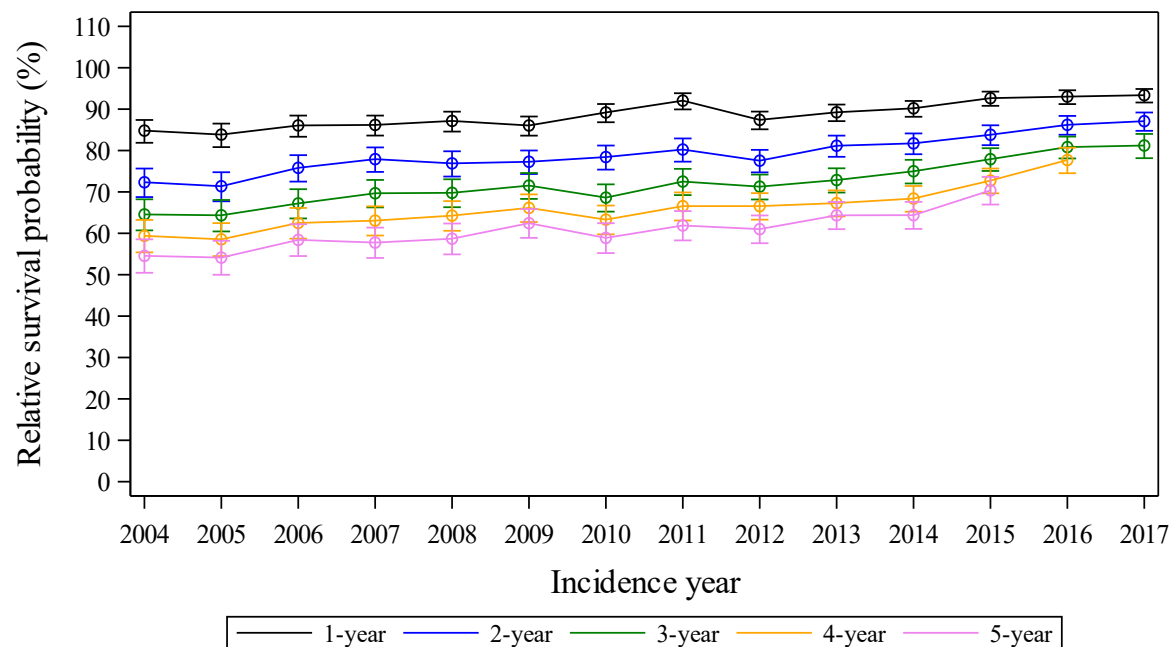
Figure 220 – NSC Lung cancers (2004-2017), Median time observed survival



Note: the error bars represent the 95% CI. When the upper error is not plotted, the upper limit could not be determined with the follow-up available.

**NSC Lung cancers, combined stage I (2004-2017)****Figure 221 – NSC Lung cancers (2004-2017), combined stage I, time trend observed survival with incidence year**

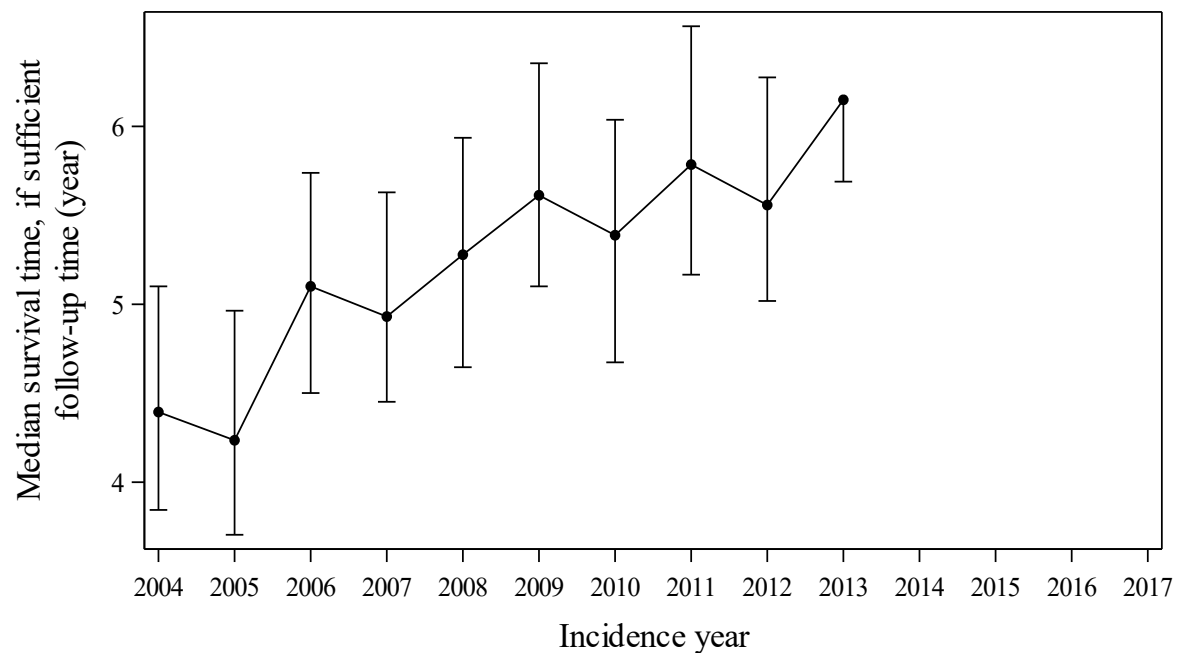
Note: the error bars represent the 95% CI.

**Figure 222 – NSC Lung cancers (2004-2017), combined stage I, time trend relative survival with incidence year**

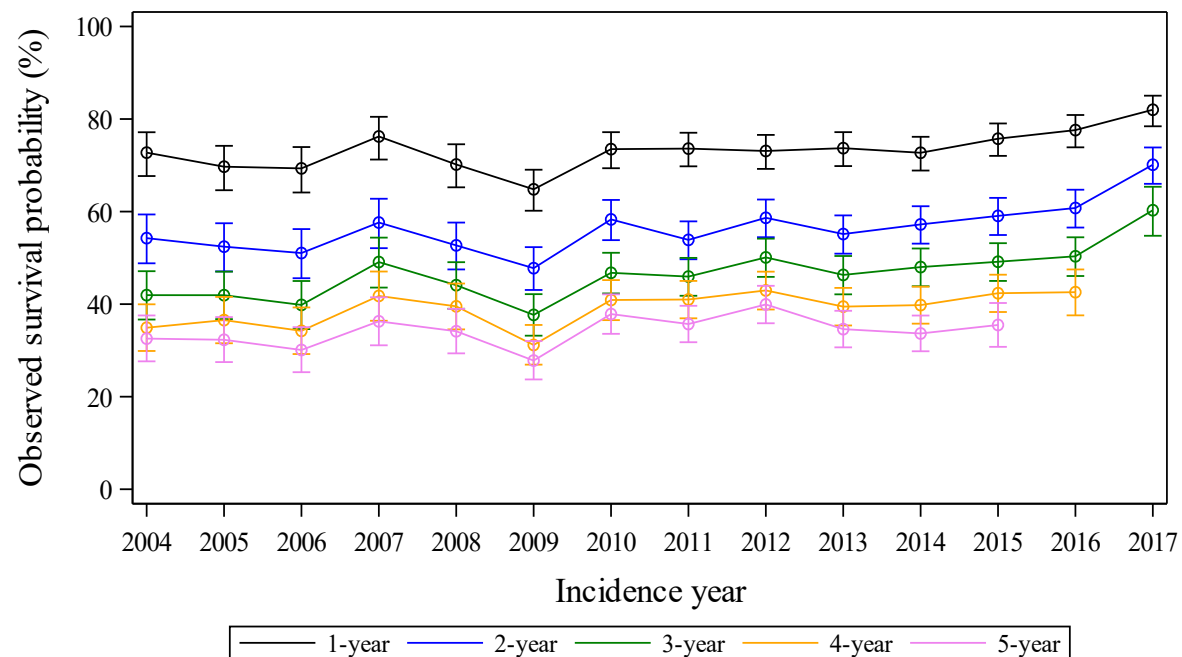
Note: the error bars represent the 95% CI.



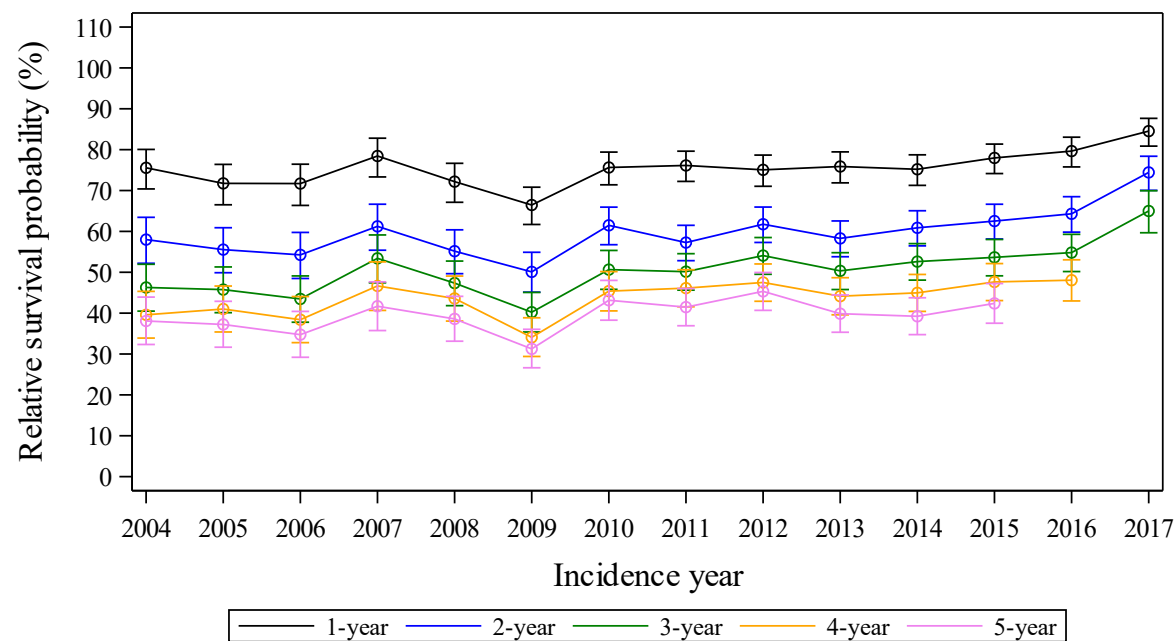
Figure 223 – NSC Lung cancers (2004-2017), combined stage I, median time observed survival



Note: the error bars represent the 95% CI. When the upper error is not plotted, the upper limit could not be determined with the follow-up available.

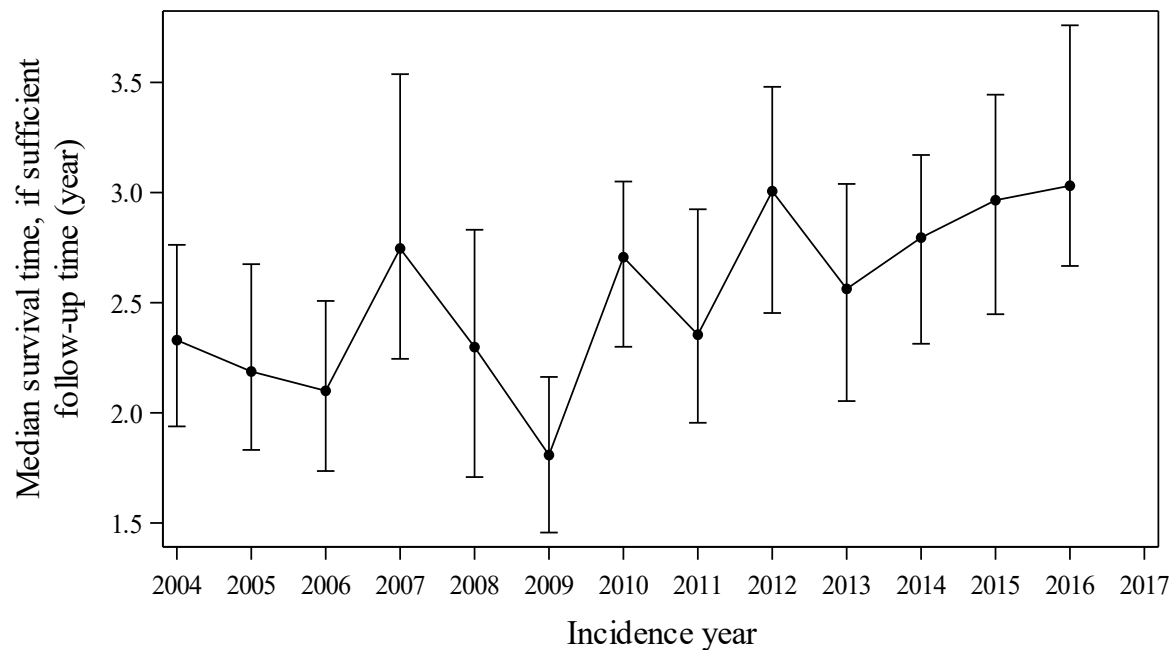
**NSC Lung cancers, combined stage II (2004-2017)****Figure 224 – NSC Lung cancers (2004-2017), combined stage II, time trend observed survival with incidence year**

Note: the error bars represent the 95% CI.

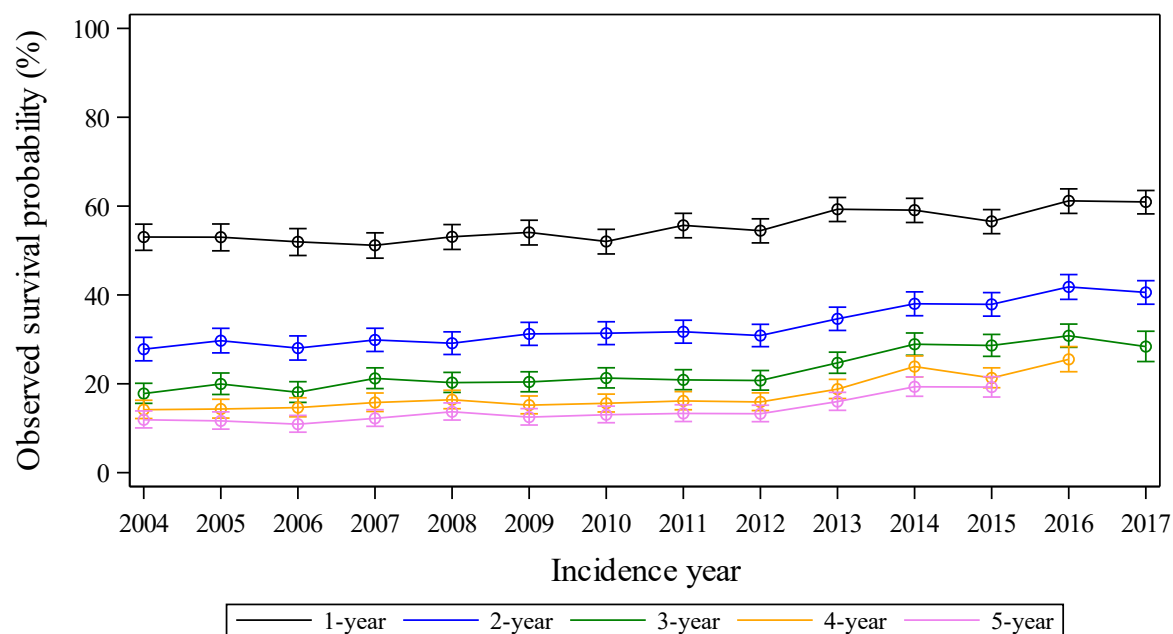
**Figure 225 – NSC Lung cancers (2004-2017), combined stage II, time trend relative survival with incidence year**

Note: the error bars represent the 95% CI.

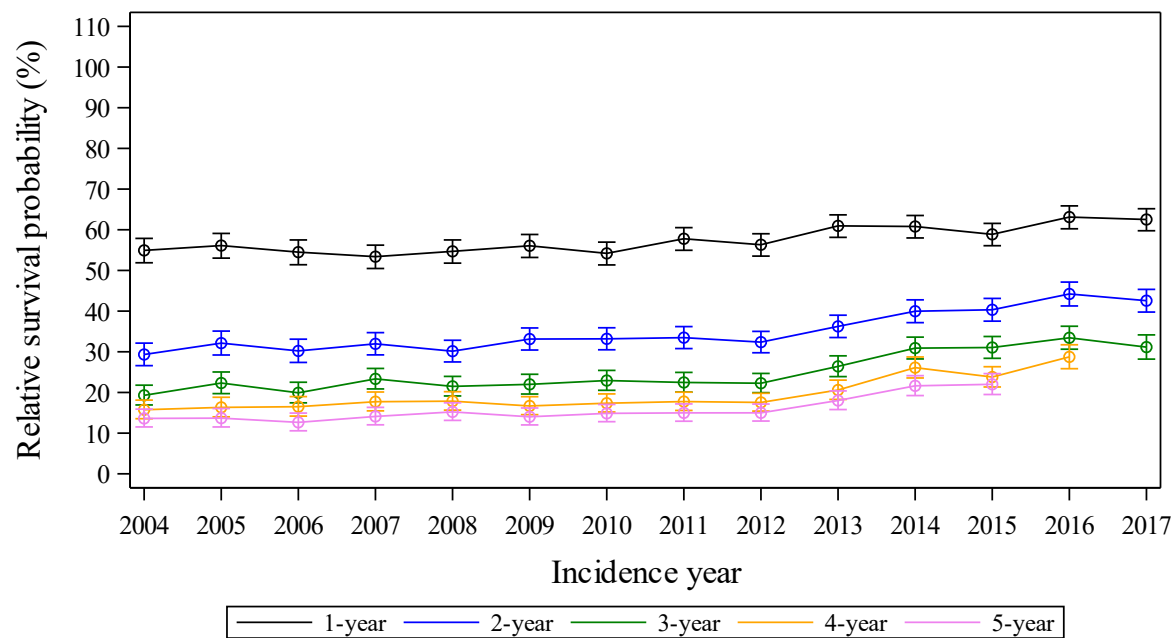
Figure 226 – NSC Lung cancers (2004-2017), combined stage II, median time observed survival



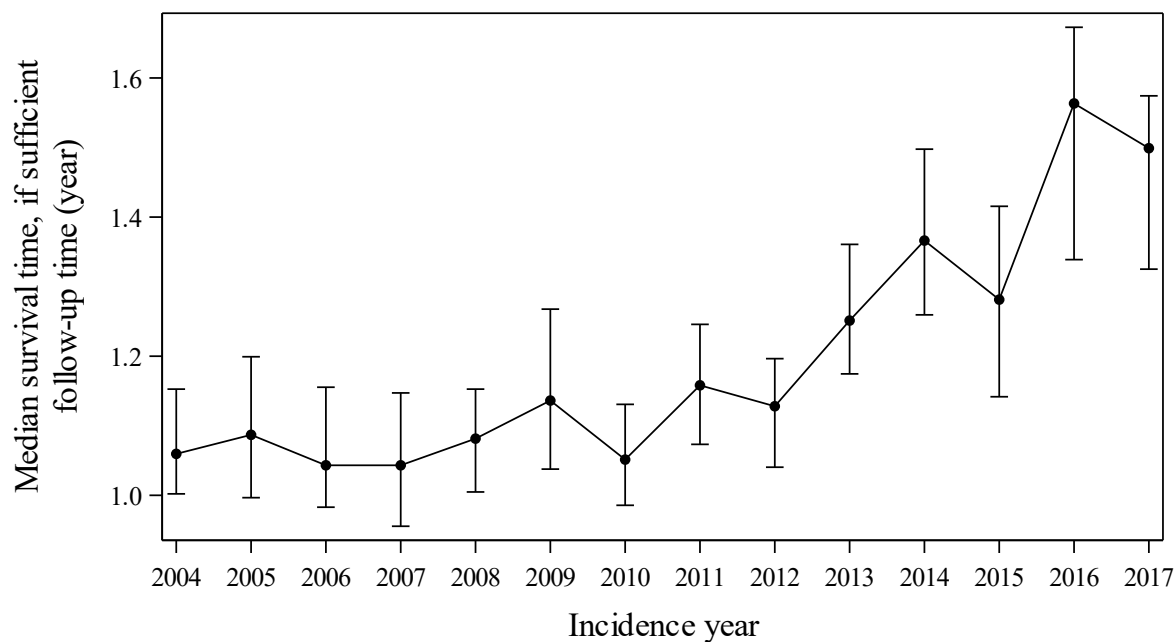
Note: the error bars represent the 95% CI. When the upper error is not plotted, the upper limit could not be determined with the follow-up available.

**NSC Lung cancers, combined stage III (2004-2017)****Figure 227 – NSC Lung cancers (2004-2017), combined stage III, time trend observed survival with incidence year**

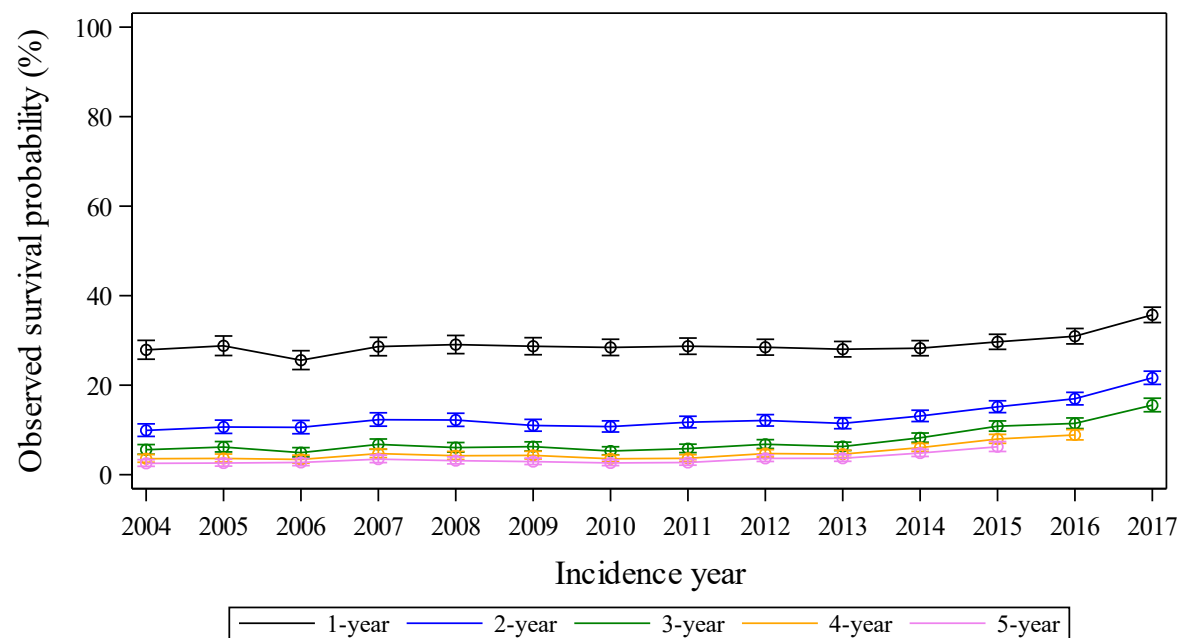
Note: the error bars represent the 95% CI.

**Figure 228 – NSC Lung cancers (2004-2017), combined stage III, time trend relative survival with incidence year**

Note: the error bars represent the 95% CI.

**Figure 229 – NSC Lung cancers (2004-2017), combined stage III, median time observed survival**

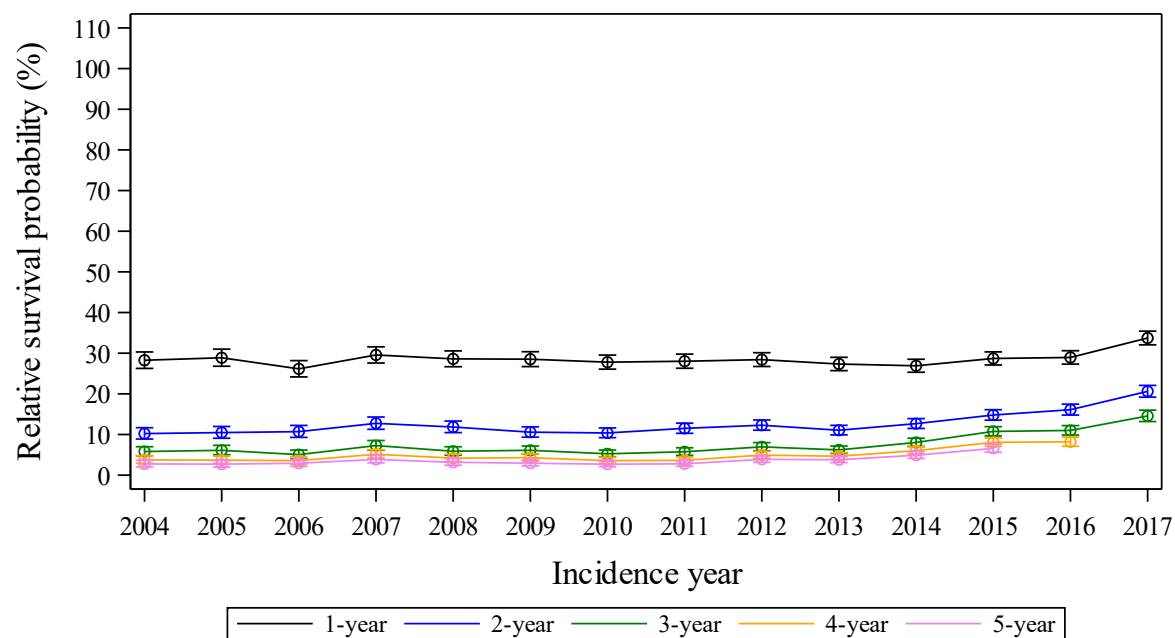
Note: the error bars represent the 95% CI. When the upper error is not plotted, the upper limit could not be determined with the follow-up available.

**NSC Lung cancers, combined stage IV (2004-2017)****Figure 230 – NSC Lung cancers (2004-2017), combined stage IV, time trend observed survival with incidence year**

Note: the error bars represent the 95% CI.

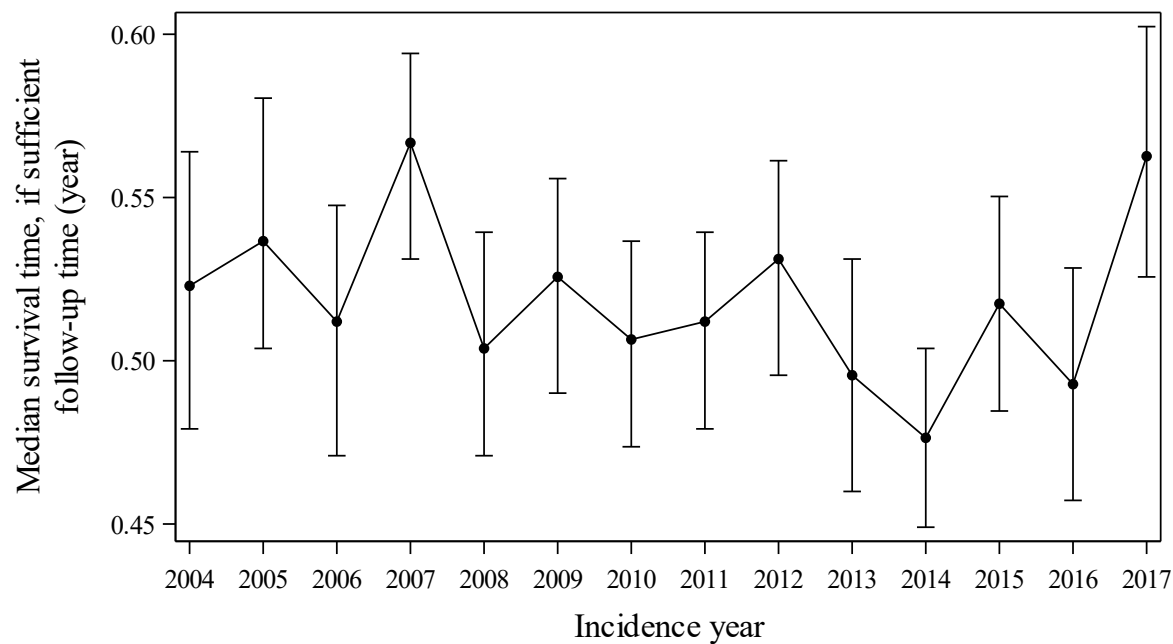


Figure 231 – NSC Lung cancers (2004-2017), combined stage IV, time trend relative survival with incidence year



Note: the error bars represent the 95% CI.

Figure 232 – NSC Lung cancers (2004-2017), combined stage IV, median time observed survival



Note: the error bars represent the 95% CI. When the upper error is not plotted, the upper limit could not be determined with the follow-up available.



Appendix 9.1.1.4. NSC Lung cancers, time trend tables Observed and Relative Survival

Table 126 – NSC Lung cancers (2004-2017), time trend observed survival with incidence year

Unadjusted observed survival, %													
Characteristic	N at risk	1 year		2 year		3 year		4 year		5 year		Median survival time (year)	
		%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI	T	95% CI
All													
2004	5,437	45.3	[44.0, 46.7]	27.7	[26.5, 28.9]	20.6	[19.5, 21.7]	17.1	[16.1, 18.1]	14.9	[14.0, 15.9]	0.8	[0.8, 0.9]
2005	5,519	45.5	[44.2, 46.9]	28.3	[27.1, 29.5]	21.7	[20.6, 22.8]	17.9	[16.9, 18.9]	15.5	[14.5, 16.4]	0.9	[0.8, 0.9]
2006	5,560	44.6	[43.3, 45.9]	28.4	[27.2, 29.6]	21.1	[20.0, 22.1]	18.0	[17.0, 19.1]	15.5	[14.6, 16.5]	0.8	[0.8, 0.9]
2007	5,721	46.6	[45.3, 47.8]	30.7	[29.5, 31.9]	23.7	[22.6, 24.8]	19.4	[18.4, 20.5]	16.5	[15.6, 17.5]	0.9	[0.9, 0.9]
2008	5,661	47.3	[46.0, 48.6]	30.2	[29.0, 31.4]	22.9	[21.8, 24.0]	19.5	[18.5, 20.6]	16.7	[15.7, 17.7]	0.9	[0.9, 0.9]
2009	5,976	46.7	[45.4, 47.9]	30.2	[29.1, 31.4]	23.3	[22.2, 24.4]	19.2	[18.2, 20.2]	16.7	[15.8, 17.7]	0.9	[0.8, 0.9]
2010	6,032	46.9	[45.6, 48.2]	30.1	[29.0, 31.3]	22.6	[21.5, 23.6]	18.9	[17.9, 19.9]	16.6	[15.7, 17.6]	0.9	[0.8, 0.9]
2011	6,159	48.7	[47.4, 49.9]	31.2	[30.1, 32.4]	23.6	[22.6, 24.7]	19.8	[18.8, 20.8]	17.1	[16.2, 18.1]	0.9	[0.9, 1.0]
2012	6,307	48.1	[46.9, 49.4]	31.6	[30.4, 32.7]	24.6	[23.5, 25.7]	20.9	[19.9, 21.9]	18.4	[17.4, 19.3]	0.9	[0.9, 1.0]
2013	6,230	49.9	[48.7, 51.1]	33.0	[31.9, 34.2]	25.7	[24.6, 26.8]	21.5	[20.5, 22.5]	19.1	[18.2, 20.1]	1.0	[0.9, 1.1]
2014	6,252	50.1	[48.8, 51.3]	34.8	[33.7, 36.0]	27.9	[26.8, 29.1]	23.6	[22.5, 24.6]	20.5	[19.5, 21.5]	1.0	[1.0, 1.1]
2015	6,388	51.0	[49.7, 52.2]	36.6	[35.4, 37.7]	30.0	[28.9, 31.1]	25.0	[24.0, 26.1]	22.3	[21.2, 23.4]	1.0	[1.0, 1.1]
2016	6,228	52.6	[51.3, 53.8]	38.5	[37.3, 39.8]	31.2	[30.1, 32.4]	27.3	[26.1, 28.5]	no FU	—	1.1	[1.1, 1.2]
2017	6,374	55.6	[54.4, 56.8]	41.7	[40.5, 42.9]	33.7	[32.4, 35.1]	no FU	—	no FU	—	1.3	[1.2, 1.4]
Combined Stage I													
2004	793	82.2	[79.4, 84.7]	68.0	[64.6, 71.1]	59.0	[55.5, 62.3]	52.7	[49.2, 56.1]	46.9	[43.4, 50.3]	4.4	[3.8, 5.1]
2005	780	81.3	[78.4, 83.8]	66.9	[63.5, 70.1]	58.4	[54.9, 61.8]	51.5	[47.9, 54.9]	46.1	[42.5, 49.5]	4.2	[3.7, 5.0]
2006	867	83.5	[80.9, 85.8]	71.5	[68.4, 74.4]	61.7	[58.4, 64.9]	55.8	[52.5, 59.1]	50.6	[47.3, 53.9]	5.1	[4.5, 5.7]
2007	963	83.7	[81.2, 85.9]	73.5	[70.6, 76.2]	63.8	[60.7, 66.8]	56.1	[52.9, 59.2]	49.9	[46.7, 53.0]	4.9	[4.5, 5.6]
2008	917	84.7	[82.2, 86.9]	72.6	[69.6, 75.4]	64.1	[60.9, 67.1]	57.5	[54.2, 60.6]	50.9	[47.6, 54.1]	5.3	[4.6, 5.9]



2009	1,057	83.5	[81.2, 85.6]	72.8	[70.0, 75.4]	65.4	[62.5, 68.2]	58.7	[55.7, 61.6]	53.7	[50.6, 56.7]	5.6	[5.1, 6.4]
2010	971	86.8	[84.5, 88.8]	74.3	[71.4, 76.9]	63.3	[60.2, 66.3]	56.8	[53.7, 59.9]	51.4	[48.2, 54.5]	5.4	[4.7, 6.0]
2011	1,007	89.6	[87.5, 91.3]	76.0	[73.2, 78.5]	66.7	[63.7, 69.5]	59.6	[56.5, 62.5]	53.8	[50.7, 56.8]	5.8	[5.2, 6.6]
2012	1,125	85.1	[82.8, 87.0]	73.5	[70.8, 76.0]	65.7	[62.9, 68.4]	59.7	[56.8, 62.5]	53.1	[50.1, 56.0]	5.6	[5.0, 6.3]
2013	1,165	86.8	[84.8, 88.7]	76.9	[74.3, 79.2]	67.1	[64.3, 69.7]	60.3	[57.4, 63.1]	56.0	[53.1, 58.8]	6.1	[5.7, .]
2014	1,190	87.7	[85.7, 89.5]	77.4	[74.9, 79.7]	69.1	[66.4, 71.6]	61.2	[58.4, 63.9]	55.9	[53.0, 58.6]	>6	
2015	1,223	90.3	[88.5, 91.8]	79.5	[77.1, 81.6]	71.8	[69.2, 74.3]	65.1	[62.3, 67.7]	61.4	[58.4, 64.3]	>5	
2016	1,231	90.7	[88.9, 92.2]	81.8	[79.5, 83.8]	74.6	[72.0, 76.9]	69.7	[66.7, 72.5]	no FU	—	>4	
2017	1,256	91.0	[89.3, 92.4]	82.6	[80.4, 84.6]	74.7	[71.7, 77.5]	no FU	—	no FU	—	>3	
Combined Stage II													
2004	341	72.7	[67.7, 77.1]	54.3	[48.8, 59.4]	41.9	[36.7, 47.1]	34.9	[29.9, 40.0]	32.6	[27.6, 37.5]	2.3	[1.9, 2.8]
2005	353	69.7	[64.6, 74.2]	52.4	[47.1, 57.5]	41.9	[36.7, 47.0]	36.5	[31.5, 41.6]	32.3	[27.5, 37.2]	2.2	[1.8, 2.7]
2006	339	69.3	[64.1, 73.9]	51.0	[45.6, 56.2]	39.8	[34.6, 45.0]	34.2	[29.2, 39.3]	30.1	[25.3, 35.0]	2.1	[1.7, 2.5]
2007	329	76.2	[71.2, 80.5]	57.6	[52.1, 62.8]	49.1	[43.6, 54.4]	41.8	[36.4, 47.0]	36.3	[31.1, 41.5]	2.7	[2.2, 3.5]
2008	372	70.2	[65.2, 74.5]	52.7	[47.5, 57.6]	44.1	[39.0, 49.1]	39.5	[34.5, 44.4]	34.1	[29.4, 39.0]	2.3	[1.7, 2.8]
2009	446	64.8	[60.2, 69.0]	47.8	[43.1, 52.3]	37.7	[33.2, 42.1]	31.2	[26.9, 35.5]	27.8	[23.7, 32.0]	1.8	[1.5, 2.2]
2010	494	73.5	[69.4, 77.1]	58.3	[53.8, 62.5]	46.8	[42.3, 51.1]	40.9	[36.5, 45.2]	37.9	[33.6, 42.1]	2.7	[2.3, 3.1]
2011	569	73.6	[69.8, 77.0]	53.9	[49.7, 57.9]	45.9	[41.8, 50.0]	41.0	[36.9, 45.0]	35.7	[31.8, 39.6]	2.4	[2.0, 2.9]
2012	561	73.1	[69.2, 76.6]	58.6	[54.5, 62.6]	50.1	[45.9, 54.1]	43.0	[38.8, 47.0]	39.9	[35.9, 44.0]	3.0	[2.5, 3.5]
2013	555	73.7	[69.8, 77.2]	55.1	[50.9, 59.2]	46.3	[42.1, 50.4]	39.5	[35.4, 43.5]	34.6	[30.7, 38.6]	2.6	[2.1, 3.0]
2014	575	72.7	[68.9, 76.1]	57.2	[53.1, 61.1]	48.0	[43.9, 52.0]	39.8	[35.8, 43.8]	33.7	[29.8, 37.5]	2.8	[2.3, 3.2]
2015	577	75.7	[72.0, 79.0]	59.1	[54.9, 63.0]	49.2	[45.0, 53.2]	42.4	[38.3, 46.4]	35.5	[30.8, 40.2]	3.0	[2.4, 3.4]
2016	549	77.6	[73.9, 80.9]	60.8	[56.5, 64.7]	50.3	[46.1, 54.4]	42.6	[37.6, 47.5]	no FU	—	3.0	[2.7, 3.8]
2017	522	82.0	[78.4, 85.0]	70.1	[66.0, 73.8]	60.3	[54.8, 65.4]	no FU	—	no FU	—	>3	
Combined Stage III													
2004	1,101	53.0	[50.0, 55.9]	27.8	[25.2, 30.5]	17.8	[15.6, 20.1]	14.2	[12.2, 16.3]	11.9	[10.1, 13.9]	1.1	[1.0, 1.2]
2005	1,047	53.0	[49.9, 56.0]	29.7	[27.0, 32.5]	20.0	[17.6, 22.4]	14.3	[12.3, 16.5]	11.7	[9.8, 13.7]	1.1	[1.0, 1.2]
2006	1,045	52.0	[48.9, 54.9]	28.0	[25.3, 30.8]	18.1	[15.8, 20.5]	14.6	[12.6, 16.9]	10.9	[9.1, 12.9]	1.0	[1.0, 1.2]



2007	1,181	51.2	[48.3, 54.0]	29.9	[27.3, 32.5]	21.2	[18.9, 23.6]	15.8	[13.8, 17.9]	12.2	[10.4, 14.2]	1.0	[1.0, 1.1]
2008	1,220	53.1	[50.2, 55.8]	29.1	[26.6, 31.7]	20.3	[18.1, 22.6]	16.4	[14.4, 18.5]	13.7	[11.8, 15.7]	1.1	[1.0, 1.2]
2009	1,231	54.1	[51.3, 56.8]	31.2	[28.7, 33.8]	20.4	[18.2, 22.7]	15.2	[13.3, 17.3]	12.5	[10.7, 14.4]	1.1	[1.0, 1.3]
2010	1,249	52.0	[49.2, 54.8]	31.4	[28.8, 34.0]	21.3	[19.1, 23.6]	15.6	[13.7, 17.7]	13.0	[11.2, 15.0]	1.1	[1.0, 1.1]
2011	1,251	55.7	[52.9, 58.4]	31.7	[29.2, 34.3]	20.9	[18.7, 23.2]	16.1	[14.2, 18.2]	13.3	[11.5, 15.3]	1.2	[1.1, 1.2]
2012	1,298	54.5	[51.7, 57.1]	30.9	[28.4, 33.4]	20.7	[18.6, 23.0]	15.9	[14.0, 18.0]	13.3	[11.5, 15.2]	1.1	[1.0, 1.2]
2013	1,266	59.3	[56.5, 61.9]	34.6	[32.0, 37.3]	24.7	[22.4, 27.1]	18.8	[16.7, 21.0]	16.0	[14.0, 18.1]	1.3	[1.2, 1.4]
2014	1,255	59.1	[56.3, 61.8]	38.0	[35.3, 40.7]	28.9	[26.4, 31.4]	23.9	[21.6, 26.3]	19.3	[17.2, 21.6]	1.4	[1.3, 1.5]
2015	1,287	56.6	[53.8, 59.2]	37.9	[35.2, 40.5]	28.6	[26.2, 31.1]	21.3	[19.1, 23.6]	19.3	[17.0, 21.6]	1.3	[1.1, 1.4]
2016	1,199	61.2	[58.4, 63.9]	41.8	[39.0, 44.6]	30.8	[28.2, 33.4]	25.5	[22.7, 28.4]	no FU	—	1.6	[1.3, 1.7]
2017	1,316	60.9	[58.2, 63.5]	40.6	[37.9, 43.2]	28.4	[25.0, 31.8]	no FU	—	no FU	—	1.5	[1.3, 1.6]
Combined Stage IV													
2004	1,741	27.9	[25.8, 30.0]	9.9	[8.5, 11.3]	5.6	[4.6, 6.7]	3.6	[2.8, 4.5]	2.5	[1.9, 3.3]	0.5	[0.5, 0.6]
2005	1,655	28.8	[26.6, 31.0]	10.6	[9.2, 12.2]	6.2	[5.1, 7.4]	3.6	[2.8, 4.6]	2.6	[1.9, 3.5]	0.5	[0.5, 0.6]
2006	1,647	25.6	[23.5, 27.7]	10.6	[9.1, 12.1]	4.9	[3.9, 6.0]	3.4	[2.6, 4.4]	2.7	[2.0, 3.6]	0.5	[0.5, 0.5]
2007	1,852	28.6	[26.6, 30.7]	12.3	[10.8, 13.8]	6.8	[5.7, 8.0]	4.7	[3.8, 5.7]	3.5	[2.7, 4.4]	0.6	[0.5, 0.6]
2008	1,923	29.1	[27.0, 31.1]	12.2	[10.8, 13.7]	6.1	[5.0, 7.2]	4.2	[3.4, 5.2]	3.1	[2.4, 4.0]	0.5	[0.5, 0.5]
2009	2,163	28.7	[26.8, 30.6]	11.0	[9.7, 12.3]	6.3	[5.3, 7.3]	4.3	[3.5, 5.2]	2.9	[2.3, 3.7]	0.5	[0.5, 0.6]
2010	2,376	28.4	[26.6, 30.2]	10.7	[9.5, 12.0]	5.3	[4.4, 6.2]	3.5	[2.9, 4.3]	2.6	[2.0, 3.3]	0.5	[0.5, 0.5]
2011	2,382	28.7	[26.9, 30.5]	11.7	[10.5, 13.0]	5.8	[4.9, 6.8]	3.7	[3.0, 4.5]	2.7	[2.1, 3.4]	0.5	[0.5, 0.5]
2012	2,513	28.5	[26.7, 30.2]	12.1	[10.9, 13.4]	6.8	[5.8, 7.8]	4.7	[3.9, 5.6]	3.6	[3.0, 4.4]	0.5	[0.5, 0.6]
2013	2,603	28.0	[26.3, 29.8]	11.5	[10.3, 12.7]	6.3	[5.4, 7.3]	4.6	[3.8, 5.4]	3.7	[3.0, 4.4]	0.5	[0.5, 0.5]
2014	2,744	28.2	[26.6, 29.9]	13.1	[11.9, 14.4]	8.2	[7.2, 9.3]	6.0	[5.2, 7.0]	4.8	[4.1, 5.7]	0.5	[0.4, 0.5]
2015	2,832	29.7	[28.0, 31.4]	15.2	[13.9, 16.5]	10.8	[9.7, 12.0]	8.0	[7.0, 9.0]	6.2	[5.2, 7.4]	0.5	[0.5, 0.6]
2016	2,767	30.9	[29.2, 32.7]	17.0	[15.6, 18.4]	11.4	[10.3, 12.7]	8.9	[7.8, 10.1]	no FU	—	0.5	[0.5, 0.5]
2017	2,994	35.7	[34.0, 37.4]	21.6	[20.2, 23.1]	15.5	[14.1, 17.1]	no FU	—	no FU	—	0.6	[0.5, 0.6]


Table 127 – NSC Lung cancers (2004-2017), time trend relative survival with incidence year

Characteristic	N at risk	Unadjusted relative survival, %									
		1 year		2 year		3 year		4 year		5 year	
		%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI
All											
2004	5,437	45.4	[44.1, 46.8]	28.3	[27.1, 29.6]	21.6	[20.5, 22.8]	18.4	[17.4, 19.5]	16.6	[15.6, 17.7]
2005	5,519	45.9	[44.6, 47.2]	29.1	[27.9, 30.4]	23.0	[21.8, 24.2]	19.5	[18.4, 20.7]	17.4	[16.4, 18.5]
2006	5,560	44.9	[43.5, 46.2]	29.1	[27.9, 30.4]	22.1	[21.0, 23.3]	19.5	[18.4, 20.6]	17.2	[16.2, 18.3]
2007	5,721	47.0	[45.7, 48.3]	31.6	[30.4, 32.9]	25.1	[23.9, 26.3]	21.2	[20.1, 22.3]	18.5	[17.5, 19.6]
2008	5,661	47.1	[45.7, 48.4]	30.6	[29.3, 31.8]	23.8	[22.6, 24.9]	20.8	[19.7, 21.9]	18.3	[17.2, 19.4]
2009	5,976	46.7	[45.4, 48.0]	30.8	[29.6, 32.0]	24.3	[23.2, 25.5]	20.6	[19.5, 21.7]	18.5	[17.4, 19.5]
2010	6,032	46.7	[45.4, 48.0]	30.5	[29.3, 31.7]	23.4	[22.3, 24.5]	20.1	[19.0, 21.2]	18.2	[17.1, 19.2]
2011	6,159	48.6	[47.3, 49.9]	31.8	[30.6, 33.0]	24.6	[23.5, 25.8]	21.2	[20.2, 22.3]	18.9	[17.8, 19.9]
2012	6,307	48.2	[46.9, 49.4]	32.2	[31.1, 33.4]	25.7	[24.6, 26.9]	22.4	[21.3, 23.5]	20.3	[19.2, 21.4]
2013	6,230	49.8	[48.5, 51.0]	33.6	[32.4, 34.8]	26.8	[25.6, 27.9]	23.0	[21.9, 24.1]	21.1	[20.0, 22.2]
2014	6,252	50.0	[48.7, 51.3]	35.6	[34.4, 36.8]	29.2	[28.0, 30.4]	25.3	[24.2, 26.5]	22.6	[21.5, 23.7]
2015	6,388	51.0	[49.7, 52.3]	37.4	[36.2, 38.6]	31.5	[30.3, 32.7]	27.0	[25.9, 28.2]	24.9	[23.7, 26.1]
2016	6,228	52.2	[50.9, 53.5]	39.2	[37.9, 40.5]	32.6	[31.4, 33.8]	29.1	[27.8, 30.4]	no FU	—
2017	6,374	55.4	[54.1, 56.7]	42.5	[41.2, 43.8]	34.9	[33.6, 36.3]	no FU	—	no FU	—
Combined Stage I											
2004	793	84.8	[81.9, 87.4]	72.3	[68.8, 75.6]	64.6	[60.7, 68.2]	59.4	[55.4, 63.2]	54.6	[50.5, 58.5]
2005	780	83.8	[80.8, 86.5]	71.4	[67.7, 74.8]	64.4	[60.5, 68.1]	58.5	[54.5, 62.5]	54.1	[50.0, 58.2]
2006	867	86.1	[83.3, 88.4]	75.8	[72.5, 78.9]	67.2	[63.6, 70.7]	62.5	[58.7, 66.1]	58.4	[54.5, 62.2]
2007	963	86.2	[83.6, 88.4]	77.9	[74.8, 80.8]	69.7	[66.3, 72.9]	63.1	[59.5, 66.5]	57.8	[54.0, 61.4]
2008	917	87.2	[84.6, 89.4]	76.9	[73.7, 79.8]	69.8	[66.3, 73.1]	64.3	[60.6, 67.8]	58.7	[54.9, 62.4]
2009	1,057	86.0	[83.6, 88.2]	77.3	[74.3, 80.0]	71.5	[68.3, 74.6]	66.1	[62.7, 69.4]	62.4	[58.9, 65.9]
2010	971	89.2	[86.8, 91.2]	78.4	[75.4, 81.2]	68.6	[65.2, 71.8]	63.3	[59.8, 66.7]	58.9	[55.2, 62.4]



2011	1,007	92.1	[89.9, 93.8]	80.2	[77.3, 82.9]	72.5	[69.2, 75.6]	66.6	[63.1, 69.9]	61.9	[58.3, 65.4]
2012	1,125	87.4	[85.1, 89.4]	77.5	[74.7, 80.2]	71.3	[68.2, 74.2]	66.6	[63.3, 69.7]	61.0	[57.6, 64.3]
2013	1,165	89.2	[87.1, 91.1]	81.2	[78.5, 83.6]	72.9	[69.8, 75.7]	67.3	[64.1, 70.4]	64.3	[61.0, 67.6]
2014	1,190	90.2	[88.2, 92.0]	81.7	[79.1, 84.1]	75.0	[72.0, 77.8]	68.4	[65.2, 71.4]	64.4	[61.1, 67.6]
2015	1,223	92.7	[90.8, 94.2]	83.8	[81.3, 86.1]	77.9	[75.1, 80.6]	72.7	[69.7, 75.7]	70.4	[66.9, 73.6]
2016	1,231	93.0	[91.2, 94.6]	86.2	[83.8, 88.4]	80.8	[78.1, 83.4]	77.7	[74.5, 80.7]	no FU	—
2017	1,256	93.4	[91.6, 94.9]	87.1	[84.8, 89.2]	81.2	[78.2, 84.0]	no FU	—	no FU	—
Combined Stage II											
2004	341	75.6	[70.4, 80.1]	58.0	[52.2, 63.4]	46.3	[40.5, 52.0]	39.6	[33.9, 45.3]	38.1	[32.3, 43.9]
2005	353	71.7	[66.5, 76.4]	55.5	[49.9, 60.9]	45.8	[40.1, 51.3]	41.0	[35.4, 46.6]	37.2	[31.7, 42.9]
2006	339	71.7	[66.4, 76.4]	54.3	[48.5, 59.7]	43.5	[37.8, 49.1]	38.4	[32.8, 44.1]	34.7	[29.2, 40.4]
2007	329	78.4	[73.3, 82.8]	61.2	[55.4, 66.6]	53.4	[47.4, 59.1]	46.7	[40.7, 52.5]	41.7	[35.7, 47.6]
2008	372	72.2	[67.1, 76.7]	55.2	[49.7, 60.4]	47.3	[41.8, 52.7]	43.6	[38.1, 49.1]	38.6	[33.1, 44.1]
2009	446	66.5	[61.7, 70.8]	50.1	[45.1, 54.9]	40.2	[35.4, 45.1]	34.1	[29.4, 38.9]	31.3	[26.6, 36.0]
2010	494	75.6	[71.4, 79.4]	61.5	[56.7, 65.9]	50.6	[45.8, 55.3]	45.4	[40.5, 50.2]	43.2	[38.3, 48.0]
2011	569	76.1	[72.2, 79.6]	57.3	[52.8, 61.5]	50.1	[45.6, 54.5]	46.1	[41.6, 50.6]	41.5	[36.9, 46.0]
2012	561	75.1	[71.0, 78.7]	61.8	[57.3, 66.0]	54.1	[49.5, 58.5]	47.5	[42.9, 52.0]	45.3	[40.7, 49.9]
2013	555	75.9	[71.9, 79.5]	58.3	[53.8, 62.6]	50.3	[45.8, 54.8]	44.1	[39.6, 48.7]	39.9	[35.3, 44.4]
2014	575	75.2	[71.3, 78.7]	60.9	[56.5, 65.1]	52.6	[48.1, 57.0]	45.0	[40.4, 49.5]	39.2	[34.7, 43.8]
2015	577	78.0	[74.2, 81.4]	62.5	[58.1, 66.6]	53.6	[49.1, 58.0]	47.6	[43.1, 52.1]	42.4	[37.5, 47.2]
2016	549	79.6	[75.8, 83.1]	64.3	[59.8, 68.5]	54.8	[50.2, 59.3]	48.1	[43.0, 53.0]	no FU	—
2017	522	84.5	[80.9, 87.7]	74.4	[70.1, 78.4]	65.0	[59.7, 69.9]	no FU	—	no FU	—
Combined Stage III											
2004	1,101	54.9	[51.9, 57.9]	29.3	[26.6, 32.1]	19.3	[16.9, 21.8]	15.8	[13.5, 18.1]	13.6	[11.5, 15.9]
2005	1,047	56.1	[53.0, 59.1]	32.1	[29.2, 35.1]	22.3	[19.7, 25.0]	16.3	[14.0, 18.8]	13.7	[11.5, 16.1]
2006	1,045	54.5	[51.4, 57.5]	30.2	[27.4, 33.1]	19.9	[17.4, 22.5]	16.5	[14.2, 19.0]	12.6	[10.6, 14.9]
2007	1,181	53.4	[50.5, 56.2]	32.0	[29.2, 34.7]	23.3	[20.9, 25.9]	17.7	[15.5, 20.1]	14.1	[12.0, 16.3]
2008	1,220	54.7	[51.8, 57.5]	30.1	[27.5, 32.8]	21.5	[19.1, 23.9]	17.9	[15.7, 20.2]	15.2	[13.1, 17.5]



2009	1,231	56.1	[53.2, 58.8]	33.1	[30.4, 35.9]	22.0	[19.6, 24.5]	16.7	[14.5, 19.0]	14.0	[12.0, 16.2]
2010	1,249	54.2	[51.4, 57.0]	33.2	[30.5, 35.9]	22.9	[20.5, 25.4]	17.4	[15.2, 19.6]	14.9	[12.8, 17.1]
2011	1,251	57.8	[55.0, 60.5]	33.5	[30.8, 36.2]	22.5	[20.1, 24.9]	17.8	[15.6, 20.1]	15.0	[12.9, 17.2]
2012	1,298	56.3	[53.5, 59.0]	32.4	[29.8, 35.0]	22.3	[20.0, 24.7]	17.5	[15.4, 19.8]	15.0	[13.0, 17.2]
2013	1,266	61.0	[58.1, 63.7]	36.2	[33.5, 39.0]	26.4	[23.9, 29.0]	20.6	[18.3, 23.0]	18.0	[15.8, 20.4]
2014	1,255	60.8	[58.0, 63.5]	40.0	[37.2, 42.8]	30.9	[28.2, 33.6]	26.1	[23.6, 28.7]	21.6	[19.2, 24.1]
2015	1,287	58.9	[56.1, 61.6]	40.3	[37.5, 43.1]	31.1	[28.4, 33.8]	23.8	[21.3, 26.3]	22.0	[19.5, 24.6]
2016	1,199	63.1	[60.2, 65.9]	44.2	[41.3, 47.1]	33.4	[30.6, 36.3]	28.7	[25.8, 31.7]	no FU	—
2017	1,316	62.5	[59.8, 65.2]	42.6	[39.8, 45.3]	31.1	[28.2, 34.2]	no FU	—	no FU	—
Combined Stage IV											
2004	1,741	28.3	[26.3, 30.3]	10.2	[8.9, 11.7]	5.8	[4.8, 7.0]	3.8	[2.9, 4.8]	2.8	[2.0, 3.6]
2005	1,655	28.9	[26.8, 31.0]	10.5	[9.1, 12.0]	6.1	[5.0, 7.3]	3.7	[2.9, 4.7]	2.7	[2.0, 3.6]
2006	1,647	26.2	[24.2, 28.2]	10.7	[9.3, 12.2]	5.1	[4.1, 6.2]	3.6	[2.7, 4.6]	2.9	[2.2, 3.9]
2007	1,852	29.6	[27.6, 31.6]	12.8	[11.3, 14.3]	7.3	[6.2, 8.5]	5.2	[4.2, 6.3]	3.9	[3.0, 4.9]
2008	1,923	28.6	[26.7, 30.6]	11.9	[10.5, 13.3]	5.9	[4.9, 7.0]	4.2	[3.3, 5.2]	3.2	[2.4, 4.0]
2009	2,163	28.5	[26.7, 30.4]	10.6	[9.4, 11.9]	6.1	[5.2, 7.2]	4.3	[3.5, 5.2]	2.9	[2.3, 3.7]
2010	2,376	27.8	[26.1, 29.5]	10.4	[9.2, 11.6]	5.3	[4.4, 6.2]	3.6	[2.9, 4.4]	2.7	[2.1, 3.4]
2011	2,382	28.0	[26.3, 29.8]	11.5	[10.3, 12.8]	5.8	[4.9, 6.7]	3.7	[2.9, 4.5]	2.8	[2.2, 3.5]
2012	2,513	28.4	[26.7, 30.1]	12.3	[11.1, 13.6]	7.0	[6.0, 8.0]	4.9	[4.1, 5.9]	3.9	[3.2, 4.7]
2013	2,603	27.3	[25.7, 29.0]	11.1	[9.9, 12.3]	6.2	[5.3, 7.2]	4.7	[3.9, 5.5]	3.8	[3.1, 4.6]
2014	2,744	26.9	[25.3, 28.5]	12.7	[11.5, 13.9]	8.0	[7.1, 9.1]	6.0	[5.2, 7.0]	4.9	[4.1, 5.8]
2015	2,832	28.7	[27.1, 30.3]	14.8	[13.5, 16.1]	10.8	[9.7, 11.9]	8.1	[7.1, 9.1]	6.6	[5.6, 7.6]
2016	2,767	29.0	[27.3, 30.6]	16.1	[14.8, 17.5]	11.0	[9.9, 12.2]	8.2	[7.1, 9.4]	no FU	—
2017	2,994	33.7	[32.1, 35.4]	20.6	[19.2, 22.1]	14.6	[13.2, 16.0]	no FU	—	no FU	—



Appendix 9.1.2. Uptake of selected drugs

Table 128 – Proportion of patients who received at least one dose during 5-year period after diagnosis (stage III NSCLC)

Drug/incidence year (n)	2004 (1101)	2005 (1048)	2006 (1046)	2007 (1181)	2008 (1221)	2009 (1232)	2010 (1249)	2011 (1253)	2012 (1299)	2013 (1269)	2014 (1255)	2015 (1292)	2016 (1202)	2017 (1321)
Erlotinib	4.3%	11.8%	17.6%	19.1%	20.1%	23.9%	19.1%	20.8%	17.4%	13.6%	9.2%	5.5%	2.4%	1.4%
Gefitinib		0.1%	0.2%	0.1%	0.4%	0.4%	0.7%	1.6%	0.8%	1.1%	1.1%	0.7%	1.3%	0.5%
Afatinib										0.2%	0.6%	0.4%	0.4%	0.2%
Osimertinib										0.1%	0.4%	0.2%	0.2%	0.1%
Crizotinib					0.1%	0.1%	0.1%	0.1%	0.2%	1.0%	0.3%	0.6%	0.7%	0.4%
Nivolumab									1.1%	2.5%	5.4%	10.1%	19.9%	12.8%
Pembrolizumab									0.4%	0.3%	0.6%	1.7%	4.1%	11.3%

* Numbers in yellow indicate the first calendar year of reimbursement. For example, erlotinib was first reimbursed in 2006. The columns in this table indicate the incidence year. For example, for incidence year 2009, 23.9% of patients received reimbursed erlotinib during the 5 years after diagnosis. Source: BCR-IMA

Table 129 – Proportion of patients who received at least one dose during 5-year period after diagnosis (stage IV NSCLC)

Drug/incidence year (n)	2004 (1747)	2005 (1658)	2006 (1648)	2007 (1856)	2008 (1924)	2009 (2165)	2010 (2381)	2011 (2386)	2012 (2515)	2013 (2603)	2014 (2746)	2015 (2837)	2016 (2772)	2017 (3002)
Erlotinib	2.4%	7.0%	18.4%	22.3%	23.6%	23.8%	21.9%	21.7%	20.2%	16.9%	13.3%	8.4%	4.6%	2.9%
Gefitinib			0.1%	0.1%	0.4%	0.6%	2.1%	3.6%	4.0%	4.0%	3.7%	3.4%	2.9%	3.0%
Afatinib										0.2%	0.6%	1.1%	0.9%	1.2%
Osimertinib									<0.1%	0.4%	0.7%	1.0%	1.3%	0.8%
Crizotinib			0.0%	0.0%	0.0%	0.1%	<0.1%	0.2%	0.7%	0.8%	1.3%	1.0%	0.8%	0.5%
Nivolumab									0.6%	1.2%	2.4%	7.4%	19.3%	15.0%
Pembrolizumab									0.2%	0.2%	0.3%	0.5%	1.9%	21.0%

* Numbers in yellow indicate the first calendar year of reimbursement. For example, erlotinib was first reimbursed in 2006. The columns in this table indicate the incidence year. For example, for incidence year 2009, 23.8% of patients received reimbursed erlotinib during the 5 years after diagnosis. Source: BCR-IMA



Appendix 9.2. reimbursement criteria for selected drugs

Table 130 – Targeted therapy in non-small cell lung cancer (NSCLC): reimbursement criteria in Belgium

Drug	Trade name	Date reimbursement	start	Indication NI	Indication Fr
Gefitinib	Iressa	1/7/2010		De specialiteit komt voor vergoeding in aanmerking indien zij wordt toegediend in monotherapie in het kader van de behandeling van een patiënt die lijdt aan een lokaal gevorderd of gemetastaseerd niet-kleincellig longcarcinoom met een activerende EGFR mutatie.	La spécialité fait l'objet d'un remboursement si elle est administrée en monothérapie dans le cadre du traitement d'un patient atteint d'un cancer du poumon localement avancé ou métastaté non à petites cellules avec mutation activatrice de l'EGFR.
Erlotinib	Tarceva	1/5/2011		De specialiteit komt voor vergoeding in aanmerking indien zij wordt toegediend in monotherapie in het kader van de eerstelijnsbehandeling van patiënten met een lokaal gevorderd of gemetastaseerd niet-kleincellig longcarcinoom van wie de tumor een activerende mutatie van de EGFR vertoont.	La spécialité fait l'objet d'un remboursement si elle est administrée en monothérapie dans le cadre du traitement de première ligne des formes localement avancées ou métastatiques du cancer bronchique non à petites cellules (CBNPC) chez les patients dont la tumeur présente une mutation activatrice de l'EGFR.
		1/5/2011		De specialiteit komt voor vergoeding in aanmerking indien zij wordt toegediend in monotherapie in het kader van de onderhoudsbehandeling van patiënten met een lokaal gevorderd of gemetastaseerd niet-kleincellig longcarcinoom die geen teken van progressieve ziekte meer vertonen na 4 cycli van standaard platinum-bevattende eerstelijnschemotherapie en van wie de tumor een activerende mutatie van de EGFR vertoont	La spécialité fait l'objet d'un remboursement si elle est administrée en monothérapie dans le cadre du traitement de maintenance des formes localement avancées ou métastatiques du cancer bronchique non à petites cellules chez les patients dont la maladie ne montre plus de signe de progression après 4 cycles d'une première ligne de chimiothérapie standard à base de sels de platine et dont la tumeur présente une mutation activante de l'EGFR
		1/7/2006		De specialiteit komt voor vergoeding in aanmerking als ze in monotherapie wordt toegediend in het raam van de behandeling van lokaal gevorderd of gemetastaseerd niet-kleincellig longcarcinoom na falen van ten minste één voorafgaande chemotherapie bij een patiënt van wie de tumor de EGFR (epidermal growth factor receptor) vertoont bij een	La spécialité fait l'objet d'un remboursement si elle est administrée en monothérapie pour le traitement des patients atteints d'un cancer bronchique non à petites cellules localement avancé ou métastatique après échec d'au moins une ligne de chimiothérapie et dont la tumeur exprime l'EGFR (epidermal growth factor receptor), ce qui doit être attesté par la



			immunohistochemische test waarbij minstens 10 % van de cellen positief reageren.	présence d'au moins 10 % de cellules réactives lors d'un test immunohistochimique.
Afatinib	Giotrif	1/7/2014	monotherapie in het kader van de behandeling van een patiënt die lijdt aan een lokaal gevorderd of gemetastaseerd niet kleincellig longcarcinoom waarvan de tumor een activerende EGFR mutatie vertoont, en die nog geen behandeling met een EGFR-TK inhibitor heeft gekregen.	administrée en monothérapie dans le cadre du traitement d'un patient atteint d'un cancer du poumon localement avancé ou métastaté non à petites cellules dont la tumeur présente une mutation activatrice de l'EGFR et qui n'a jamais reçu de traitement par un inhibiteur de l'EGFR-TK
Crizotinib	Xalkori	1/8/2013	behandeling van niet-kleincellig, gevorderd longcarcinoom, dat ALK-positief is zoals werd aangetoond door middel van een IHC test gevalideerd voor longcarcinoom die werd bevestigd door een gevalideerde FISH-test: volwassen patiënten die tumorprogressie hebben vertoond na minstens twee cycli van een standaard chemotherapie die minstens twee cytostatica bevat patiënten > 65 jaar of volwassen patiënten met een 'Poor Performance Status' (PS) ≥ 2 die tumorprogressie vertoonden na minstens 2 cycli van een standaard chemotherapie die minstens 1 cytostaticum bevat	traitement d'un cancer du poumon, non à petites cellules, avancé, ALK positif démontré par un test IHC validé pour le cancer du poumon qui a été confirmé par un test FISH validé. des patients adultes qui ont démontré une progression de tumeur après au moins 2 cycles d'une chimiothérapie standard qui contient au moins deux cytostatiques des patients âgés de > 65 ans ou des patients adultes avec un 'Poor Performance Status' (PS) ≥ 2 qui ont démontré une progression de tumeur après au moins 2 cycles d'une chimiothérapie standard qui contient au moins un cytostatique
Crizotinib	Xalkori	1/4/2018	toegediend in het kader van de behandeling van een niet-kleincellige, gevorderde longcarcinoom, dat ROS1 positief is zoals werd aangetoond door middel van een IHC test gevalideerd voor longcarcinoom die werd bevestigd door een gevalideerde FISH-test. De testen moeten worden uitgevoerd in laboratoria die de validatie van de analyseprocedures garanderen. De betrokken specialiteit komt in aanmerking voor terugbetaling bij patiënten met een 'Performance Status' (PS) ≤ 1 .	administrée dans le cadre du traitement d'un cancer du poumon, non à petites cellules, avancé, ROS1 positif démontré par un test IHC validé pour le cancer du poumon qui a été confirmé par un test FISH validé. Les tests doivent être effectués dans les laboratoires qui garantissent la validation des procédures d'analyses. La spécialité concernée fait l'objet d'un remboursement chez les patients avec un 'Performance Status' (PS) ≤ 1 .



Table 131 – Immunotherapy in NSCLC

Drug	Trade name	Date reimbursement	start	Indication NI	Indication Fr
Nivolumab	Opdivo	1/1/2017		behandeling van lokaal gevorderd of gemetastaseerd niet-kleincellige longkanker (NSCLC, Non-Small Cell Lung Cancer), na eerdere behandeling met chemotherapie bij volwassenen	traitement des patients adultes atteints d'un cancer bronchique non à petites cellules (CBNPC) localement avancé ou métastatique après une chimiothérapie antérieure
Pembrolizumab	Keytruda	1/5/2017		de eerstelijnsbehandeling van gemetastaseerd niet-kleincellig longcarcinoom (NSCLC) bij volwassenen met tumoren die PD-L1-expressie vertonen met een tumour proportion score (TPS) > of = 50 % zonder EGFR- of ALK-positieve tumormutaties (monotherapie)	le traitement de première ligne des patients adultes atteints d'un cancer bronchique non à petites cellules (CBNPC) métastatique dont les tumeurs expriment PD-L1 avec un score de proportion tumorale (TPS) > ou = 50 %, sans mutations tumorales d'EGFR ou d'ALK (monothérapie)
		1/5/2017		de behandeling van lokaal gevorderd of gemetastaseerd NSCLC bij volwassenen met tumoren die PD-L1-expressie vertonen met een TPS > of = 1 % en die ten minste één eerdere chemotherapie hebben ondergaan (monotherapie). Patiënten met EGFR- of ALK-positieve tumormutaties moeten tevens een hierop gerichte behandeling hebben ondergaan vóór behandeling met KEYTRUDA	le traitement des patients adultes atteints de CBNPC localement avancé ou métastatique dont les tumeurs expriment PD-L1 avec un TPS > ou = 1 %, et ayant reçu au moins une chimiothérapie antérieure (monothérapie). Les patients présentant des mutations tumorales d'EGFR ou d'ALK doivent également avoir reçu une thérapie ciblée avant de recevoir KEYTRUDA
		1/10/2018		eerstelijnsbehandeling van gemetastaseerd niet-plaveiselcel-NSCLC bij volwassenen met tumoren zonder EGFR- of ALK-positieve mutaties, in combinatie met pemetrexed en platineumbestrijdende chemotherapie	le traitement de première ligne des patients adultes atteints de le cancer bronchique non à petites cellules (CBNPC) métastatique non-épidermoïde dont les tumeurs ne présentent pas de mutations d'EGFR ou d'ALK, en association à une chimiothérapie pemetrexed et sel de platine
		01/04/2019		de eerstelijnsbehandeling van gemetastaseerd plaveiselcel-NSCLC bij volwassenen in combinatie met carboplatine en ofwel paclitaxel of nab-paclitaxel (ter info: nab-paclitaxel wordt niet vergoed in deze indicatie)	le traitement de première ligne des patients adultes atteints de CBNPC métastatique épidermoïde en association au carboplatine et au paclitaxel ou au nab-paclitaxel (pour information: le nab-paclitaxel n'est pas remboursé dans cette indication)



Appendix 9.3. Medical literature: search for evidence

Appendix 9.3.1. Search medical literature (systematic reviews)

The search for systematic reviews in MEDLINE, PreMedline and the Cochrane library of systematic reviews (inception to search date) specifically developed for this research question, yielded 1431 records (Figure 364). After de-duplication, 423 (2020-2016) of the in total 699 reviews were screened based on title and abstract, of which 330 were excluded. In total 93 full text articles were assessed for eligibility. Based on full text evaluation, 86 reviews were excluded (Figure 365).

Figure 233 – NSCLC: Selection of SRs - Study flow

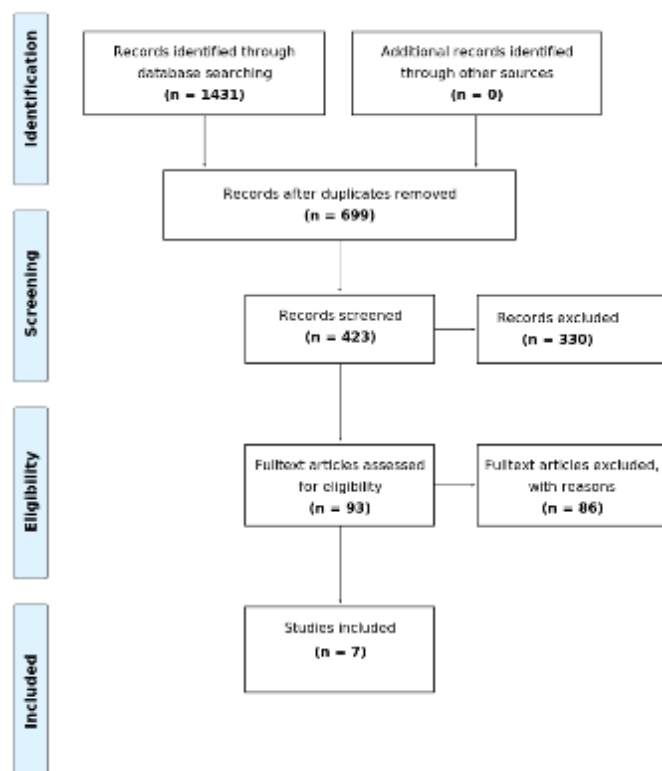


**Table 132 – NSCLC: excluded reviews and reason for exclusion**

	Year	Publication	Reason for exclusion
1	2020	Wang, C. Qiao, W. Jiang, Y. et al. The landscape of immune checkpoint inhibitor plus chemotherapy versus immunotherapy for advanced non-small-cell lung cancer: A systematic review and meta-analysis. <i>J Cell Physiol</i> 2020; 235(5):4913-4927	Included
2	2020	Shi, Y. Duan, J. Guan, Q. et al. Effectivity and safety of PD-1/PD-L1 inhibitors for different level of PD-L1-positive, advanced NSCLC: A meta-analysis of 4939 patients from randomized controlled trials. 2020; 84:106452	No additional information
3	2020	Mo, J. Hu, X. Gu, L. et al. Smokers or non-smokers: who benefits more from immune checkpoint inhibitors in treatment of malignancies? An up-to-date meta-analysis. <i>World J Surg Oncol</i> 2020; 18(1):15	No additional information
4	2020	Liu, J. Li, C. Seery, S. Identifying optimal first-line interventions for advanced non-small cell lung carcinoma according to PD-L1 expression: a systematic review and network meta-analysis. <i>Oncoimmunology</i> 2020; 9(1):1746112	No additional relevant information
5	2020	Landre, T. Des Guez, G. Chouahnia, K. et al. First-line PD-1/PD-L1 inhibitor plus chemotherapy vs chemotherapy alone for negative or < 1% PD-L1-expressing metastatic non-small-cell lung cancers <i>J Cancer Res Clin Oncol</i> 2020; 146(2):441-448	Full text could not be obtained
6	2020	Lai, L. T. Zhan, Z. Y. Feng, M. et al. Immune checkpoint inhibitors for the management of advanced non-small-cell lung carcinoma: a meta-analysis <i>Anticancer Drugs</i> 2020; 13:13	No additional information
7	2020	Hoang, T. Myung, S. K. Pham, T. T. Park, B. Efficacy of Crizotinib, Ceritinib, and Alectinib in ALK-Positive Non-Small Cell Lung Cancer Treatment: A Meta-Analysis of Clinical Trials. <i>Cancers (Basel)</i> 2020; 12(3):25	No critical appraisal
8	2020	Hoang, T. Myung, S. K. Pham, T. T. et al. Comparative Efficacy of Targeted Therapies in Patients with Non-Small Cell Lung Cancer: A Network Meta-Analysis of Clinical Trials. <i>J Clin Med</i> 2020; 9(4):9	No separate data for crizotinib (OS)
9	2020	Elliott, J. Bai, Z. Hsieh, S. C. et al. ALK inhibitors for non-small cell lung cancer: A systematic review and network meta-analysis. <i>PLoS ONE</i> 2020; 15(2):e0229179	Included
10	2020	Breadner, D. Blanchette, P. Shanmuganathan, S. et al. Efficacy and safety of ALK inhibitors in ALK-rearranged non-small cell lung cancer: A systematic review and meta-analysis. <i>Lung Cancer</i> 2020; 144:57-63	No additional information
11	2020	Li, X. Y. Lin, J. Z. Yu, S. H. Front-Line Therapy in Advanced Non-Small Cell Lung Cancer With Sensitive Epidermal Growth Factor Receptor Mutations: a Network Meta-Analysis. <i>Clin Ther</i> 2020; 11:11	No additional information
12	2019	Zhao, Y. Liu, J. Cai, X. Efficacy and safety of first line treatments for patients with advanced epidermal growth factor receptor mutated, non-small cell lung cancer: systematic review and network meta-analysis <i>BMJ</i> 2019;367:l5460	No additional information
13	2019	Zhang, Z. Zeng, K. Zhao, S. et al. Pemetrexed/carboplatin plus gefitinib as a first-line treatment for EGFR-mutant advanced nonsmall cell lung cancer: a Bayesian network meta-analysis. <i>Ther Adv Med Oncol</i> 2019;11:1-17	No additional information



Year	Publication	Reason for exclusion
14	2019 Zhang, L. Sun, L. Yu, J. et al. Comparison of Immune Checkpoint Inhibitors between Older and Younger Patients with Advanced or Metastatic Lung Cancer: A Systematic Review and Meta-Analysis Biomed Res Int 2019;9853701	Wrong comparison
15	2019 Zhang, H. Chen, J. Liu, T. et al. First-line treatments in EGFR-mutated advanced non-small cell lung cancer: A network meta-analysis. PLoS ONE 2019;14(10): e0223530	Included
16	2019 Zhang, C. Zhang, S. Xu, D. et al. Incidence risk of PD-1/PD-L1 related diarrhea in non-small cell lung cancer (NSCLC) patients: a systematic review and meta-analysis. Cancer Manag Res 2019;11:3957-3969	Wrong outcome
17	2019 Zhang, L. Ren, H. W. Wu, Q. L. et al. The Effect of Next-Generation TKI in Non-Small Cell Lung Cancer after Failure of First-Line Treatment: a Meta-Analysis. Pathol Oncol Res 2019;31:31	Wrong comparison
18	2019 Zeng, T. Qin, Q. Bian, Z. Li, J. Clinical efficacy and safety of anti-PD-1/PD-L1 treatments in non-small cell lung cancer (NSCLC). Artif Cells Nanomed Biotechnol 2019;47(1):4194-4201	No critical appraisal
19	2019 Yu, Y. Zeng, D. Ou, Q. et al. Association of Survival and Immune-Related Biomarkers With Immunotherapy in Patients With Non-Small Cell Lung Cancer: A Meta-analysis and Individual Patient-Level Analysis. JAMA netw 2019;2(7): e196879	Wrong research question
20	2019 Xu, Z. Yi, F. Yu, D. et al. Nivolumab provides improved effectiveness and safety compared with docetaxel as a second-line treatment for advanced non-small cell lung cancer: A systematic review and meta-analysis. Cancer Med 2019;8(2):629-642	No additional information
21	2019 Xu, Y. Wan, B. Chen, X. et al. The association of PD-L1 expression with the efficacy of anti-PD-1/PD-L1 immunotherapy and survival of non-small cell lung cancer patients: a meta-analysis of randomized controlled trials. Transl 2019;8(4):413-428	Wrong research question
22	2019 Xu, R. Zhu, J. Comment on: Pneumonitis in advanced non-small-cell lung cancer patients treated with EGFR tyrosine kinase inhibitor: Meta-analysis of 153 cohorts with 15,713 patients: Meta-analysis of incidence and risk factors of EGFR-TKI pneumonitis in NSCLC. Lung cancer 2019;127:167	Not a systematic review
23	2019 Wu, F. Z. Song, J. J. Zhao, Z. W. et al. The efficacy and safety of erlotinib compared with chemotherapy in previously treated NSCLC: A meta-analysis. Math Biosci Eng 2019;16(6)	Inclusion criteria not followed
24	2019 Wang, X. J. Lin, J. Z. Yu, S. H. et al. First-line checkpoint inhibitors for wild-type advanced non-small-cell cancer: a pair-wise and network meta-analysis. Immunotherapy 2019;11(4):311-320	No additional information
25	2019 Wang, M. Wang, G. Ma, H. Shan, B. Crizotinib Versus Chemotherapy on ALK-positive NSCLC: A Systematic Review of Efficacy and Safety. Curr Cancer Drug Targets 2019;19(1):41-49	Full text could not be obtained
26	2019 Wang, C. Li, Y. Ke, L. et al. The Impact of Afatinib on Survival in Advanced Non-Small Cell Lung Cancer: A Meta-Analysis of Randomized Controlled Trials. 2019;10(4):885-892	No additional information
27	2019 Wan, N. Ji, B. Li, J. et al. A pooled meta-analysis of PD-1/L1 inhibitors incorporation therapy for advanced non-small cell lung cancer. Onco Targets Ther 2019;12:4955-4973	No additional information
28	2019 Vickers, A. D. Winfree, K. B. Cuyun Carter, G. et al. Relative efficacy of interventions in the treatment of second-line non-small cell lung cancer: a systematic review and network meta-analysis 2019;19(1):353	No critical appraisal of included studies



	Year	Publication	Reason for exclusion
29	2019	Tartarone, A. Roviello, G. Lerose, R. et al. Anti-PD-1 versus anti-PD-L1 therapy in patients with pretreated advanced non-small-cell lung cancer: a meta-analysis. <i>Fut Oncol</i> 2019;15(20):2423-2433	Wrong research question
30	2019	Sun, X. Roudi, R. Dai, T. et al. Immune-related adverse events associated with programmed cell death protein-1 and programmed cell death ligand 1 inhibitors for non-small cell lung cancer: a PRISMA systematic review and meta-analysis. <i>BMC Cancer</i> 2019;19(1):558	Wrong outcome
31	2019	Suh, C. H. Kim, K. W. Pyo, J. et al. The incidence of ALK inhibitor-related pneumonitis in advanced non-small-cell lung cancer patients: A systematic review and meta-analysis. <i>Lung Cancer</i> 2019;132:79-86	Wrong outcome
32	2019	Schulz, C. Gandara, D. Berardo, C. G. et al. Comparative Efficacy of Second- and Subsequent-line Treatments for Metastatic NSCLC: A Fractional Polynomials Network Meta-analysis of Cancer Immunotherapies. <i>Clin Lung Cancer</i> 2019;20(6):451-460	No additional information
33	2019	Rossi, A. Noia, V. D. Gkountakos, A. et al. PD-L1 for selecting non-small-cell lung cancer patients for first-line immuno-chemotherapy combination: a systematic review and meta-analysis. <i>Immunotherapy</i> 2019;11(10):921-930	No additional information
34	2019	Rapport, B. Arani, R. B. Mathieson, N. Krendyukov, A. Meta-analysis comparing incidence of grade 3-4 neutropenia with ALK inhibitors and chemotherapy in patients with non-small-cell lung cancer. <i>Fut Oncol</i> 2019;15:2163-2174	Wrong outcome
35	2019	Raphael, J. Vincent, M. Boldt, G. Adjuvant Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors (TKIs) in Resected Non-Small Cell Lung Cancer (NSCLC): A Systematic Review and Meta-analysis 2019;42:440-445	Adjuvant TKIs not reimbursed in Belgium
36	2019	Rahouma, M. Baudou, M. Yahia, M. et al. Pneumonitis as a complication of immune system targeting drugs?-a meta-analysis of anti-PD/PD-L1 immunotherapy randomized clinical trials <i>Journal of Thoracic Disease</i> 2019;11(2):521-534	Studies in NSCLC and melanoma combined
37	2019	Peng, Y. Li, Q. Zhang, J. Update review of skin adverse events during treatment of lung cancer and colorectal carcinoma with epidermal growth receptor factor inhibitors 2019;12(6):537-552	Wrong outcome
38	2019	Peng, T. R. Wu, T. W. Efficacy of PD-1/PD-L1 inhibitors in patients with advanced non-small cell lung cancer: A meta-analysis of randomized clinical trials. <i>Thorac Cancer</i> 2019;10(5):1176-1181	No additional information
39	2019	Nguyen, C. T. T. Petrelli, F. Scuri, S. et al. A systematic review of pharmacoeconomic evaluations of erlotinib in the first-line treatment of advanced non-small cell lung cancer. <i>Eur J Health Econ</i> 2019;20(5):763-777	No full HTA report with primary economic evaluation
40	2019	Liu, Y. Zhou, S. Du, Y. et al. Efficacy and safety of programmed death 1 inhibitors in patients with advanced non-small cell lung cancer: a meta-analysis. <i>Cancer Manag Res</i> 2019; 11:4619-4630	No additional information
41	2019	Liu, T. Ding, S. Dang, J. et al. First-line immune checkpoint inhibitors for advanced non-small cell lung cancer with wild-type epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK): a systematic review and network meta-analysis. <i>J Thor disease</i> 2019;11(7):2899-2912	No additional information
42	2019	Lin, L. Lin, G. F. Luo, Q. Chen, X. Q. The incidence and relative risk of PD-1/PD-L1 inhibitors-related colitis in non-small cell lung cancer: A meta-analysis of randomized controlled trials. <i>Int Immunopharmacol</i> 2019;77:105975	Wrong outcome



Year	Publication	Reason for exclusion
43	2019 Li, Y. X. Yang, J. Y. Xu, Y. F. et al. A meta-analysis of the comparing of the first-generation and next-generation TKIs in the treatment of NSCLC Math Biosci Eng 2019;16(5):5687-5696	No additional information
44	2019 Li, J. Yuan, Z. Wang, Q. et al. Meta-analysis of overall incidence and risk of ALK inhibitors-induced liver toxicities in advanced non-small-cell lung cancer. Medicine (Baltimore) 2019;1:e13726	Wrong outcome
45	2019 Li, J. He, Q. Yu, X. et al. Complete response associated with immune checkpoint inhibitors in advanced non-small-cell lung cancer: a meta-analysis of nine randomized controlled trials. Cancer Manag Res 2019;11:1623-1629	Wrong outcome
46	2019 Li, J. Gu, J. PD-L1 expression and EGFR status in advanced non-small-cell lung cancer patients receiving PD-1/PD-L1 inhibitors: a meta-analysis. Fut Oncol 2019;15(14):1667-1678	Wrong research question
47	2019 Lee, Y. C. Hsieh, C. C. Lee, Y. L. Li, C. Y. Which Should Be Used First for ALK-Positive Non-Small-Cell Lung Cancer: Chemotherapy or Targeted Therapy? A Meta-Analysis of Five Randomized Trials Medicina (Kaunas) 2019; 55(2):29	No additional information
48	2019 Kim, R. Keam, B. Hahn, S. et al. First-line Pembrolizumab Versus Pembrolizumab Plus Chemotherapy Versus Chemotherapy Alone in Non-small-cell Lung Cancer: A Systematic Review and Network Meta-analysis. Clin Lung Cancer 2019;20(5):331-338.e4	Wrong research question
49	2019 Kim, J. Y. Lee, K. H. Eisenhut, M. et al. Efficacy of Cancer Immunotherapy: An Umbrella Review of Meta-analyses of Randomized Controlled Trials. Cancers (Basel) 2019;11(11):15	No additional information
50	2019 Kassem, L. Shohdy, K. S. Lasheen, S. et al. Safety issues with the ALK inhibitors in the treatment of NSCLC: A systematic review Crit Rev Oncol Hematol 2019; 134:56-64	Searched only 1 database
51	2019 Hou, H. Sun, D. Liu, K. et al. The safety and serious adverse events of approved ALK inhibitors in malignancies: a meta-analysis Cancer Manag Res 2019; 11:4109-4118	No comparator arm
52	2019 Holleman, M. S. van Tinteren, H. Groen, H. J. et al. First-line tyrosine kinase inhibitors in EGFR mutation-positive non-small-cell lung cancer: a network meta-analysis. Onco Targets Ther 2019;12:1413-1421	No additional information
53	2019 Frederickson, A. M. Arndorfer, S. Zhang, I. et al. Pembrolizumab plus chemotherapy for first-line treatment of metastatic nonsquamous non-small-cell lung cancer: a network meta-analysis. Immunotherapy 2019; 11(5): 407-428	Trials employing PD-L1 selection criteria were not included.
54	2019 Franek, J. Cappelleri, J. C. Larkin-Kaiser, K. A. et al. Systematic review and network meta-analysis of first-line therapy for advanced EGFR-positive non-small-cell lung cancer. Fut Oncol 2019;15(24):2857-2871	No additional information
55	2019 El-Osta, H. E. Mott, F. E. Burt, B. M. et al. Predictors of benefits from frontline chemoimmunotherapy in stage IV non-small-cell lung cancer: a meta-analysis. Oncoimmunology 2019; 8(12):e16665974	No additional information
56	2019 El-Osta, H. Jafri, S. Predictors for clinical benefit of immune checkpoint inhibitors in advanced non-small-cell lung cancer: a meta-analysis. Immunotherapy 2019;11(3):189-199	Wrong research question
57	2019 Dafni, U. Tsourti, Z. Vervita, K. Peters, S. Immune checkpoint inhibitors, alone or in combination with chemotherapy, as first-line treatment for advanced non-small cell lung cancer. A systematic review and network meta-analysis. Lung Cancer 2019;134:127-140	No additional information



Year	Publication	Reason for exclusion
58	2019 Connock, M. Armoiry, X. Tsertsvadze, A. et al. Comparative survival benefit of currently licensed second or third line treatments for epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) negative advanced or metastatic non-small cell lung cancer: a systematic review and secondary analysis of trials. <i>BMC Cancer</i> 2019;19(1):392	Included
59	2019 Chen, R. L. Zhou, J. X. Cao, Y. et al. The efficacy of PD-1/PD-L1 inhibitors in advanced squamous-cell lung cancer: a meta-analysis of 3112 patients. <i>Immunotherapy</i> 2019;11(17):1481-1490	No additional information
60	2019 Chen, R. Hou, X. Yang, L. Zhao, D. Comparative efficacy and safety of first-line treatments for advanced non-small cell lung cancer with immune checkpoint inhibitors: A systematic review and meta-analysis. <i>Thorac Cancer</i> 2019; 10(4):607-623	No additional information
61	2019 Chai, Q. Q. Du, J. Y. Zhu, J. Wu, B. The Differences in the Safety and Tolerability of Immune Checkpoint Inhibitors as Treatment for Non-Small Cell Lung Cancer and Melanoma: Network Meta-Analysis and Systematic Review. <i>Front Pharmacol</i> 2019;10:1260	No additional information
62	2019 Cavanna, L. Citterio, C. Orlandi, E. Immune checkpoint inhibitors in EGFR-mutation positive TKI-treated patients with advanced non-small-cell lung cancer network meta-analysis. <i>Oncotarget</i> 2019;10(2):209-215	No additional information
63	2019 Cao, R. Ma, J. T. Zhang, S. L. et al. Rational application of the first-line chemotherapy and immune checkpoint inhibitors in advanced nonsmall cell lung cancer: A meta-analysis. <i>Cancer Med</i> 2019;8(11):5033-5046	No additional information
64	2019 Barrows, S. M. Wright, K. Copley-Merriman, C. et al. Systematic review of sequencing of ALK inhibitors in ALK-positive non-small-cell lung cancer. <i>Lung Cancer (Auckl)</i> 2019;10:11-20	No additional information
65	2019 Almutairi, A. R. Alkhatib, N. Martin, J. et al. Comparative efficacy and safety of immunotherapies targeting the PD-1/PD-L1 pathway for previously treated advanced non-small cell lung cancer: A Bayesian network meta-analysis. <i>Crit Rev Oncol Hematol</i> 2019;142:16-25	No additional information
66	2019 Addeo, A. Banna, G. L. Metro, G. Di Maio, M. Chemotherapy in Combination With Immune Checkpoint Inhibitors for the First-Line Treatment of Patients With Advanced Non-small Cell Lung Cancer: A Systematic Review and Literature-Based Meta-Analysis. <i>Front</i> 2019;9:264	No additional information
67	2018 Zhang, W. Wei, Y. Yu, D. et al. Gefitinib provides similar effectiveness and improved safety than erlotinib for advanced non-small cell lung cancer: A meta-analysis. <i>Medicine (Baltimore)</i> 2018;97(16):e0460	Wrong comparison
68	2018 Zhang, N. Guo, N. Tian, L. et al. Systematic review and meta-analysis of third-line salvage therapy for the treatment of advanced non-small-cell lung cancer: A meta-analysis of randomized controlled trials. <i>Oncotarget</i> 2018;9(83):35439-35447	No results per drug
69	2018 Wo, H. He, J. Zhao, Y. et al. The Efficacy and Toxicity of Gefitinib in Treating Non-small Cell Lung Cancer: A Meta-analysis of 19 Randomized Clinical Trials. 2018; <i>J Cancer</i> 2018;9(8):1455-1465	No additional information
70	2018 Vestergaard, H. H. Christensen, M. R. Lassen, U. N. A systematic review of targeted agents for non-small cell lung cancer. <i>Acta Oncol</i> 2018;57(2):176-186.	No meta-analysis
71	2018 Suh, C. H. Park, H. S. Kim, K. W. et al. Pneumonitis in advanced non-small-cell lung cancer patients treated with EGFR tyrosine kinase inhibitor: Meta-analysis of 153 cohorts with 15,713 patients: Meta-	Wrong outcome



Year	Publication	Reason for exclusion
	analysis of incidence and risk factors of EGFR-TKI pneumonitis in NSCLC. Lung Cancer 2018;123:60-69	
72	2018 Sim, E. H. Yang, I. A. Wood-Baker, R. et al. Gefitinib for advanced non-small cell lung cancer. Cochrane Database Syst Rev 2018;1: CD006847	Included
73	2018 Pellegrino, B. Facchinetti, F. Bordin, P. et al. Lung Toxicity in Non-Small-Cell Lung Cancer Patients Exposed to ALK Inhibitors: Report of a Peculiar Case and Systematic Review of the Literature. 2018;19(2):e151-e161	Wrong outcome
74	2018 Liu, B. Yuan, M. Sun, Y. et al. Incidence and risk of hepatic toxicities associated with anaplastic lymphoma kinase inhibitors in the treatment of non-small-cell lung cancer: a systematic review and meta-analysis. Oncotarget 2018;9(10):9480-9488	Wrong outcome
75	2018 Lin, J. Z. Ma, S. K. Wu, S. X. et al. A network meta-analysis of nonsmall-cell lung cancer patients with an activating EGFR mutation: Should osimertinib be the first-line treatment? Medicine (Baltimore) 2018;97(30):e11569	Wrong comparison
76	2018 Li, J. Sasane, M. Zhao, J. et al. Comparative Efficacy of Treatments for Previously Treated Advanced or Metastatic Non-Small-Cell Lung Cancer: A Network Meta-Analysis. Adv Ther 2018;35(7):1035-1048	No additional information
77	2018 Lee, C. K. Man, J. Lord, S. et al. Clinical and Molecular Characteristics Associated With Survival Among Patients Treated With Checkpoint Inhibitors for Advanced Non-Small Cell Lung Carcinoma: A Systematic Review and Meta-analysis. JAMA Oncol 2018;4(2):210-216	Wrong research question
78	2018 Fan, J. Fong, T. Xia, Z. et al. The efficacy and safety of ALK inhibitors in the treatment of ALK-positive non-small cell lung cancer: A network meta-analysis. Cancer Med 2018;7(10):4993-5005	No additional information
79	2018 De Mello, R. A. Escrivu, C. Castelo-Branco, P. et al. Comparative outcome assessment of epidermal growth factor receptor tyrosine kinase inhibitors for the treatment of advanced non-small-cell lung cancer: a network meta-analysis. Oncotarget 2018;9(14):11805-11815	Wrong comparison
80	2018 Costa, R. B. Costa, R. L. B. Talamantes, S. M. et al. Systematic review and meta-analysis of selected toxicities of approved ALK inhibitors in metastatic non-small cell lung cancer. Oncotarget 2018;9(31):22137-22146	No additional information
81	2018 Bearz, A. Berretta, M. Tirelli, U. Clinical Effectiveness and Cost-effectiveness of Target Therapies for Adult Patients with Locally Advanced or Metastatic Non-small Cell Lung Cancer: A Systematic Review. Curr Cancer Drug Targets 2018;18(5):405-409	No additional information
82	2018 Armoiry, X. Tsertsvadze, A. Connock, M. Comparative efficacy and safety of licensed treatments for previously treated non-small cell lung cancer: A systematic review and network meta-analysis. PLoS ONE 2018;13(7): e0199575	No additional information
83	2017 Crequit, P. Chaimani, A. Yavchitz, A. et al. Comparative efficacy and safety of second-line treatments for advanced non-small cell lung cancer with wild-type or unknown status for epidermal growth factor receptor: a systematic review and network meta-analysis. BMC Med 2018;15(1):193	No additional information
84	2017 Batson, S. Mitchell, S. A. Windisch, R. et al. Tyrosine kinase inhibitor combination therapy in first-line treatment of non-small-cell lung cancer: systematic review and network meta-analysis. Onco Targets Ther 2017;10:2473-2482	No additional information



	Year	Publication	Reason for exclusion
85	2017	Ellis, P. M. Vella, E. T. Ung, Y. C. Immune Checkpoint Inhibitors for Patients With Advanced Non-Small-Cell Lung Cancer: A Systematic Review. Immune Checkpoint Inhibitors for Patients With Advanced Non-Small-Cell Lung Cancer: A Systematic Review. Clin Lung Cancer 2017;18(5):444-459.e1	No additional information
86	2017	Wu, D. Duan, C. Wu, F. et al. Which treatment is preferred for advanced non-small-cell lung cancer with wild-type epidermal growth factor receptor in second-line therapy? A meta-analysis comparing immune checkpoint inhibitor, tyrosine kinase inhibitor and chemotherapy. Oncotarget 2017;8(39):66491-66503	No additional information
87	2017	Wang, B. Zuo, Z. Li, F. et al. Gefitinib versus Docetaxel in Treated Non-small-cell Lung Cancer: A Meta-analysis. Open Med (Wars) 2017;12:86-91	Included
88	2017	Liu, Y. Zhang, Y. Zhang, L. et al. Efficacy of epidermal growth factor receptor-tyrosine kinase inhibitors for lung squamous carcinomas harboring EGFR mutation: A multicenter study and pooled analysis of published reports. Oncotarget 2017;8(30):49680-49688	Not a systematic review
89	2016	Ma, H. Tian, X. Zeng, X. T. et al. The Efficacy of Erlotinib Versus Conventional Chemotherapy for Advanced Nonsmall-Cell Lung Cancer: A PRISMA-Compliant Systematic Review With Meta-Regression and Meta-Analysis. Medicine (Baltimore) 2017;95(2):e2495	No additional information
90	2016	Liu, J. Sheng, Z. Zhang, Y. Li, G. Retraction Note to: The Efficacy of Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors for Molecularly Selected Patients with Non-Small Cell Lung Cancer: A Meta-Analysis of 30 Randomized Controlled Trials. Target 2017;11(6):837	Not a systematic review
91	2016	Li, G. Gao, S. Sheng, Z. Li, B. The Efficacy of Single-Agent Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor Therapy in Biologically Selected Patients with Non-Small-Cell Lung Cancer: A Meta-Analysis of 19 Randomized Controlled Trials. Chemotherapy 2017;61(4):179-89	No additional information
92	2016	An, N. Zhang, Y. Niu, H. et al. EGFR-TKIs versus taxanes agents in therapy for nonsmall-cell lung cancer patients: A PRISMA-compliant systematic review with meta-analysis and meta-regression. Medicine (Baltimore) 2017;95(50):e5601	No additional information
93	2016	Greenhalgh, J. Dwan, K. Boland, A. et al. First-line treatment of advanced epidermal growth factor receptor (EGFR) mutation positive non-squamous non-small cell lung cancer. Cochrane Database Syst Rev 2016;5: CD010383	Included



Appendix 9.3.2. Critical appraisal systematic reviews

	Greenhalgh 2016 ²¹⁶		Zhang 2019 ²¹⁷	
	Score	Rationale/comment	score	Rationale/comment
1. PICO	Y		Y	
2. A priori study design	N		N	
3. Inclusion study designs	Y		Y	
4. Comprehensive literature search	Partial Y	Consultation of experts in the fields not explicitly mentioned, no search of trial registries	Partial Y	No search of references, no consultation of content experts, no search of trial registers
5. Duplicate study selection	Y		N	Unclear
6. Duplicate data extraction	Y		Y	
7. List of excluded studies and rationale	Y		N	
8. Characteristics of included studies provided	Y		Y	
9. Assessment of risk of bias	Y		Y	
10. Sources of funding reported	Y		N	
11. Appropriate methods to combine findings	Y		Y	
12. Assessment of impact RoB in included studies on results MA	Y	(but too few studies included)		
13. RoB assessment used in interpretation of results and in conclusions	Y			
14. Explanation for and discussion of any observed heterogeneity	Y	(but too few studies included)		
15. Adequate investigation of publication bias and its impact on the results	Y	(but too few studies included)	Y	(based on PFS)
16. Potential sources of conflict of interest reported	Y		N	



	Wang 2020 ²¹⁸		Elliott 2020 ²¹⁹	
	Score	Rationale/comment	score	Rationale/comment
1. PICO	Y		Y	
2. A priori study design	N		(partial) Y	did not check content of registered protocol
3. Inclusion study designs	Y		Y	
4. Comprehensive literature search	Partial Y	No search of trial registries, no content experts consulted,	Partial Y	reference lists not searched, content experts not consulted
5. Duplicate study selection	N	unclear	Y	
6. Duplicate data extraction	Y		Y	
7. List of excluded studies and rationale	N		N	
8. Characteristics of included studies provided	Partial Yes		Y	
9. Assessment of risk of bias	Y		Y	
10. Sources of funding reported	Y	"all included studies were funded by the pharmaceutical industry"	Y	
11. Appropriate methods to combine findings	Y		Y	unclear: inclusion of study with cross-over design
12. Assessment of impact RoB in included studies on results MA	Y		N	
13. RoB assessment used in interpretation of results and in conclusions	N		N	
14. Explanation for and discussion of any observed heterogeneity	N		N	
15. Adequate investigation of publication bias and its impact on the results	Y		N	
16. Potential sources of conflict of interest reported	Y		Y	



	Connock 2019 ²²⁰		Sim 2018 ²²¹	
	Score	Rationale/comment	score	Rationale/comment
1. PICO	Y		Y	
2. A priori study design	Y		N	
3. Inclusion study designs	Y		Y	
4. Comprehensive literature search	Partial Y	no search of trial registries, no content experts consulted	Y	
5. Duplicate study selection	Y		Y	
6. Duplicate data extraction	Y		Y	
7. List of excluded studies and rationale	N	aggregated data only	Y	
8. Characteristics of included studies provided	Y		Y	
9. Assessment of risk of bias	Y		Y	
10. Sources of funding reported	N	funding of included studies not reported	Y	
11. Appropriate methods to combine findings	Y		Y	
12. Assessment of impact RoB in included studies on results MA	N		Y	
13. RoB assessment used in interpretation of results and in conclusions	N		Y	
14. Explanation for and discussion of any observed heterogeneity	N		Y	
15. Adequate investigation of publication bias and its impact on the results	N		Y	
16. Potential sources of conflict of interest reported	Y		Y	



Wang 2017 ²²²		
	Score	Rationale/comment
1. PICO	Y	
2. A priori study design	N	
3. Inclusion study designs	Y	
4. Comprehensive literature search	Partial Yes	No search of reference lists, no search of trial databases
5. Duplicate study selection	Y	
6. Duplicate data extraction	Y	
7. List of excluded studies and rationale	N	
8. Characteristics of included studies provided	Y	
9. Assessment of risk of bias	N	
10. Sources of funding reported	N	
11. Appropriate methods to combine findings	Y	
12. Assessment of impact RoB in included studies on results MA	N	
13. RoB assessment used in interpretation of results and in conclusions	N	
14. Explanation for and discussion of any observed heterogeneity	N	
15. Adequate investigation of publication bias and its impact on the results	N	
16. Potential sources of conflict of interest reported	Y	



Appendix 9.3.3. Search strategy

Appendix 9.3.3.1. Cochrane library of systematic reviews

Date	25/06/2020 22:44:39	
Database	Cochrane@Wiley.com	
Search strategy		
#1	[mh ^"Carcinoma, Non-Small-Cell Lung"]	4185
#2	[mh "ADENOCARCINOMA OF LUNG"]	88
#3	#1 or #2	4236
#4	NSCLC:ab,ti	8841
#5	LCLC:ab,ti	6
#6	#4 or #5	8846
#7	[mh ^"carcinoma, large cell"]	92
#8	[mh ^"carcinoma, squamous cell"]	2720
#9	[mh ^"adenocarcinoma"]	3583
#10	#7 or #8 or #9	5724
#11	((("large cell" or "large cells") NEAR/3 carcinoma?):ab,ti	150
#12	((squamous or epidermoid or planocellular or "plano-cellular") NEAR/3 carcinoma?):ab,ti	5396
#13	adenocarcinoma?:ab,ti	7386
#14	#11 or #12 or #13	12204
#15	[mh "lung"]	4111
#16	[mh ^"lung neoplasms"]	6909
#17	#15 or #16	10842
#18	#10 and #17	692
#19	(lung? or pulmonary or alveolar or bronchio*):ab,ti	85670
#20	#10 and #19	772
#21	((("large cell" or "large cells") NEAR/3 carcinoma?) or ((squamous or epidermoid or planocellular or "plano-cellular") NEAR/3 carcinoma?) or adenocarcinoma?) NEAR/3 (lung? or pulmonary or alveolar or bronchio*)):ab,ti	681
#22	carcinoma*:ab,ti	28449
#23	cancer:ab,ti	135117
#24	(tumor* or tumour*):ab,ti	59464
#25	neoplasm*:ab,ti	5493
#26	#22 or #23 or #24 or #25	174760
#27	lung?:ab,ti	48239
#28	pulmonary:ab,ti	44133
#29	alveolar:ab,ti	5199



Date	25/06/2020 22:44:39	
#30	bronchio*:ab,ti	1396
#31	#27 or #28 or #29 or #30	85670
#32	((carcinoma* or cancer or tumor* or tumour* or neoplasm*) NEAR/3 (lung? or pulmonary or alveolar or bronchio*)):ab,ti	18565
#33	("non-small cell" or "non-small cells"):ab,ti	0
#34	("nonsmall cell" or "nonsmall cells"):ab,ti	8497
#35	("large cell" or "large cells"):ab,ti	557
#36	squamous:ab,ti	8143
#37	epidermoid:ab,ti	170
#38	(planocellular or "plano-cellular"):ab,ti	4
#39	#33 or #34 or #35 or #36 or #37 or #38	15864
#40	((("non-small cell" or "non-small cells" or "nonsmall cell" or "nonsmall cells" or "large cell" or "large cells" or squamous or epidermoid or planocellular or "plano-cellular") NEAR/3 (carcinoma* or cancer or tumor* or tumour* or neoplasm*) NEAR/3 (lung? or pulmonary or alveolar or bronchio*)):ab,ti	8590
#41	[mh "lung"[mj]]	2407
#42	[mh "neoplasms"[mj]]	51358
#43	#41 and #42	108
#44	[mh "lung neoplasms"]	7480
#45	#43 or #44	7511
#46	#39 and #45	2988
#47	#40 or #46	8916
#48	#3 or #6 or #18 or #20 or #21 or #40 or #47	13171
#49	[mh ^"Erlotinib Hydrochloride"]	535
#50	Erlotinib:ab,ti	1518
#51	Tarceva:ab,ti	204
#52	"OSI 774":ab,ti	33
#53	OSI774:ab,ti	0
#54	"CP 358774":ab,ti	0
#55	CP358774:ab,ti	0
#56	J4T82NDH7E:ab,ti	0
#57	"RG-1415":ab,ti	0
#58	RG1415:ab,ti	1
#59	"R-1415":ab,ti	0
#60	R1415:ab,ti	1
#61	CP35877401:ab,ti	0
#62	"CP 35877401":ab,ti	0
#63	"183319-69-9":ab,ti	27



Date	25/06/2020 22:44:39	
#64	"183321-74-6":ab,ti	33
#65	#50 or #51 or #52 or #53 or #54 or #55 or #56 or #57 or #58 or #59 or #60 or #61 or #62 or #63 or #64	1546
#66	#49 or #65	1581
#67	[mh ^"Gefitinib"]	300
#68	gefitinib:ab,ti	890
#69	lressa:ab,ti	154
#70	geftinat:ab,ti	0
#71	ZD1839:ab,ti	85
#72	"ZD 1839":ab,ti	5
#73	S65743JHBS:ab,ti	0
#74	"184475-35-2":ab,ti	12
#75	"184475-55-6":ab,ti	0
#76	"184475-56-7":ab,ti	0
#77	#68 or #69 or #70 or #71 or #72 or #73 or #74 or #75 or #76	962
#78	#67 or #77	980
#79	[mh ^"crizotinib"]	67
#80	CRIZOTINIB:ab,ti	300
#81	Xalkori:ab,ti	8
#82	"PF-02341066":ab,ti	10
#83	"PF-2341066":ab,ti	0
#84	PF2341066:ab,ti	0
#85	PF02341066:ab,ti	0
#86	53AH36668S:ab,ti	0
#87	"pf 1066":ab,ti	0
#88	pf1066:ab,ti	0
#89	"877399-52-5":ab,ti	6
#90	#80 or #81 or #82 or #83 or #84 or #85 or #86 or #87 or #88 or #89	304
#91	#79 or #90	306
#92	[mh ^"afatinib"]	57
#93	AFATINIB:ab,ti	365
#94	Gilotrif:ab,ti	0
#95	giotrif:ab,ti	13
#96	TOMTOVOK:ab,ti	0
#97	TOVOK:ab,ti	1
#98	BIBW 2992*:ab,ti	66
#99	BIBW2992*:ab,ti	14



Date	25/06/2020 22:44:39	
#100	41UD74L59M:ab,ti	0
#101	"439081-18-2":ab,ti	0
#102	"850140-72-6":ab,ti	5
#103	"850140-73-7":ab,ti	2
#104	#93 or #94 or #95 or #96 or #97 or #98 or #99 or #100 or #101 or #102 or #103	391
#105	#92 or #104	392
#106	[mh ^"nivolumab"]	395
#107	Nivolumab:ab,ti	1566
#108	"bms 936558":ab,ti	121
#109	bms936558:ab,ti	36
#110	"mdx 1106":ab,ti	16
#111	mdx1106:ab,ti	22
#112	"ono 4538":ab,ti	61
#113	ono4538:ab,ti	0
#114	opdivo:ab,ti	85
#115	"cmab 819":ab,ti	0
#116	cmab819:ab,ti	0
#117	"946414-94-4":ab,ti	81
#118	31YO63LBSN:ab,ti	0
#119	#107 OR #108 OR #109 OR #110 OR #111 OR #112 OR #113 OR #114 OR #115 OR #116 OR #117 OR #118	1587
#120	#106 or #119	1604
#121	pembrolizumab:ab,ti	1354
#122	lambrolizumab:ab,ti	2
#123	keytruda:ab,ti	69
#124	"mk 3475":ab,ti	270
#125	mk3475:ab,ti	5
#126	"sch 900475":ab,ti	2
#127	sch900475:ab,ti	9
#128	"1374853-91-4":ab,ti	101
#129	DPT0O3T46P:ab,ti	0
#130	#121 OR #122 OR #123 OR #124 OR #125 OR #126 OR #127 OR #128 OR #129	1366
#131	#66 or #78 or #91 or #105 or #120 or #130	5567
#132	[mh "ErbB Receptors"/AI]	275
#133	(erbb NEAR/5 (inhibit* or antagonist? or target* or block* or against or anti or "multi-target" or "multi-targets" or "multi-targeting" or reduc*)):ab,ti	91



Date	25/06/2020 22:44:39	
#134	("epidermal growth factor" NEAR/5 (inhibit* or antagonist? or target* or block* or against or anti or "multi-target" or "multi-targets" or "multi-targeting" or reduc*)):ab,ti	879
#135	(egf NEAR/5 (inhibit* or antagonist? or target* or block* or against or anti or "multi-target" or "multi-targets" or "multi-targeting" or reduc*)):ab,ti	86
#136	(tgf NEAR/5 (inhibit* or antagonist? or target* or block* or against or anti or "multi-target" or "multi-targets" or "multi-targeting" or reduc*)):ab,ti	201
#137	((her or her2) NEAR/5 (inhibit* or antagonist? or target* or block* or against or anti or "multi-target" or "multi-targets" or "multi-targeting" or reduc*)):ab,ti	1064
#138	#133 or #134 or #135 or #136 or #137	2222
#139	#132 or #138	2342
#140	[mh "Anaplastic Lymphoma Kinase"/AI]	5
#141	(alk NEAR/5 (inhibit* or antagonist? or target* or block* or against or anti or "multi-target" or "multi-targets" or "multi-targeting" or reduc*)):ab,ti	230
#142	(cd246 NEAR/5 (inhibit* or antagonist? or target* or block* or against or anti or "multi-target" or "multi-targets" or "multi-targeting" or reduc*)):ab,ti	0
#143	("anaplastic lymphoma kinase" NEAR/5 (inhibit* or antagonist? or target* or block* or against or anti or "multi-target" or "multi-targets" or "multi-targeting" or reduc*)):ab,ti	35
#144	#141 or #142 or #143	240
#145	#140 or #144	242
#146	[mh ^"Proto-Oncogene Proteins c-met"/AI]	12
#147	("hepatocyte growth factor" NEAR/5 (inhibit* or antagonist? or target* or block* or against or anti or "multi-target" or "multi-targets" or "multi-targeting" or reduc*)):ab,ti	22
#148	(hgf NEAR/5 (inhibit* or antagonist? or target* or block* or against or anti or "multi-target" or "multi-targets" or "multi-targeting" or reduc*)):ab,ti	47
#149	(c-met NEAR/5 (inhibit* or antagonist? or target* or block* or against or anti or "multi-target" or "multi-targets" or "multi-targeting" or reduc*)):ab,ti	69
#150	("met receptor" NEAR/5 (inhibit* or antagonist? or target* or block* or against or anti or "multi-target" or "multi-targets" or "multi-targeting" or reduc*)):ab,ti	14
#151	("receptor c-met" NEAR/5 (inhibit* or antagonist? or target* or block* or against or anti or "multi-target" or "multi-targets" or "multi-targeting" or reduc*)):ab,ti	0
#152	("oncogene c-met" NEAR/5 (inhibit* or antagonist? or target* or block* or against or anti or "multi-target" or "multi-targets" or "multi-targeting" or reduc*)):ab,ti	0
#153	("c-met proto-oncogene" NEAR/5 (inhibit* or antagonist? or target* or block* or against or anti or "multi-target" or "multi-targets" or "multi-targeting" or reduc*)):ab,ti	0
#154	("scatter factor" NEAR/5 (inhibit* or antagonist? or target* or block* or against or anti or "multi-target" or "multi-targets" or "multi-targeting" or reduc*)):ab,ti	3
#155	(met NEAR/5 (inhibit* or antagonist? or targeting* or block*)):ab,ti	347
#156	#147 OR #148 OR #149 OR #150 OR #151 OR #152 OR #153 OR #154 OR #155	395



Date	25/06/2020 22:44:39	
#157	#146 or #156	395
#158	[mh ^"Programmed Cell Death 1 Receptor"/AI]	25
#159	((PD-1 or PD1 or CD279) NEAR/3 (inhibit* or antagonist? or target* or block* or against or anti or mutli-target* or reduc*)):ab,ti	1254
#160	#158 or #159	1262
#161	[mh ^"Protein Kinase Inhibitors"]	762
#162	[mh "Protein-Tyrosine Kinases"/AI]	640
#163	[mh "Antibodies, Monoclonal"]	12727
#164	[mh ^"Molecular Targeted Therapy"]	133
#165	#161 or #162 or #163 or #164	13741
#166	tki:ab,ti	1225
#167	(kinase? NEAR/3 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)):ab,ti	3959
#168	((("new class" or "new classes" or innovative or target*) NEAR/3 (drug? or therapy or therapies or therapeutic* or treatment? or chemotherap*)):ab,ti	11940
#169	(monoclonal NEAR/3 antibod*):ab,ti	8824
#170	#166 or #167 or #168 or #169	24255
#171	#165 or #170	34760
#172	#139 or #145 or #157 or #160 or #171	36831
#173	#48 and #131	2670
#174	#48 and #172	2769
#175	#173 or #174	4085
#176	#175 in Cochrane Reviews	7
Comments		

Appendix 9.3.3.2. Medline + PreMedline

Date	June 23, 2020	
Database	Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946 to June 23, 2020>	
Search strategy		
1	Carcinoma, Non-Small-Cell Lung/	52795
2	exp "ADENOCARCINOMA OF LUNG"/	8341
3	1 or 2	60144
4	NSCLC.ab,ti,kf.	43245
5	LCLC.ab,ti,kf.	108
6	4 or 5	43334
7	carcinoma, large cell/	2400



Date	June 23, 2020	
8	carcinoma, squamous cell/	128984
9	adenocarcinoma/	152715
10	7 or 8 or 9	260918
11	(large cell? adj3 carcinoma?).ab,ti,kf.	3920
12	((squamous or epidermoid or planocellular or plano-cellular) adj3 carcinoma?).ab,ti,kf.	112271
13	adenocarcinoma?.ab,ti,kf.	148017
14	11 or 12 or 13	246239
15	exp lung/	272132
16	lung neoplasms/	216646
17	15 or 16	469397
18	10 and 17	36996
19	(lung? or pulmonary or alveolar or bronchio*).ab,ti,kf.	1097985
20	10 and 19	36945
21	((large cell? adj3 carcinoma?) or ((squamous or epidermoid or planocellular or plano-cellular) adj3 carcinoma?) or adenocarcinoma?) adj3 (lung? or pulmonary or alveolar or bronchio*).ab,ti,kf.	26237
22	carcinoma*.ab,ti,kf.	666692
23	cancer.ab,ti,kf.	1717944
24	tumo?r*.ab,ti,kf.	1703151
25	neoplasm*.ab,ti,kf.	274193
26	22 or 23 or 24 or 25	3101581
27	lung?.ab,ti,kf.	673068
28	pulmonary.ab,ti,kf.	543188
29	alveolar.ab,ti,kf.	95601
30	bronchio*.ab,ti,kf.	19877
31	27 or 28 or 29 or 30	1097985
32	((carcinoma* or cancer or tumo?r* or neoplasm*) adj3 (lung? or pulmonary or alveolar or bronchio*).ab,ti,kf.	213960
33	"non-small cell?".ab,ti,kf.	64089
34	nonsmall cell?.ab,ti,kf.	3039
35	large cell?.ab,ti,kf.	17469
36	squamous.ab,ti,kf.	134147
37	epidermoid.ab,ti,kf.	12458
38	(planocellular or plano-cellular).ab,ti,kf.	103
39	33 or 34 or 35 or 36 or 37 or 38	219439
40	((("non-small cell?" or "nonsmall cell?" or "large cell?" or squamous or epidermoid or (planocellular or plano-cellular)) adj3 (carcinoma* or cancer or tumo?r* or neoplasm*) adj3 (lung? or pulmonary or alveolar or bronchio*).ab,ti,kf.	69370
41	exp *lung/	154654



Date	June 23, 2020	
42	exp *neoplasms/	2918734
43	41 and 42	12882
44	exp *lung neoplasms/	184217
45	43 or 44	187673
46	39 and 45	55943
47	40 or 46	77014
48	3 or 6 or 18 or 20 or 21 or 40 or 47	125488
49	Erlotinib Hydrochloride/	3864
50	Erlotinib.ab,ti,kf,rn.	6814
51	Tarceva.ab,ti,kf,rn.	322
52	OSI 774.ab,ti,kf,rn.	104
53	OSI774.ab,ti,kf,rn.	1
54	CP 358774.ab,ti,kf,rn.	4
55	CP358774.ab,ti,kf,rn.	2
56	J4T82NDH7E.ab,ti,kf,rn.	1
57	RG-1415.ab,ti,kf,rn.	0
58	RG1415.ab,ti,kf,rn.	0
59	R-1415.ab,ti,kf,rn.	1
60	R1415.ab,ti,kf,rn.	0
61	CP35877401.ab,ti,kf,rn.	0
62	CP 35877401.ab,ti,kf,rn.	0
63	183319-69-9.ab,ti,kf,rn.	0
64	183321-74-6.ab,ti,kf,rn.	1
65	50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64	6868
66	49 or 65	6868
67	Gefitinib/	4414
68	gefitinib.ab,ti,kf,rn.	7163
69	Iressa.ab,ti,kf,rn.	803
70	geftinat.ab,ti,kf,rn.	0
71	ZD1839.ab,ti,kf,rn.	447
72	ZD 1839.ab,ti,kf,rn.	43
73	S65743JHBS.ab,ti,kf,rn.	4415
74	184475-35-2.ab,ti,kf,rn.	1
75	184475-55-6.ab,ti,kf,rn.	0
76	184475-56-7.ab,ti,kf,rn.	0
77	68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76	7319



Date	June 23, 2020	
78	67 or 77	7319
79	crizotinib/	1205
80	CRIZOTINIB.ab,ti,kf,rn.	2386
81	Xalkori.ab,ti,kf,rn.	33
82	PF-02341066.ab,ti,kf,rn.	41
83	PF-2341066.ab,ti,kf,rn.	25
84	PF2341066.ab,ti,kf,rn.	10
85	PF02341066.ab,ti,kf,rn.	19
86	53AH36668S.ab,ti,kf,rn.	1206
87	pf 1066.ab,ti,kf,rn.	1
88	pf1066.ab,ti,kf,rn.	0
89	877399-52-5.ab,ti,kf,rn.	1
90	80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89	2409
91	79 or 90	2409
92	afatinib/	660
93	AFATINIB.ab,ti,kf,rn.	1402
94	Gilotrif.ab,ti,kf,rn.	12
95	giotrif.ab,ti,kf,rn.	7
96	TOMTOVOK.ab,ti,kf,rn.	1
97	TOVOK.ab,ti,kf,rn.	2
98	BIBW 2992*.ab,ti,kf,rn.	60
99	BIBW2992*.ab,ti,kf,rn.	23
100	41UD74L59M.ab,ti,kf,rn.	661
101	439081-18-2.ab,ti,kf,rn.	0
102	850140-72-6.ab,ti,kf,rn.	1
103	850140-73-7.ab,ti,kf,rn.	0
104	93 or 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102 or 103	1428
105	92 or 104	1428
106	nivolumab/	2385
107	Nivolumab.ab,ti,kf,rn.	5049
108	bms 936558.ab,ti,kf,rn.	24
109	bms936558.ab,ti,kf,rn.	0
110	mdx 1106.ab,ti,kf,rn.	6
111	mdx1106.ab,ti,kf,rn.	1
112	ono 4538.ab,ti,kf,rn.	16
113	ono4538.ab,ti,kf,rn.	0



Date	June 23, 2020	
114	opdivo.ab,ti,kf,rn.	65
115	cmab 819.ab,ti,kf,rn.	0
116	cmab819.ab,ti,kf,rn.	0
117	946414-94-4.ab,ti,kf,rn.	1
118	31YO63LBSN.ab,ti,kf,rn.	2386
119	107 or 108 or 109 or 110 or 111 or 112 or 113 or 114 or 115 or 116 or 117 or 118	5058
120	106 or 119	5058
121	pembrolizumab.ab,ti,kf,rn.	3986
122	lambrolizumab.ab,ti,kf,rn.	23
123	keytruda.ab,ti,kf,rn.	75
124	mk 3475.ab,ti,kf,rn.	50
125	mk3475.ab,ti,kf,rn.	4
126	sch 900475.ab,ti,kf,rn.	2
127	sch900475.ab,ti,kf,rn.	0
128	1374853-91-4.ab,ti,kf,rn.	1
129	DPT0O3T46P.ab,ti,kf,rn.	1675
130	121 or 122 or 123 or 124 or 125 or 126 or 127 or 128 or 129	4012
131	66 or 78 or 91 or 105 or 120 or 130	21875
132	exp ErbB Receptors/ai	11721
133	(erbb adj5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)).ab,ti,kf.	1520
134	("epidermal growth factor" adj5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)).ab,ti,kf.	13802
135	(egf adj5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)).ab,ti,kf.	7632
136	(tgf adj5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)).ab,ti,kf.	18757
137	((her or her2) adj5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)).ab,ti,kf.	11624
138	133 or 134 or 135 or 136 or 137	50103
139	132 or 138	55739
140	Anaplastic Lymphoma Kinase/ai	162
141	(alk adj5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)).ab,ti,kf.	2443
142	(cd246 adj5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)).ab,ti,kf.	4
143	(anaplastic lymphoma kinase adj5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)).ab,ti,kf.	650
144	141 or 142 or 143	2601
145	140 or 144	2633
146	Proto-Oncogene Proteins c-met/ai	1031



Date	June 23, 2020	
147	(hepatocyte growth factor adj5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)).ab,ti,kf.	1021
148	(hgf adj5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)).ab,ti,kf.	2548
149	(c-met adj5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)).ab,ti,kf.	1685
150	(met receptor adj5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)).ab,ti,kf.	177
151	(receptor c-met adj5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)).ab,ti,kf.	46
152	(oncogene c-met adj5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)).ab,ti,kf.	3
153	(c-met proto-oncogene adj5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)).ab,ti,kf.	2
154	(scatter factor adj5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)).ab,ti,kf.	53
155	(met adj5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)).ab,ti,kf.	8067
156	147 or 148 or 149 or 150 or 151 or 152 or 153 or 154 or 155	10437
157	146 or 156	10584
158	Programmed Cell Death 1 Receptor/ai	2579
159	((PD-1 or PD1 or CD279) adj3 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)).ab,ti,kf.	8416
160	158 or 159	9292
161	Protein Kinase Inhibitors/	45263
162	exp Protein-Tyrosine Kinases/ai	38056
163	exp Antibodies, Monoclonal/	235325
164	Molecular Targeted Therapy/	27959
165	161 or 162 or 163 or 164	321630
166	tki.ab,ti,kf.	7579
167	(kinase? adj3 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)).ab,ti,kf.	118162
168	((new class* or innovative or target*) adj3 (drug? or therapy or therapies or therapeutic* or treatment? or chemotherap*)).ab,ti,kf.	330433
169	(monoclonal adj3 antibod*).ab,ti,kf.	196475
170	166 or 167 or 168 or 169	619184
171	165 or 170	772085
172	139 or 145 or 157 or 160 or 171	813388
173	((systematic review or systematic literature review or systematic scoping review or systematic narrative review or systematic qualitative review or systematic evidence review or systematic quantitative review or systematic meta-review or systematic critical review or systematic mixed studies review or systematic mapping review or systematic cochrane review or "systematic search and review" or systematic integrative review).ti. not comment.pt. not (protocol or protocols).ti. not medline.st.) or (Cochrane Database Syst Rev.ja. and review.pt.) or systematic review.pt.	159535
174	meta-analys*.ti.	109097
175	meta-analysis.pt.	116362



Date	June 23, 2020	
176	exp Technology Assessment, Biomedical/	11075
177	health technology assessment.ti,kf.	1925
178	HtA.ti,kf.	596
179	173 or 174 or 175 or 176 or 177 or 178	253258
180	48 and 131	10570
181	48 and 172	26441
182	180 or 181	28634
183	179 and 182	676
Comments		

Appendix 9.4. Economic literature

Appendix 9.4.1. Search economic literature (HTA reports)

The search strategy in CRD's HTA database identified 271 references (Table 133). In a first round, 24 references were selected based on a review of title, keywords and abstract. The 247 remaining references were excluded for the following reasons: intervention (226), design (8), language (7) or population (6). In a second round, the full text of the 24 selected references was reviewed. 17 references were excluded (design (13), update available (2), full text could not be retrieved (2)). Seven references were retained. These references are indicated in Table 27 with an asterisk (*).

Furthermore, in May 2020, the website of the National Institute for Health Research (NIHR) was searched for relevant reports. The following search terms were used: erlotinib (27 hits, 5 with a focus on NSCLC, 3 not previously identified); gefitinib (21 hits, 3 with a focus on NSCLC, 1 not previously identified); afatinib (11 hits, 1 with a focus on NSCLC, 1 not previously identified); crizotinib (15 hits, 3 with a focus on NSCLC, 3 not previously identified); nivolumab (24 hits, 2 with a focus on NSCLC, 2 not previously identified); pembrolizumab (22 hits, 5 with a focus on NSCLC, 5 not previously identified).

Finally, also in May 2020, the website of the National Institute for Health and Care Excellence (NICE) was searched. The following search terms were used: erlotinib (25 hits, 4 relevant Technology Assessments (TAs), 2 not previously identified); gefitinib (15 hits, 3 relevant TAs, 1 not previously identified); afatinib (14 hits, 2 relevant TAs, 1 not previously identified); crizotinib (19 hits, 4 relevant TAs, 4 not previously identified); nivolumab (65 hits, 2 relevant TAs, 2 not previously identified); pembrolizumab (60 hits, 5 relevant TAs, 5 not previously identified).

An overview of the identified references is provided in Table 134.



Table 133 – Search strategy and results for CRD: HTA

Date			
Date covered	All		
Search Strategy	1	MeSH DESCRIPTOR Lung Neoplasms EXPLODE ALL TREES	1151
	2	MeSH DESCRIPTOR Carcinoma, Non-Small-Cell Lung EXPLODE ALL TREES	668
	3	* IN HTA	17351
	4	#2 AND #3	132
	5	#1 AND #3	271 references
Note	The 'MeSH DESCRIPTOR Carcinoma, Non-Small-Cell Lung EXPLODE ALL TREES' is indexed under the 'MeSH DESCRIPTOR Lung Neoplasms EXPLODE ALL TREES'. The widest descriptor was used to avoid that studies including both NSCLC and other types of lung cancer would not be missed.		

Table 134 – Non-small cell lung cancer – Identified HTA reports for the selected drugs

Selected reports	
Afatinib	
<ul style="list-style-type: none"> NICE, TA444. May 2017. Afatinib for treating advanced squamous non-small-cell lung cancer after platinum-based chemotherapy (terminated appraisal).^{223 β} NICE, TA310. April 2014. Afatinib for treating epidermal growth factor receptor mutation-positive locally advanced or metastatic non-small-cell lung cancer.^{224 * β} <ul style="list-style-type: none"> Fleeman N, Bagust A, Beale S, Dwan K, Boland A, Greenhalgh J, Dundar Y, Richardson M, McEntee J, Marshall E. Afatinib for treating epidermal growth factor receptor mutation positive locally advanced or metastatic non-small cell lung cancer: A Single Technology Appraisal. LRIg, University of Liverpool, 2013.^{225 α} 	
Crizotinib	
<ul style="list-style-type: none"> NICE, TA529. July 2018. Crizotinib for treating ROS1-positive advanced non-small-cell lung cancer.^{226 β} <ul style="list-style-type: none"> Greenhalgh J, Stainthorpe S, Richardson M, Duarte R, Boland A, Kotas E, McEntee J and Green J. Crizotinib for treating ROS1-positive advanced non-small cell lung cancer [ID1098]: A Single Technology Appraisal. LRIg, University of Liverpool, 2017.^{227 α} NICE, TA422. December 2016. Crizotinib for previously treated anaplastic lymphoma kinase-positive advanced non-small-cell lung cancer.^{228 β} <ul style="list-style-type: none"> Crizotinib for the treatment of previously-treated anaplastic lymphoma kinase fusion gene, non small-cell lung cancer (review of TA296)(ID1010) → No link to full report. Only link to TA422.^α NICE, TA406. September 2016. Crizotinib for untreated anaplastic lymphoma kinase-positive advanced non-small-cell lung cancer.^{229 β} <ul style="list-style-type: none"> Hodgson R, Biswas M, Morgan P, Mebrahtu T, Harden M, Woolacott N. Crizotinib for untreated anaplastic lymphoma kinase-positive advanced non-small-cell lung cancer: A Single Technology Appraisal. CRD and CHE, University of York, Technology Assessment Group, 2016.^{230 α} 	
Erlotinib & gefitinib	
<ul style="list-style-type: none"> NICE, TA374. December 2015. Erlotinib and gefitinib for treating non-small-cell lung cancer that has progressed after prior chemotherapy.^{231 β} 	

**Selected reports**

- Greenhalgh J, Bagust A, Boland A, Dwan K, Beale S, Hockenhull J, et al. Erlotinib and gefitinib for treating non-small cell lung cancer that has progressed following prior chemotherapy (review of NICE technology appraisals 162 and 175): a systematic review and economic evaluation. *Health Technol Assess* 2015;19(47).^{232 α}

Erlotinib

- NICE, TA258. June 2012. Erlotinib for the first-line treatment of locally advanced or metastatic EGFR-TK mutation-positive non-small-cell lung cancer.^{233 * β}
 - Greenhalgh J, Bagust A, Boland A, Blundell M, Beale S, Dundar Y, Dickson R, Proudlove C, Green J A, Mooney J. Erlotinib for the first-line treatment of EGFR-TK mutation positive non-small-cell lung cancer: A Single Technology Appraisal. LRIg, The University of Liverpool, 2011.^{234 α}
- NICE, TA227. June 2011. Erlotinib monotherapy for maintenance treatment of non-small-cell lung cancer.^{235 * ** β}
 - Dickson, R; Bagust, A; Boland, A; Blundell, M; Davis, H; Dundar et al. Erlotinib monotherapy for the maintenance treatment of non-small cell lung cancer after previous platinum-containing chemotherapy. *PharmacoEconomics* 2011. Dec;29(12):1051-62.^{236 * ** α}

Gefitinib

- NICE, TA192. July 2010. Gefitinib for the first-line treatment of locally advanced or metastatic non-small-cell lung cancer.^{237 * β}
 - Brown T, Boland A, Bagust A, Oyee J, Hockenhull J, Dundar Y, Dickson R, Ramani VS and Proudlove C. Gefitinib for the first-line treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC): A Single Technology Appraisal. LRIg, The University of Liverpool, 2009.^{238 α}
 - Brown T, Boland A, Bagust A, Oyee J, Hockenhull J, Dundar Y et al. Gefitinib for the first-line treatment of locally advanced or metastatic non-small cell lung cancer. *Health Technol Assess* 2010;14(Suppl 2 Article 10).^{239 * α}

Nivolumab

- NICE, TA484. November 2017. Nivolumab for previously treated non-squamous non-small-cell lung cancer.^{240 β}
 - Nivolumab for treating metastatic, non-squamous, non-small-cell lung cancer after chemotherapy [ID900] → No link to full report. Only link to TA484.^α
- NICE, TA483. November 2017. Nivolumab for previously treated squamous non-small-cell lung cancer.^{241 β}
 - Fleeman N, Bagust A, Richardson M, Boland A, Krishan A, Beale S, Stainthorpe A, Abdulla A, Kotas E, McEntee J, Greystoke A. Nivolumab for previously treated locally advanced or metastatic squamous-cell non-small cell lung cancer [ID811]: A Single Technology Appraisal. LRIg, University of Liverpool, 2015.^{242 α}

Pembrolizumab

- NICE, TA600. September 2019. Pembrolizumab with carboplatin and paclitaxel for untreated metastatic squamous non-small-cell lung cancer.^{243 β}
 - Uttley L, Tappenden P, Ren S, Scope A, Navega Biz A, Clowes M, Hadjiyiannakis, D, Doherty G, Cove-Smith L. Pembrolizumab with carboplatin and paclitaxel or nab-paclitaxel for untreated metastatic squamous non-small-cell lung cancer: A Single Technology Appraisal. School of Health and Related Research (SchARR), 2018.^{244 α}
- NICE, TA557. January 2019. Pembrolizumab with pemetrexed and platinum chemotherapy for untreated, metastatic, non-squamous non-small-cell lung cancer.^{245 β}
 - Griffin E, Farmer C, Packman D, Nikram E, Matthews J, Barnish M, Briscoe S, Dorey N, Dangoor A, Mujica Mota M. Pembrolizumab with pemetrexed and platinum chemotherapy for untreated metastatic non-squamous non-small-cell lung cancer [ID1173]: A Single Technology Appraisal. Peninsula Technology Assessment Group (PenTAG), 2018.^{246 α}
- NICE, TA531. July 2018. Pembrolizumab for untreated PD-L1-positive metastatic non-small-cell lung cancer.^{247 β}

**Selected reports**

- Beale S, Mahon J, Boland A. Pembrolizumab for untreated PD-L1 positive metastatic non-small cell lung cancer: CDF review of TA447 [ID990], University of Liverpool, 2018.²⁴⁸ ^α
- NICE, TA428. January 2017 (updated September 2017). Pembrolizumab for treating PD-L1-positive non-small-cell lung cancer after chemotherapy.^β
 - Pembrolizumab after platinum chemotherapy for treating advanced, recurrent, PD-L1 positive, non small cell lung cancer [ID840] → no link to full report, only to TA428.^α

Excluded reports**Crizotinib**

- NICE, TA296. September 2013. Crizotinib for previously treated non-small-cell lung cancer associated with an anaplastic lymphoma kinase fusion gene.²⁴⁹ ^β
 - This guidance has been updated and replaced by NICE technology appraisal guidance 422.

Erlotinib

- NICE, TA162. November 2008 (updated December 2012). Erlotinib for the treatment of non-small-cell lung cancer.²⁵⁰ ^β
 - Bagust A, Boland A, Dundar Y, Davis H, Dickson R, Green J, Hockenhull J, Macbeth F, McLeod C, Proudlove C, Stevenson J, Walley T. Erlotinib for the treatment of relapsed non-small cell lung cancer. Liverpool Reviews and Implementation Group. September 2006.²⁵¹ ^α
 - McLeod C, Bagust A, Boland A, Hockenhull J, Dundar Y, Proudlove C, Davis H, Green J, Macbeth F, Stevenson J, Walley T and Dickson R. Erlotinib for the treatment of relapsed non-small cell lung cancer. Health Technology Assessment 2009; Vol. 13: Suppl. 1.²⁵² → This paper presents a summary of the ERG report for the STA of erlotinib for the treatment of relapsed non-small cell lung cancer (NSCLC).^{*} ^α
 - This guidance has been updated and replaced by NICE technology appraisal guidance 374.
- Brown T, Pilkington G, Bagust A, Boland A, Oyee J, Tudur Smith C, et al. Clinical effectiveness and cost-effectiveness of first-line chemotherapy for adult patients with locally advanced or metastatic non-small cell lung cancer: a systematic review and economic evaluation. Health Technol Assess 2013;17(31).²⁵³ ^{*}
 - No incremental cost-effectiveness ratios are presented for one of our selected drugs.

Gefitinib

- NICE, TA175. July 2009. Gefitinib for the second-line treatment of locally advanced or metastatic non-small-cell lung cancer (terminated appraisal).²⁵⁴ ^β
 - This guidance has been updated and replaced by NICE technology appraisal guidance 374.

Pembrolizumab

- NICE, TA447. June 2017. Pembrolizumab for untreated PD-L1-positive metastatic non-small-cell lung cancer.²⁵⁵ ^β
 - Pembrolizumab for treating untreated PD-L1 positive metastatic non-small-cell lung cancer [ID990] → No link to full report. Only link to TA447.^α
 - This guidance has been updated and replaced by NICE technology appraisal guidance 531.

** These references were identified in CRD's HTA database. ** This reference was identified under the same url of the main report. As a result, in the above table, 8 references instead of 7 are related to CRD's HTA database. ^α References identified on NIHR's website. ^β References identified on NICE's website.*



Appendix 9.4.2. Results economic literature (HTA reports)

Appendix 9.4.2.1. NICE, TA444 (2017): afatinib

- “NICE is unable to make a recommendation about the use in the NHS of afatinib for treating locally advanced or metastatic squamous non-small-cell lung cancer after platinum-based chemotherapy because no evidence submission was received from Boehringer Ingelheim.”²²³

Appendix 9.4.2.2. NICE, TA310 (2014): afatinib

- QoL:
 - “EQ-5D (UK and Belgium) and EQ-VAS data collected during the LUX-Lung 3 clinical trial reported no statistically significant difference in values between afatinib and chemotherapy with an absolute improvement in utility of 0.008 (UK) and 0.007 (Belgium).”²²⁴
 - “In the base-case model the utility value used in the progression-free health state was 0.78 (from LUX-Lung 3) and utility values from the literature were used for the progressive disease health state (0.73 and 0.46 for second- and third-line treatment respectively). Alternative utility values derived from the literature for the progression-free health state were used in a sensitivity analysis. Utility values did not change over time.”²²⁴
- Results:
 - “The deterministic pairwise results of the base-case analysis showed that afatinib was associated with an ICER of £10 076 per QALY gained (incremental costs £1723, incremental QALYs 0.171) compared with erlotinib and an ICER of £17 933 per QALY gained (incremental costs £3113, incremental QALYs 0.173) compared with gefitinib. The manufacturer stated that there was a 100% probability of afatinib being cost effective compared with erlotinib at £20,000 and £30,000 per QALY gained. Compared with gefitinib, there was a 72% and 81% probability of afatinib being cost effective at £20,000 and £30,000 per QALY gained respectively.”²²⁴
- Uncertainty/sensitivity:
 - “There was no head-to-head randomised controlled trial comparing the effectiveness of afatinib with erlotinib or gefitinib for progression-free survival or overall survival”²²⁴
 - Impact on OS: “The LUX-Lung trials provided sufficient evidence to conclude that afatinib was clinically effective in prolonging progression-free survival but because of the immaturity of the overall survival data available, there was uncertainty about whether treatment with afatinib resulted in an overall survival benefit compared with chemotherapy.”²²⁴
 - “The main drivers of cost effectiveness were: the mixed treatment comparison-based hazard ratios for progression-free and overall survival, the cost per month for the progression-free health state and the cost per month for the best supportive care period of the progressive disease health state.”²²⁴
 - “Overall, the ICERs estimated for the one-way sensitivity analyses ranged from £7135 to £54,800 per QALY gained for afatinib compared with gefitinib, and from -£10,302 to £34,970 per QALY gained for afatinib compared with erlotinib.”²²⁴
- Conclusions:



- “The ERG concludes that it is currently not possible to compare the clinical effectiveness or cost effectiveness of afatinib vs erlotinib or afatinib vs gefitinib. The two major areas of concern are (i) there are no results from head to head clinical trials comparing afatinib with erlotinib or gefitinib (ii) the manufacturer’s modelled PFS survival projection for afatinib does not reflect the afatinib LUX-lung 3 trial data from which it was derived.”²²⁴
- “The Committee concluded that on balance afatinib is likely to have similar clinical efficacy to erlotinib and gefitinib.”²²⁴
- “The Committee concluded that methodological issues related to the assumption of proportional hazards, the extrapolation of progression-free survival and the population of the base-case model prevented the Committee from assessing the cost effectiveness of afatinib compared with erlotinib and gefitinib based on the manufacturer’s model. Therefore a most plausible ICER could not be estimated.”²²⁴
- “The Committee concluded that afatinib is likely to be clinically and cost effective as a second-line treatment for the minority of patients who have received chemotherapy as first-line treatment. The Committee therefore recommended afatinib as a treatment option in line with its marketing authorisation.”²²⁴
- (Confidential) prices:
 - “Afatinib, erlotinib and gefitinib are all available as tablets and PAS prices are available for all three products.”²²⁵



Reference Costs (list prices & remarks)	Population, Intervention & comparator IC, IE and ICERs	Remarks on use of generic utility instrument (e.g. EQ- 5D) to measure impact on QoL in economic evaluations	Most uncertain variables or important variables in sensitivity analysis																														
Afatinib																																	
NICE, TA310 (2014) ²²⁴ Fleeman (2013) ²²⁵	Adults with epidermal growth factor receptor mutation-positive locally advanced or metastatic non-small-cell lung cancer. Afatinib compared with erlotinib and gefitinib.																																
List prices, negotiated discounts are hidden.* Drug costs per month: Afatinib: £2197.82 Erlotinib: £1654.19 Gefitinib: £12 200 on receipt of third pack.**	Results are taken from the manufacturer's approved PAS submission: <table><tr><td></td><td>Costs (£)</td><td>IC</td><td>QALYs</td><td>IE</td><td>ICER</td></tr><tr><td>Gefitinib</td><td>conf.</td><td></td><td>1.421</td><td></td><td></td></tr><tr><td>Erlotinib vs gef..</td><td>conf.</td><td>1390</td><td>1.423</td><td>0.002</td><td>695 000 (ED)</td></tr><tr><td>Afatinib vs erl.</td><td>conf.</td><td>1723</td><td>1.594</td><td>0.171</td><td>10 079</td></tr><tr><td>Afatinib vs gef.</td><td>conf.</td><td>3113</td><td>1.594</td><td>0.173</td><td>17 933</td></tr></table> Remark: Given the complexity and depth of the problems associated with the submitted economic model, the ERG is unable to provide a set of revised ICERs for the Appraisal Committee. Therefore the ERG is of the opinion that there is <u>no reliable cost-effectiveness evidence available</u> to support the use of afatinib compared with erlotinib or compared with gefitinib.		Costs (£)	IC	QALYs	IE	ICER	Gefitinib	conf.		1.421			Erlotinib vs gef..	conf.	1390	1.423	0.002	695 000 (ED)	Afatinib vs erl.	conf.	1723	1.594	0.171	10 079	Afatinib vs gef.	conf.	3113	1.594	0.173	17 933	EQ-5D (UK and Belgium) and EQ-VAS data collected during the LUX-Lung 3 clinical trial reported no statistically significant difference in values between afatinib and chemotherapy with an absolute improvement in utility of 0.008 (UK) and 0.007 (Belgium).	Overall survival benefit Cost progression-free health state and the best supportive care period.
	Costs (£)	IC	QALYs	IE	ICER																												
Gefitinib	conf.		1.421																														
Erlotinib vs gef..	conf.	1390	1.423	0.002	695 000 (ED)																												
Afatinib vs erl.	conf.	1723	1.594	0.171	10 079																												
Afatinib vs gef.	conf.	3113	1.594	0.173	17 933																												

Conf.: confidential; ED: extended dominance; erl.: erlotinib; gef: gefitinib; PAS: patient access scheme.

* Afatinib, erlotinib and gefitinib are all available as tablets and PAS prices are available for all three products. ** The PAS for gefitinib: a cost of £12 200 is applied on receipt of the third monthly pack.



Appendix 9.4.2.3. NICE, TA529 (2018): crizotinib

- QoL:
 - The company states “that HRQoL data were not collected during the PROFILE 1001 study. This means that there are no direct HRQoL data for patients with ROS1+ advanced NSCLC.”²²⁷
 - “HRQoL data for treatment with crizotinib in patients with ROS1+ advanced NSCLC were not collected during the PROFILE 1001 study. Instead, the company used utility data collected from the PROFILE 1014 and PROFILE 1007 trials ... on the assumption that HRQoL data from the ALK+ advanced NSCLC population would be an appropriate proxy for HRQoL for the ROS1+ advanced NSCLC population. Utility data were collected in the PROFILE 1014 and PROFILE 1007 trials using the EQ-5D questionnaire.”²²⁷
 - “The company has summarised the HRQoL data collected during the PROFILE 1014 and 1007 trials using the EuroQol-Five Dimensions (EQ-5D-3L79) questionnaire.”²²⁷ However, in the table presenting this information, all details on QoL (completion rates, EQ-5D index scores, difference between groups, change from baseline in EQ-5D index scores) are kept confidential.
- Results:
 - The exact ICERs were presented as commercial in confidence and therefore were not presented.
- Uncertainty/sensitivity:
 - “Varying the HR for OS has the biggest effect on the company’s cost effectiveness results, followed by varying the covariates for OS, PFS and TTD [time to treatment discontinuation], and the utility value for BSC [best supportive care].”²²⁷
 - “Evidence for crizotinib in ROS1-positive advanced NSCLC comes from a small, single-arm study.” ... “Because of the limited evidence in ROS1-positive NSCLC, the company presented data from 2 randomised controlled trials for crizotinib in ALK-positive NSCLC instead (comparing crizotinib with chemotherapy) as proxy data for ROS1-positive advanced NSCLC. However, using data from a proxy population is far from ideal, and makes the assessment of clinical and cost effectiveness highly uncertain.”²²⁶
 - Furthermore, “the committee concluded that even with the new analyses from the company, there was considerable uncertainty around the size of survival benefit in the progression free and progressed states because the relationship between overall survival and progression-free survival is unclear.”²²⁶



- Conclusions:
 - “Crizotinib meets NICE's criteria to be considered a life-extending end-of-life treatment, but there are uncertainties in the clinical- and cost-effectiveness estimates. For previously treated disease, the range of cost-effectiveness estimates was broader than for untreated disease and all estimates are higher than what NICE normally considers acceptable for end-of-life treatments. Crizotinib therefore cannot be recommended for routine use in the NHS to treat ROS1-positive advanced NSCLC.”²²⁶
 - “The ICER based on the current evidence is higher than the range normally considered to be a cost-effective use of NHS resources.” However, “collecting further data on its use in the Cancer Drugs Fund would help address uncertainties in crizotinib's survival benefit, and the comparability of ROS1-positive and ALK-positive advanced NSCLC. Using crizotinib in a managed approach would also encourage standardisation of ROS1 status testing in non-squamous NSCLC. Therefore, crizotinib can be recommended for use within the Cancer Drugs Fund to treat ROS1-positive NSCLC.”²²⁶
 - “The committee concluded that it could recommended crizotinib as an option for use within the Cancer Drugs Fund to treat ROS1-positive NSCLC, only if the conditions in the managed access agreement are followed.”²²⁶
- (Confidential) prices:
 - “The company has a commercial arrangement. This makes crizotinib available to the NHS with a discount.”²²⁶



Reference Costs (list prices & remarks)	Population, Intervention & comparator IC, IE and ICERs	Remarks on use of generic utility instrument (e.g. EQ- 5D) to measure impact on QoL in economic evaluations	Most uncertain variables or important variables in sensitivity analysis
Crizotinib			
NICE, TA529 (2018) ²²⁶ Greenhalgh (2017) ²²⁷	Adults with ROS1-positive advanced non-small-cell lung cancer (NSCLC) Untreated disease: pemetrexed plus platinum-based therapy is the appropriate comparator. Previously treated disease: it is inappropriate to exclude standard care docetaxel plus nintedanib as a comparator (which has not been included as a comparator in this appraisal).		
List prices, negotiated discounts for crizotinib are hidden. Drug costs (per treatment cycle): Crizotinib (30d) £4689 Pemetrexed (21d) £1385.4 (or £1465.4 with wastage) Cisplatin (21d) £10.97 (or £14.64 with wastage) Carboplatin (21d) £22.66 (or £23.64 with wastage) Docetaxel (21d) £17.25 (or £20.59 with wastage)	<u>Exact ICERs were presented as commercial in confidence.</u> For crizotinib compared with pemetrexed plus platinum-based chemotherapy in untreated disease: Around or above £50,000 per quality-adjusted life year (QALY) gained (the exact ICERs were presented as commercial in confidence and therefore cannot be presented here). However, the committee agreed that this estimate came with far too much uncertainty to conclude on a figure below £50,000 without further evidence. For crizotinib compared with docetaxel in previously treated disease: Well above £50,000 per QALY gained (the exact ICERs were presented as commercial in confidence and therefore cannot be presented here). The committee agreed that had crizotinib been compared with nintedanib plus docetaxel, the ICER would be even higher. Remark: The committee agreed that the new ICERs presented by the company were highly uncertain because of the use of proxy data from ALK-positive advanced NSCLC and uncertainties in the overall survival extrapolation. Conclusion: the committee concluded that it could not recommend crizotinib for routine use in the NHS to treat ROS1-positive advanced NSCLC.	HRQoL data were not collected during the PROFILE 1001 study. HRQoL data collected during the PROFILE 1014 and 1007 trials using the EQ-5D-3L questionnaire were presented as confidential.	Hazard ratio for OS Covariates for OS, PFS and TTD Utility value for BSC



Appendix 9.4.2.4. NICE, TA422 (2016): crizotinib

- QoL:
 - The committee “welcomed the collection of EQ-5D data in PROFILE 1007.”²²⁸
 - “Utility estimates in the post-progression state remained uncertain because of the lack of data in the post-progression period.”²²⁸
- Results:
 - NICE TA296 “The committee therefore concluded that the ICER on which to base a decision for crizotinib compared with docetaxel would be more than £100 000 per QALY gained.”²²⁸
 - “The ICER on which to base a decision for crizotinib compared with best supportive care would be more than £50 200 per QALY gained. However, the committee further concluded that this ICER was associated with substantial uncertainty, which it was not possible to quantify because of the lack of a robust mixed treatment comparison between crizotinib and best supportive care.”²²⁸
 - NICE TA422: “The committee concluded that the most plausible ICER for crizotinib compared with docetaxel would be less than £50 000 per QALY gained including the revised patient access scheme, assuming a hazard ratio of 0.49 for overall survival and allowing for crizotinib treatment after progression.”²²⁸
- Uncertainty/sensitivity:
 - NICE TA296: “The committee concluded that the exact gain in overall survival from treatment with crizotinib was very uncertain and an exact value could not be reliably established from the available data.”²²⁸
 - NICE TA422: “The committee noted that more mature data were available in the CDF [Cancer Drugs Fund] reconsideration submission.”²²⁸
- Conclusions:
 - TA296: “The committee concluded that treatment with crizotinib for previously treated ALK-positive advanced non-small-cell lung cancer should not be recommended for use within the NHS.”²²⁸
 - TA422: “Taking into account the new cost-effectiveness analyses, which apply to a population that is likely to be getting smaller, including the revised patient access scheme, and considering the end-of-life criteria, the committee recommended crizotinib as a cost-effective use of NHS resources for people with previously treated anaplastic lymphoma kinase-positive advanced non-small-cell lung cancer.”²²⁸
- (Confidential) prices:
 - The company has agreed a patient access scheme with the Department of Health. This involves a discount applied to the list price of crizotinib. The level of the discount is commercial in confidence.



Reference Costs (list prices & remarks)	Population, Intervention & comparator IC, IE and ICERs	Remarks on use of generic utility instrument (e.g. EQ- 5D) to measure impact on QoL in economic evaluations	Most uncertain variables or important variables in sensitivity analysis
Crizotinib			
NICE, TA422 (2016) ²²⁸	Adults with previously treated anaplastic lymphoma kinase (ALK)-positive advanced non-small-cell lung cancer. Crizotinib versus docetaxel and best supportive care.		
List prices, negotiated discounts are hidden. The list price of crizotinib is £4689 for 60 capsules*	<p>NICE TA296: ICERs</p> <ul style="list-style-type: none"> - Crizotinib versus docetaxel: >£100 000 per QALY gained. - Crizotinib versus BSC: >£50 200 per QALY gained. <p>NICE TA422: ICERs updated analysis</p> <ul style="list-style-type: none"> - Crizotinib versus docetaxel: <£50 000 per QALY gained. <p>Conclusion: The committee concluded that the most plausible ICER for crizotinib compared with docetaxel would be less than £50 000 per QALY gained <u>including the revised patient access scheme</u>, assuming a hazard ratio of 0.49 for overall survival and allowing for crizotinib treatment after progression.</p> <p>The committee had previously concluded that if crizotinib were cost effective compared with docetaxel, it was also likely to be cost effective compared with best supportive care.</p>	Collection of EQ-5D data in PROFILE 1007. Uncertainty post-progression utilities.	Exact gain in overall survival was very uncertain.

BSC: best supportive care.

* No treatment cost per months or cycle is provided. However, the list price is the same as in the previous NICE TA were the cycle-treatment cost (30 days) is exactly the same as this list price for 60 capsules.



Appendix 9.4.2.5. NICE, TA406 (2016): crizotinib

- QoL:
 - Data on EQ-5D were collected in the underlying PROFILE 1014 trial. However, all information (e.g. completion rates, baseline values, improvement from baseline, etc.) was kept confidential.
 - “Crizotinib had statistically significant benefits in terms of HRQoL measures including EORTC QLQ-C30 and the EORTC QLQ LC-13 (which is a lung cancer-specific module), and EQ-5D, which is the measure preferred by NICE.”²³⁰
 - There was uncertainty on the utility value for the progression-free health state for platinum-based chemotherapy and for the period after a patient's disease has progressed but the patient continues to take crizotinib.²²⁹
- Results:
 - All information on incremental costs and incremental effects and ICERs without the PAS is kept confidential.
 - “The committee considered 4 results for the cost effectiveness of crizotinib compared with pemetrexed plus either cisplatin or carboplatin for people with advanced ALK-positive NSCLC: These are estimates including a (higher) patient access scheme discount.
 - Company's revised base case: £49,186 per quality-adjusted life year (QALY) gained
 - Company's independent parametric curve analysis: £47,921 per QALY gained
 - ERG's revised exploratory analysis: £58,029 per QALY gained
 - ERG's independent parametric curves analysis: £55,131 per QALY gained”²²⁹
 - The committee concluded that “the company's independent parametric curve analysis (with an estimated ICER of £47,291 per QALY gained) most closely reflected the committee's preferred assumptions. ... However, the committee acknowledged that this used some assumptions that the committee did not prefer or that the committee considered to be uncertain and therefore acknowledged that uncertainty on the cost-effectiveness of crizotinib remained fairly large.”²²⁹
- Uncertainty/sensitivity:
 - “The committee concluded that crizotinib is very likely to increase overall survival compared with pemetrexed plus either cisplatin or carboplatin in people with ALK-positive NSCLC, but the size of the increase is uncertain.”
 - The committee also noted “the ERG's comments that the results for overall survival were based on relatively immature data (that is, few patients had died at the time of data analysis).”²²⁹
 - It was also noted that “using different parametric curves for overall survival had a major effect on the ICERs.”²²⁹



- Conclusions:
 - “The committee concluded that even after accounting for the uncertainty in the cost effectiveness, the most plausible ICER was likely to be at a level at which crizotinib could be considered a cost-effective use of NHS resources when the end-of-life criteria to apply.”²²⁹
- (Confidential) prices:
 - “The company has agreed a patient access scheme with the Department of Health. This scheme provides a simple discount to the list price of crizotinib, with the discount applied at the point of purchase or invoice. The level of the discount is commercial in confidence.”²²⁹

Reference Costs (list prices & remarks)	Population, Intervention & comparator IC, IE and ICERs	Remarks on use of generic utility instrument (e.g. EQ- 5D) to measure impact on QoL in economic evaluations	Most uncertain variables or important variables in sensitivity analysis
Crizotinib			
NICE, TA406 (2016) ²²⁹ Hodgson (2016) ²³⁰	Adults with untreated anaplastic lymphoma kinase-positive advanced non-small-cell lung cancer Crizotinib compared with pemetrexed plus either cisplatin or carboplatin		
List prices, negotiated discounts for crizotinib are hidden. Drug costs (per treatment cycle): Crizotinib (30d) £4689 Pemetrexed (21d) £1385.4 (or £1440 with wastage) Cisplatin (21d) £19.98 or £25.72 (or £47 with wastage) Carboplatin (21d) £22.41 or £28.27 (or £34.18 with wastage)	Results of the incremental analysis (with PAS): A) Company's revised base case: £49 186/QALY gained B) Company's independent parametric curve analysis: £47 921/QALY gained C) ERG's revised exploratory analysis: £58 029/QALY gained D) ERG's independent parametric curves analysis: £55 131/QALY gained Remark: All information on incremental costs and effects is kept confidential. Conclusion: the committee concluded that even after accounting for the uncertainty in the cost effectiveness, the most plausible ICER was likely to be at a level at which crizotinib could be considered a cost-effective use of NHS resources when the end-of-life criteria to apply.	HRQoL data collected during the PROFILE 1014 trial using the EQ-5D questionnaire were presented as confidential.	ICER estimates were most sensitive to: - (i) the curve fit and scale parameters for OS; - (ii) time horizon; - (iii) NSCLC population-Squamous rather than non-squamous ; - (iv) the method of adjustment for crossover.



Appendix 9.4.2.6. NICE, TA374 (2015): erlotinib and gefitinib

- QoL:
 - “The company used pooled chemotherapy EQ-5D utility values from the PROFILE-1007 trial of crizotinib for both the erlotinib and best supportive care treatment groups. Utility values were used for the progression-free disease and progressed disease health states.”²³¹
 - “The Assessment Group noted several concerns with the utility values from the PROFILE-1007 trial used by the company:
 - Results were not published or peer reviewed.
 - No assessment of bias was possible because no information was available on the patients completing the EQ-5D.
 - The utility values included the effects of treatment-related adverse reactions for a treatment not considered in this technology appraisal and measured in a different population (adults with non-small-cell lung cancer that is anaplastic lymphoma kinase positive).”²³¹
 - “Because of these limitations, the Assessment Group used alternative utility values from Nafees et al. (2008).²⁵⁶ But still, these were not based on studies comparing the interventions under consideration in the relevant indication.”²³¹
- Results:
 - Epidermal growth factor mutation-positive population: “In the absence of any relevant clinical trial evidence in this population there is no reliable basis on which to assess the cost-effectiveness of available treatments.”²³²
 - Epidermal growth factor mutation-negative population:
 - “erlotinib is dominated by docetaxel, yielding a reduced mean survival and fewer QALYs.
 - The estimated mean OS advantage of using erlotinib rather than BSC is 2.2 months. ... The corresponding gain in mean discounted QALYs is 0.116 per patient. The estimated ICER of £54 687 per QALY gained is above the range normally considered cost-effective.”²³²
 - Epidermal growth factor mutation status unknown population: “The estimated survival advantage of using erlotinib rather than BSC is 2.1 months The corresponding gain in mean discounted QALYs is 0.103 per patient. The overall incremental cost per patient is higher for erlotinib use (£6314 discounted), primarily because of the acquisition cost of erlotinib (£5677 discounted). The estimated ICER of £61 132 per QALY gained is well beyond the range normally considered cost-effective.”²³²
- Uncertainty/sensitivity:
 - “The Assessment Group considered that the evidence available for the EGFR-TK mutation-positive population was weak and not sufficiently robust to inform decision-making. The Committee agreed that these retrospective analyses were based on small patient numbers, were subject to imbalances in baseline patient characteristics (and so were highly selective) and lacked statistical power.”²³¹
 - “The EGFR-TK mutation-positive population was not considered because no trials were identified that solely assessed the relative effectiveness of erlotinib or gefitinib for treating non-small-cell lung cancer that has progressed after chemotherapy in this population.”²³¹



- Another limitation is “that the cost-effectiveness analyses rely on the QALY values modelled from data obtained from a sample of the general population, as highlighted by the AG, these values do not reflect directly patient experience or patients’ preference for the mode of treatment (oral vs. i.v. treatments).”²³²
- EGFR M- population:
 - docetaxel versus erlotinib: “Use of generic docetaxel in place of the branded product is the major factor in establishing docetaxel as the preferred option.”²³²
 - Erlotinib versus BSC: “Results are most affected by projective survival model parameters (especially for the OS model), utility model parameters and the incidence of key AEs.”²³²
- EGFR mutation-unknown population:
 - “Results are unaffected by uncertainty. The only exceptions are the baseline NSCLC population utility value in patients with stable disease and the incidence of febrile neutropenia when docetaxel is used.”²³²
- Conclusions:
 - The assessment group (AG):²³²
 - For the EGFR M+ population, the AG was not able to carry out a cost-effectiveness analysis of available treatments, as there is an absence of relevant direct clinical trial evidence in this patient population.
 - For the EGFR M– population, docetaxel yielded a survival advantage over erlotinib of 2.5 months. The overall treatment cost of docetaxel was £545 lower than the cost of erlotinib.
 - For the EGFR M– population, The AG estimated the size of the erlotinib versus BSC ICER to be £54,687 per QALY gained. This ICER is above the range normally accepted to be cost-effective.
 - For the EGFR unknown population, the AG estimated the size of the erlotinib versus BSC ICER to be £61,132 per QALY gained. This ICER is outside the range normally accepted to be cost-effective.
 - The Committee:²³¹
 - EGFR-TK M+ population: Erlotinib is recommended as an option for treating locally advanced or metastatic non-small-cell lung cancer that has progressed in people who have had non-targeted chemotherapy because of delayed confirmation that their tumour is epidermal growth factor receptor tyrosine kinase (EGFR-TK) mutation-positive, only if the company provides erlotinib with the discount agreed in the patient access scheme. The Committee considered it would be unfair to disadvantage this small group of people because of a delayed diagnosis.
 - EGFR-TK M+ population: Gefitinib is not recommended
 - EGFR-TK mutation-unknown population with clinical characteristics suggestive of EGFR-TK mutation-positive tumours: The Committee considered that it would be unfair to disadvantage this small group of people. It therefore concluded that erlotinib should be recommended as a treatment



option (under specific conditions, one of which is that the result of an EGFR-TK mutation diagnostic test is unobtainable because of an inadequate tissue sample or poor-quality DNA).

- EGFR-TK M- population: erlotinib could not be recommended for the EGFR-TK mutation-negative population for whom treatment with docetaxel is suitable. For whom docetaxel is unsuitable, the most plausible ICER is likely to be over £50 000 per QALY gained compared with best supportive care. Therefore, the Committee concluded that erlotinib could not be recommended for this population.
- (Confidential) prices:
 - "For erlotinib, the manufacturer has agreed a patient access scheme with the Department of Health. The level of discount is commercial in confidence."²³¹

Reference Costs (list prices & remarks)	Population, Intervention & comparator IC, IE and ICERs	Remarks on use of generic utility instrument (e.g. EQ- 5D) to measure impact on QoL in economic evaluations	Most uncertain variables or important variables in sensitivity analysis
Erlotinib and gefitinib			
NICE, TA374 (2015) ²³¹ Greenhalgh (2015) ²³²	Patients with locally advanced or metastatic non-small-cell lung cancer that has progressed after prior chemotherapy. Three distinct populations are modelled: EGFR-TK mutation-positive; EGFR-TK mutation-negative; and EGFR-TK mutation-unknown population. EGFR-TK mutation-positive population: No clinical trials. EGFR-TK mutation-negative population: erlotinib compared with best supportive care and docetaxel EGFR-TK mutation-unknown population: erlotinib compared with best supportive care Gefitinib: no economic evaluation was performed for this drug.		
List prices, negotiated discounts are hidden.	Base-case deterministic cost-effectiveness results (Commercial-in-confidence information has been removed):	No utilities were available from direct head-to-head trials comparing the interventions under consideration	Use of generic docetaxel. Changes in utility values. Survival model parameters.
Drug costs per cycle:	A) Erlotinib vs. docetaxel second-line treatment in the EGFR M– population		
Docetaxel:	Costs IC QALYs IE ICER		
BNF prices: £922.81	Docetaxel £13 504 0.5930		
eMit prices: £44.88*	Erlotinib £14 049 £545 0.4863 -0.1067 dominated		
Erlotinib (30d) £1631.53			
Gefitinib: £12 200 / patient**	B) Erlotinib vs. BSC second-line treatment in the EGFR M– population		
	Costs IC QALYs IE ICER		
	BSC £8075 0.3416		
	Erlotinib £14 437 £6362 0.4579 0.1163 £54 687		



C) Erlotinib vs. BSC second-line treatment in the EGFR unknown population

	Costs	IC	QALYs	IE	ICER
BSC	£8133		0.3452		
Erlotinib	£14 446	£6314	0.4484	0.1033	£61 162

Conclusion: see text.

BSC: best supportive care; EGFR M-: Epidermal growth factor mutation-negative

* The eMit provides estimated mean product prices for generic medicines drawn from information from about 95% of NHS trusts.²³²

** Patient access scheme price per patient applies only to patients receiving treatment beyond 60 days.²³²

Appendix 9.4.2.7. NICE, TA258 (2012): erlotinib

- QoL:
 - “EQ-5D was not used to measure HRQoL in EURTAC²⁵⁷ or IPASS.^{258”²³⁴}
 - “The Committee noted the lack of quality of life data from the EURTAC trial and heard from the clinical specialists that a common problem with studies in this patient population is the failure to complete questionnaires.”²³³
 - “The manufacturer undertook a review of the literature to identify relevant HRQoL data for use in the economic evaluation. The manufacturer concluded that there was an absence of relevant utility estimates and adopted utility estimates from a single study by Nafees.^{256”²³⁴}
- Results:
 - The base case incremental results generated by the manufacturer's model provide an ICER of £21 874 per QALY gained. Disaggregated results were confidential.
 - However, “in the Committee's view, the survival benefit for erlotinib compared with gefitinib was uncertain.”²³³ Differences in (confidential) costs were considered further in the analysis.
- Uncertainty/sensitivity:
 - “There was no evidence from a direct comparison of erlotinib and gefitinib.”²³³ “The Committee noted that the overall survival data from the trials were incomplete. The Committee was not convinced of a survival benefit for erlotinib compared with gefitinib.”²³³
 - “In the Committee's view the main factors affecting cost-effectiveness were the difference in efficacy between erlotinib and gefitinib and the proportion of patients incurring the fixed charge for gefitinib under the patient access scheme.”²³³



- Conclusions:
 - “The Committee concluded there was insufficient evidence to suggest a difference in clinical effectiveness between erlotinib and gefitinib and it heard from clinical specialists that erlotinib and gefitinib are very similar treatments with similar efficacy. The Committee concluded that the cost effectiveness of erlotinib compared with gefitinib could be best assessed from the updated economic model which assumes equal clinical benefit for the treatments and focuses on their differential costs.”²³³ “The results from the economic model showed that on balance the sums of money lost or saved are small given the uncertainties in the analysis, and so it recommended erlotinib as a treatment option.”²³³
 - “The Committee concluded that at the price agreed under the patient access scheme (as revised in 2012) erlotinib should be recommended as an option for the first-line treatment of locally advanced or metastatic EGFR-TK mutation-positive NSCLC.”²³³
- (Confidential) prices:
 - The Committee noted the patient access scheme (as revised in 2012) for erlotinib based on a confidential discount on the list price.



Reference Costs (list prices & remarks)	Population, Intervention & comparator IC, IE and ICERs						Remarks on use of generic utility instrument (e.g. EQ- 5D) to measure impact on QoL in economic evaluations	Most uncertain variables or important variables in sensitivity analysis
Erlotinib								
NICE, TA258 (2012) ²³³ Greenhalgh (2011) ²³⁴	Patients with first-line treatment of locally advanced or metastatic EGFR-TK mutation-positive non-small-cell lung cancer. Erlotinib is compared with gefitinib Remark: ERG comment – no comparison with pemetrexed is made.							
List prices, negotiated discounts are hidden.	Results from the <u>manufacturer's base-case analyses (including the discount)</u> under the patient access scheme as revised in 2012):						No generic utility instrument applied in the underlying studies.	Efficacy data Proportion of patients incurring the fixed charge for gefitinib under the PAS.
		Costs	IC	QALYs	IE	ICER		
Drug costs per cycle: Erlotinib (30d) £1631.53 Gefitinib: £12 200 / patient*	Gefitinib	£16 046		1.015				
	Erlotinib	Conf.	Conf.	Conf.	Conf.	£21 874		
	Remark: Impact of patient access scheme (PAS) on the ICER: without the confidential discount, the ICER is £74 300 per QALY gained. Remark: The Committee concluded that the cost effectiveness of erlotinib compared with gefitinib could be best assessed from the updated economic model which assumes equal clinical benefit for the treatments and focuses on their differential costs.							
	Conclusion: The Committee agreed that the results from the economic model showed that on balance the sums of money lost or saved are small given the uncertainties in the analysis, and so it recommended erlotinib as a treatment option.							

Conf.: confidential; EGFR-TK: epidermal growth factor receptor tyrosine kinase; PAS: patient access scheme.

* there is a single fixed cost of £12 200 per patient when the third monthly pack of gefitinib is supplied.



Appendix 9.4.2.8. NICE, TA227 (2011): erlotinib

- QoL:
 - No generic utility instrument is used in the underlying trials. The same utility values are used for PFS health state and progressed health state as those used in a previous NICE technology appraisal guidance (TA190, 'Pemetrexed for the maintenance treatment of non-small-cell lung cancer').²³⁵
- Results:
 - "The Committee considered that the most plausible ICERs for erlotinib compared with best supportive care would be higher than those estimated by the ERG (£44,800 and £68,100 per QALY gained for treatment of patients with squamous and non-squamous disease respectively), and considerably higher than £50,000 per QALY gained for treatment of the whole stable disease population."²³⁵
 - "The Committee discussed evidence for the cost effectiveness of erlotinib compared with pemetrexed. It noted that this was based on the manufacturer's new economic analysis in which various relative efficacy scenarios were modelled because of the lack of data for erlotinib compared directly with pemetrexed. The Committee considered that erlotinib was likely to be associated with cost savings per QALY lost compared with pemetrexed in patients with stable, non-squamous disease, but that it was not possible to establish a robust estimate."²³⁵
- Uncertainty/sensitivity:
 - "The Committee acknowledged that the factors that had the greatest effect on the manufacturer's new ICERs were assumptions about how much time a patient spent on treatment in the progression-free health state, and the costs attributed to best supportive care."²³⁵
- Conclusions:
 - "The Committee concluded that erlotinib could not be considered a cost-effective use of NHS resources when used as monotherapy for maintenance treatment in patients with locally advanced or metastatic non-small-cell lung cancer who have stable disease following platinum-based first-line chemotherapy."²³⁵
 - The Committee agreed that "no specific recommendation could be made related to the use of erlotinib compared with pemetrexed."²³⁵
- (Confidential) prices:
 - "Erlotinib is given orally at a recommended dose of 150 mg/day. The normal acquisition cost of a pack of 30 tablets (150 mg) is £1631.53 (excluding VAT; 'British national formulary' [BNF] edition 60). The manufacturer of erlotinib has agreed a patient access scheme with the Department of Health in which the acquisition cost of erlotinib is reduced by 14.5% and deducted at the time of supply to the NHS (that is, £1394.96 for a pack of 30 tablets [150 mg])."²³⁵



Reference	Costs (list prices & remarks)	Population, Intervention & comparator IC, IE and ICERs						Remarks on use of generic utility instrument (e.g. EQ-5D) to measure impact on QoL in economic evaluations	Most uncertain variables or important variables in sensitivity analysis
Erlotinib									
NICE, TA227 (2011) ²³⁵ Dickson (2011) ²³⁶		Patients with locally advanced or metastatic non-small-cell lung cancer who have stable disease after platinum-based first-line chemotherapy. Based on clinical grounds, the squamous and non-squamous populations were considered separately. Erlotinib versus best supportive care or pemetrexed.							
	List prices and negotiated price for erlotinib, including a discount of 14.5%: Drug costs per cycle Erlotinib: List price (30d): £1631.53 PAS (30d): £1394.96	Results of the incremental analysis (with PAS): A) Stable, squamous disease Costs IC QALYs IE ICER BSC £9233 0.5077 Erlotinib £16 362 £7129 0.6668 0.1591 £44 812 B) Stable, non-squamous disease Costs IC QALYs IE ICER BSC £9808 0.6998 Erlotinib £18 148 £8340 0.8222 0.1224 £68 120 Pemetrexed £26 608 £8460 0.9229 0.1007 £84 029						No generic utility instrument is used in the underlying trials.	Time on treatment in PF health state. Cost BSC.

BSC: best supportive care.



Appendix 9.4.2.9. NICE, TA192 (2010): gefitinib

- QoL:
 - “Treatment with gefitinib may reduce the amount of time spent in hospital towards the end of life, which is likely to be important for patients' quality of life and for their carers. The Committee concluded that these benefits were not fully captured in the utility values used in the economic model. The Committee concluded that these quality of life benefits were an important aspect of treatment with gefitinib and that taking these into account would have reduced the ICERs for gefitinib.”²³⁷ Unfortunately, “EQ-5D was not used to measure HRQoL in IPASS.”²³⁸ “The manufacturer undertook a review of the literature to identify relevant HRQoL data for use in the economic evaluation. The manufacturer concluded that there was an absence of relevant utility estimates and adopted utility estimates from a single UK study by Nafees.”²⁵⁶²³⁸ “The Committee was aware that the manufacturer used utility estimates from a study examining second-line chemotherapy for patients with NSCLC,”²³⁷ while the economic evaluation included chemotherapy-naïve patients.
- Results:
 - “In the manufacturer's base case [including a patient access scheme], the incremental cost-effectiveness ratios (ICERs) for EGFR-TK mutation-positive patients ranged from £19,402 per QALY gained (gefitinib compared with paclitaxel and carboplatin) to £35,992 per QALY gained (gefitinib compared with vinorelbine and cisplatin) using a 16.6% prevalence for EGFR-TK mutation.”²³⁷
 - “The ERG's revised base-case analysis indicated that ICERs ranged from £59,016 to £72,908 per QALY gained depending on the comparator used. The ERG highlighted that it appeared from this analysis that gefitinib was dominated by pemetrexed and cisplatin (that is, gefitinib was both more expensive and less effective).”²³⁷
- Uncertainty/sensitivity:
 - “There is considerable uncertainty around both the manufacturer's and the ERG's methods of extrapolating overall survival data.”²³⁷ “There was uncertainty about the costs of first-line chemotherapy and the number of cycles of first-line chemotherapy used in the model.”²³⁷ “There was uncertainty around the sensitivity of the ICER for gefitinib to the prevalence of EGFR-TK mutations (which the manufacturer varied between 5% and 17%), the number of EGFR-TK mutation tests and the associated cost.”²³⁷ The results of the cost-effectiveness analysis were sensitive to the following parameters: overall survival, progression-free survival and the maximum number of chemotherapy cycles.²³⁷
 - “Major weaknesses in the clinical section of the manufacturer's submission identified by the ERG include: (i) the clinical results of IPASS²⁵⁸ are not generalisable to the majority of patients with NSCLC in clinical practice in England and Wales; and (ii) to date, there are no direct clinical trial data to demonstrate that use of gefitinib as a first-line treatment by EGFR M+ patients leads to improved OS compared with the use of paclitaxel/carboplatin.”²³⁹
 - Further research: “There is a need for directly relevant evidence of clinical effectiveness for this new technology. Ideally this would involve at least one additional RCT involving a substantial proportion of Caucasian patients, preferably with a significant UK element, compared to at least one of the treatments currently recommended by NICE for first-line CTX [chemotherapy] for patients with NSCLC and would include EGFR testing of all patients.”²³⁹



- Conclusions:
 - “The Committee concluded that it was not possible to make a judgement about the most appropriate method for applying the hazard ratios and noted the differences in the ICERs depending on the method used. Taking into account this uncertainty, together with advice received on the variation in the number of chemotherapy cycles received by patients, and the probable underestimation in the modelling of quality-of-life benefits associated with gefitinib, the Committee agreed that the results of the ERG’s additional analyses comparing gefitinib with pemetrexed plus cisplatin suggested, on balance, that gefitinib would be cost effective. The Committee concluded that based on the available evidence and the fixed price agreed under the patient access scheme, gefitinib is a cost-effective use of NHS resources for the first-line treatment of locally advanced or metastatic NSCLC in EGFR-TK mutation-positive patients.”²³⁷
- (Confidential) prices:
 - “The manufacturer has agreed with the Department of Health a patient access scheme in which gefitinib for first-line treatment of NSCLC will be available at a single fixed cost of £12,200 per patient irrespective of the duration of treatment. The manufacturer will not invoice the NHS until the third monthly pack of gefitinib is supplied.”²³⁷

Reference Costs (list prices & remarks)	Population, Intervention & comparator IC, IE and ICERs	Remarks on use of generic utility instrument (e.g. EQ- 5D) to measure impact on QoL in economic evaluations	Most uncertain variables or important variables in sensitivity analysis
Gefitinib			
NICE, TA192 (2010) ²³⁷ Brown (2009) ²³⁸	Chemotherapy-naïve patients with locally advanced or metastatic non-small-cell lung cancer (NSCLC). The decision problem focused on EGFR-TK mutation-positive patients. Intervention: gefitinib Comparator: The manufacturer limits consideration to four different chemotherapy combinations: paclitaxel/carboplatin; gemcitabine/cisplatin; gemcitabine/carboplatin and vinorelbine/cisplatin. The ERG also adds docetaxel/cisplatin and pemetrexed/cisplatin as relevant comparators.		
Gefitinib PAS: Gefitinib: £12 200 / patient* Drug costs per cycle:** manufacturer ERG	Results of the incremental analysis (with PAS): A) Manufacturer's base case: the IC, IE & ICER are those of Gef/Car versus the included comparators.	No EQ-5D used in the underlying trial. Absence of relevant utility estimates in the literature.	Extrapolation survival data. Costs first-line chemotherapy. Prevalence EGFR-TK mutation and associated test costs.
Gem/Car: Man. £999 ERG £940	Gef/Car Comparator: Gem/Car	Costs Conf. 1.1110	
Pac/Car: Man. £1489	Pac/Car Vin/Cis	£27,902 £8,024	0.9235 0.2229
		£3,666 £3,637 £20,744 £19,402 £35,992	0.1767 0.1874



ERG	£838	Gem/Cis	£4,138	0.1445	£28,633		
Vin/Cis:							
Man.	£403	B) Results after amendments made by ERG to the manufacturer's model: the IC, IE & ICER are those of Gef/Car versus the included comparators.					
ERG	£346						
Gem/Cis:							
Man.	£793		Costs	IC	QALYs	IE	ICER
ERG	£820	Gef/Car	Conf.		1.2223		
Doc/Cis:		Comparator:					
Man.	N/A	Gem/Car		£7,554		0.1253	£60,273
ERG	£1081	Pac/Car	£24,574	£8,746	1.0988	0.1235	£70,822
Pem/Cis:		Vin/Cis		£8,842		0.1256	£70,390
Man.	N/A	Gem/Cis		£7,322		0.1241	£59,016
ERG	£1536	Doc/Cis		£6,285		0.0862	£72,908
		Pem/Cis		£1,574		-0.0560	dominated

Conf.: confidential; Doc/Cis: Docetaxel/cisplatin; ERG: Evidence Review Group; Gef/Car: Gefitinib/carboplatin; Gem/Car: Gemcitabine/carboplatin; Gem/Cis: Gemcitabine/cisplatin; Man.: manufacturer. Pac/Car: Paclitaxel/carboplatin; Pem/Cis: Pemetrexed/cisplatin; Vin/Cis: Vinorelbine/cisplatin;

* There is a single fixed cost of £12 200 per patient when the third monthly pack of gefitinib is supplied.

** Differences in costs per cycle are related to different assumed doses (see full report for further details).²³⁸



Appendix 9.4.2.10. NICE, TA484 (2017): nivolumab

- QoL:
 - “The committee noted that EQ-5D data were collected in CheckMate 057 and these results were used in the company's model to calculate the utility values. The committee noted the ERG's view on the utility values and its comment that in the study, completion rates for filling out EQ-5D questionnaires declined over time. The ERG highlighted that this might have resulted in selection bias and could have influenced the utility values.” “The committee considered that, in its final revised modelling approach, the company changed the utility values and applied the committee's preferred values.”²⁴⁰
- Results:
 - Comparison with docetaxel: after including several corrections, “the most plausible ICER for nivolumab compared with docetaxel changed to £49,160 per QALY gained the full non-squamous NSCLC population.”²⁴⁰
 - Comparison with nintedanib and docetaxel: “The committee considered the cost-effectiveness estimates of nivolumab compared with nintedanib plus docetaxel for treating locally advanced or metastatic NSCLC that has progressed after chemotherapy in adults. The committee noted that the most plausible cost-effectiveness estimate, which included the committee's preferred assumptions and the confidential patient access schemes for nivolumab and nintedanib, resulted in an ICER above £100,000 per QALY gained (the exact ICER is commercial in confidence so cannot be reported here).”²⁴⁰
 - Comparison with BSC: “The committee noted that neither the company nor the ERG presented cost-effectiveness results comparing nivolumab with BSC.”²⁴⁰
 - “On request, the company presented cost-effectiveness results including subgroup analyses based on PD-L1 expression. ... The results of the subgroup analyses were considered as commercial in confidence, so the exact ICERs cannot be reported here. ... Having concluded that nivolumab had shown no convincing overall-survival benefit compared with docetaxel for patients whose tumours were PD-L1 negative or in whom the PD-L1 level was unquantifiable in the clinical evidence presented to it, the committee considered it reasonable to exclude those patients from the cost-effectiveness considerations. Considering that the most plausible ICER ... for the full non-squamous NSCLC population was £49,160 per QALY gained ..., it considered it reasonable to recommend nivolumab for inclusion in the Cancer Drugs Fund for people with tumours that are PD-L1 positive.”²⁴⁰
- Uncertainty/sensitivity:
 - “The committee considered the following key areas of uncertainty: the methods used for extrapolating overall survival; the methods used for extrapolating progression-free survival; utility values used in the model for the progression-free and progressed-disease health states; duration of the continued benefit of nivolumab; application of a 2-year clinical stopping rule.”²⁴⁰ “The committee noted that the approaches used by the company and the ERG to extrapolate overall survival had a major effect on the results of the economic model.”²⁴⁰
- Conclusions:
 - The committee “did not recommend nivolumab as a cost-effective use of NHS resources for treating locally advanced or metastatic non-squamous NSCLC after chemotherapy in people for whom nintedanib plus docetaxel is an option.”²⁴⁰
 - “There was no ICER presented for nivolumab compared with BSC and the committee did not make a recommendation for people who cannot have docetaxel and for whom BSC would be the only treatment option.”²⁴⁰



- Subgroup of patients with PD-L1-positive tumours: “The committee took into account the company's further new analysis which included a 3-year data cut from CheckMate 057, a new commercial access agreement and new clinical data. It concluded that nivolumab had shown plausible potential for cost effectiveness for the subgroup of patients with PD-L1-positive tumours compared with docetaxel and with nintedanib plus docetaxel. It therefore recommended nivolumab for treating locally advanced or metastatic non-squamous NSCLC in adults after chemotherapy for use within the Cancer Drugs Fund, only if their tumours are PD-L1 positive and the conditions of the managed access agreement are followed. For nivolumab compared with BSC, the committee was not able to make a recommendation because it has not been presented with cost-effectiveness results for this population.”²⁴⁰
- (Confidential) prices:
 - “There is a patient access scheme for nintedanib which is a confidential simple discount. The committee noted that the company had proposed a revised patient access scheme for nivolumab which was replaced with a managed access agreement. The financial terms of the agreement are commercial in confidence.”²⁴⁰



Reference Costs (list prices & remarks)	Population, Intervention & comparator IC, IE and ICERs	Remarks on use of generic utility instrument (e.g. EQ- 5D) to measure impact on QoL in economic evaluations	Most uncertain variables or important variables in sensitivity analysis
Nivolumab			
NICE, TA484 (2017) ²⁴⁰	Patients with previously treated locally advanced or metastatic non-squamous non-small-cell lung cancer. Nivolumab compared with docetaxel, nintedanib plus docetaxel, and BSC.		
List prices, negotiated discounts are hidden.	Results of the incremental analysis (including a new commercial access agreement):	EQ-5D data were collected in CheckMate 057 (with a decline in completing the questionnaires over time).	Extrapolation OS & PFS Utility values
Drug costs per month: Nivolumab (4 weeks) £5268	A) Full non-squamous NSCLC population: nivolumab compared with docetaxel:		Duration of continued benefit of nivolumab
	Costs IC QALYs IE ICER		Treatment duration (application 2-year stopping rule)
	Docetaxel Conf. Conf. Conf. Conf.		
	Nivolumab Conf. Conf. Conf. Conf. £49 160		
	B) Locally advanced or metastatic NSCLC that has progressed after chemotherapy		
	Costs IC QALYs IE ICER		
	Nintedanib +Doc. Conf. Conf. Conf. Conf.		
	Nivolumab Conf. Conf. Conf. Conf. >£100 000		
	Remark: no results comparing nivolumab with BSC.		
	Remark: subgroup analyses based on PD-L1 expression → confidential results.		

Doc.: docetaxel; OS: overall survival; PFS: progression-free survival.



Appendix 9.4.2.11. NICE, TA483 (2017): nivolumab

- QoL:
 - “In CheckMate 017, data were collected using the EQ-5D questionnaire and response rates were low, which suggests self-selection bias. This bias may have been due to the fact that those patients who were very sick were unable, or unwilling, to complete the questionnaires.”²⁴² “The committee noted limitations in this evidence. It considered that the negative correlation between the EQ-5D score and the number of respondents strongly suggested that the results were influenced by selection bias, that is, the people who completed the EQ-5D (particularly at later time points) did not represent the wider population.”²⁴¹
 - The utilities measured in the two treatment arms at the different moments in time are not published. “Although EQ-5D data were collected in the CheckMate 017 trial, the response rates were poor and patchy. Only ***** of randomised patients completed the baseline EQ-5D assessment, and participation (relative to the number of patients still progression-free) fell to ***** at *****, ***** at ***** and ***** at *****.”²⁴²
- Results:
 - “The committee concluded that given its preferred assumptions, the incorporation of 3-year clinical-effectiveness data, the commercial access agreement and the DSU's corrections, nivolumab had shown plausible potential for cost effectiveness, based on an ICER of £50,014 per QALY gained.”²⁴¹
 - This contrast with the results from the underlying HTA report: “After all of the ERG's modifications have been made to the company's model, both the ERG's estimated ICER (£132,989 per QALY gained) and the company's ICER (£85,950 per QALY gained) exceed the willingness to pay thresholds employed in the appraisal of other treatments considered under NICE's end of life criteria.”²⁴²
- Uncertainty/sensitivity:
 - “The committee considered the following key areas of uncertainty: the methods used for extrapolating overall survival; the methods used for extrapolating progression-free survival; utility values used in the model for the progression-free and progressed-disease health states; application of a 2-year clinical stopping rule; duration of the continued benefit of nivolumab.”²⁴¹
 - “The committee noted that the approaches used by the company and the ERG to extrapolate overall survival had a major effect on the results of the economic model, and were a key difference between the company's analyses and the ERG's exploratory and revised analyses.”²⁴¹
- Conclusions:
 - “Having concluded that nivolumab for locally advanced or metastatic squamous NSCLC after chemotherapy could not be recommended for routine use, the committee then considered whether it could be considered for inclusion in the Cancer Drugs Fund.”²⁴¹
 - “The committee took into account the company's further new analysis, which included a 3-year data cut from CheckMate 017 and a new commercial access agreement. It concluded that based on the clinical evidence presented at the fifth appraisal committee meeting it would not be reasonable to differentiate between subgroups according to PD-L1 expression, and an ICER of £50,014 per QALY gained for the full squamous NSCLC population, nivolumab had shown plausible potential for cost effectiveness. It therefore recommended nivolumab for treating locally advanced or metastatic



squamous NSCLC in adults after chemotherapy for use within the Cancer Drugs Fund, only if the conditions of the managed access agreement are followed.”²⁴¹

- (Confidential) prices:
 - “The committee noted that the company had proposed a revised patient access scheme which was replaced with a managed access agreement. The financial terms of the agreement are commercial in confidence.”²⁴¹
 - “Chemotherapy regimens used as comparators to nivolumab, or for subsequent post-progression additional lines of treatment are all assigned unit costs in the company model based on published list prices. In many cases these products may be obtained at lower cost to the NHS either as generic equivalent products, or based on NICE-approved patient access scheme discounted prices.”²⁴²



Reference Costs (list prices & remarks)	Population, Intervention & comparator IC, IE and ICERs						Remarks on use of generic utility instrument (e.g. EQ- 5D) to measure impact on QoL in economic evaluations	Most uncertain variables or important variables in sensitivity analysis
Nivolumab								
NICE, TA483 (2017) ²⁴¹	Patients with previously treated locally advanced or metastatic squamous non-small-cell lung cancer							
Fleeman (2015) ²⁴²	Nivolumab compared with docetaxel.							
List prices, negotiated discounts are hidden.	Results of the incremental analysis (with list prices):						EQ-5D data were collected but problems with completion rates over time.	OS extrapolation PFS extrapolation Utility values PFS & PD Stopping rule nivolumab Duration continued benefit nivolumab.
Drug costs per month or cycle: Nivolumab (4 weeks) £5268 Docetaxel (3 weeks) £900	A) Company's base case published in Fleeman, 2015:							
		Costs	IC	QALYs	IE	ICER		
	Docetaxel	£21 243		0.539				
	Nivolumab	£86 599	£65 355	1.299	0.760	£85 950		
	B) ERG's revised base case published in Fleeman, 2015:							
		Costs	IC	QALYs	IE	ICER		
	Docetaxel	£12 780		0.332				
	Nivolumab	£60 292	£47 512	0.689	0.357	£132 989		
Results of the incremental analysis (including commercial access agreement as published in NICE, TA483):								
		Costs	IC	QALYs	IE	ICER		
	Docetaxel	NA		NA				
	Nivolumab	NA	NA	NA	NA	£50 014		

PD: progressed disease; PFS: progression-free survival.



Appendix 9.4.2.12. NICE, TA600 (2019): pembrolizumab

- QoL:
 - “The company clarified that the EQ-5D-3L questionnaire was used [in KEYNOTE-407 study] to inform HRQoL parameters in the model.”²⁴⁴ However, results were kept confidential: “No significant difference between treatment groups was noted using the EQ-5D VAS at week 9. At week 18, a statistically significant difference in EQ-5D scores was noted (least squares mean [LSM] ****, 95% CI *****, p=*****) with the pembrolizumab combination group showing a slight increase over baseline (LSM ****, 95% CI *****), and the control group showing a slight decrease (LSM ****, 95% CI *****). Results for the EQ-5D questionnaire were not reported in the CS.”²⁴⁴
 - The committee also noted “the issue of informative censoring (because EQ-5D assessments for people whose disease progressed were done only shortly after disease progression) for the progressed population in KEYNOTE-407.”²⁴³
- Results:
 - “Because the clinical evidence is immature, the cost-effectiveness estimates for pembrolizumab combination therapy are very uncertain.”²⁴³
 - “Based on a fully incremental analysis of the company’s model, including the correction of model errors identified by the ERG during the clarification process, the ICER for pembrolizumab combination therapy versus cisplatin/carboplatin plus gemcitabine is estimated to be £51,240 per QALY gained”²⁴⁴
 - “The ICER (recalculated by the ERG to include the confidential commercial arrangements for pembrolizumab and subsequent treatments) was higher than £50,000 per quality-adjusted life year (QALY) gained. However, the ICER was considered highly uncertain. This was because of the short duration of interim KEYNOTE-407 data and concerns that subsequent treatment benefits in the standard chemotherapy arm were not adequately captured in the modelling. The committee concluded that the most plausible ICER was above £50,000 per QALY gained but considered this estimate to be highly uncertain.”²⁴³
- Uncertainty/sensitivity:
 - “The ERG considers there to be considerable uncertainty surrounding the expected long-term survival of patients receiving pembrolizumab combination therapy or SC chemotherapy (including those who go on to receive second-line immunotherapy). ... The ERG’s exploratory analyses indicate that the use of alternative parametric OS models may substantially increase the ICER for pembrolizumab combination therapy compared with the company’s base case estimates.”²⁴⁴
- Conclusions:
 - “The committee decided that the ICER was not within the range usually considered a cost-effective use of resources. The committee concluded not to recommend pembrolizumab combination therapy for routine use in adults with untreated metastatic squamous NSCLC.”²⁴³
 - “Pembrolizumab combination therapy has the potential to be cost effective, but more evidence is needed to address the clinical uncertainties. Therefore, it is recommended for use in the Cancer Drugs Fund for untreated metastatic squamous NSCLC in adults.”²⁴³



- (Confidential) prices:
 - “The company has a commercial arrangement. This makes pembrolizumab available to the NHS with a discount.”²⁴³

Reference Costs (list prices & remarks)	Population, Intervention & comparator IC, IE and ICERs	Remarks on use of generic utility instrument (e.g. EQ- 5D) to measure impact on QoL in economic evaluations	Most uncertain variables or important variables in sensitivity analysis																																																
Pembrolizumab																																																			
NICE, TA600 (2019) ²⁴³ Uttley (2018) ²⁴⁴	Patients with untreated metastatic squamous non-small-cell lung cancer. Pembrolizumab in combination with carboplatin plus paclitaxel/nab-paclitaxel (pembrolizumab combination therapy) compared with: <ul style="list-style-type: none">- Within the overall squamous PD-L1 unselected NSCLC population: Carboplatin plus paclitaxel/nab-paclitaxel; Cisplatin/carboplatin plus docetaxel; Cisplatin/carboplatin plus gemcitabine; Cisplatin/carboplatin plus paclitaxel.- Within the company's PD-1L subgroup analyses: Carboplatin plus paclitaxel/nab-paclitaxel (PD-L1 TPS<1%, 1-49% and ≥50% subgroups); Pembrolizumab monotherapy (PD-L1 TPS ≥50% subgroup only).																																																		
List prices, negotiated discounts are hidden.	Results of the incremental analysis (including confidential price for pembrolizumab): ERG corrected results of pembrolizumab combination therapy and all comparators, deterministic model:	EQ-5D is used in the KEYNOTE-407 trial, but there is an issue of informative censoring.	OS extrapolation The best treatment duration is unknown.																																																
Drug costs per 3-week cycle: Pembrolizumab comb. ther.:	<table><thead><tr><th></th><th>Costs</th><th>IC</th><th>QALYs</th><th>IE</th><th>ICER</th></tr></thead><tbody><tr><td>confidential</td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>Pembrolizumab</td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>combination</td><td>£72 695</td><td>£43,389</td><td>2.95</td><td>0.85</td><td>£51 240</td></tr><tr><td>Plat.+gem.</td><td>£29 306</td><td>£4,572</td><td>2.11</td><td>0.49</td><td>£9401</td></tr><tr><td>Plat.+pac.</td><td>£24 734</td><td>£606</td><td>1.62</td><td>0.07</td><td>£8243</td></tr><tr><td>Plat.+doc.</td><td>£24 128</td><td>-</td><td>1.55</td><td>0.82</td><td>-</td></tr><tr><td>Carb.+pac/np.</td><td>£24 417</td><td>-</td><td>1.27</td><td>-</td><td>dominated</td></tr></tbody></table>		Costs	IC	QALYs	IE	ICER	confidential						Pembrolizumab						combination	£72 695	£43,389	2.95	0.85	£51 240	Plat.+gem.	£29 306	£4,572	2.11	0.49	£9401	Plat.+pac.	£24 734	£606	1.62	0.07	£8243	Plat.+doc.	£24 128	-	1.55	0.82	-	Carb.+pac/np.	£24 417	-	1.27	-	dominated		
	Costs	IC	QALYs	IE	ICER																																														
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Carboplatin+ paclitaxel/nab- paclitaxel: £576.69																																																			
Platinum+ docetaxel: £48.90																																																			
Platinum+ gemcitabine: £60.13																																																			
Platinum+ paclitaxel: £53.06																																																			
	Remark: The committee considered the subgroup analysis not robust enough for decision making. Therefore, the results of these subgroup analyses are not included in this table.																																																		

Carb.+pac/np.: Carboplatin+paclitaxel/ nab-paclitaxel; comb. ther.: combination therapy; Plat.+doc.: Platinum+docetaxel; Plat.+gem.: Platinum+gemcitabine; Plat.+pac.: Platinum+paclitaxel.



Appendix 9.4.2.13. NICE, TA557 (2019): pembrolizumab

- QoL:
 - EQ-5D VAS data were gathered in the underlying KEYNOTE-189 trial. “Overall, the ERG considered that the analysis was acceptable for understanding the short-term impact of pembrolizumab combination therapy, although is limited in quality due to high levels of missing data and the short follow-up time-point.”²⁴⁶ “By the 21 week follow-up, data was only available for 61.0% of patients in the pembrolizumab combination arm, and 51.1% of patients in the control arm.”²⁴⁶
 - Unfortunately, information related to HRQoL following treatment with pembrolizumab combination therapy was considered to be confidential. It is mentioned that “there was no statistically significant difference in the change in HRQoL in the two arms between baseline and 12 and 21 weeks follow-up. However, following adjustment for covariates (treatment by study visit interaction, PD-L1 $\geq 1\%$ vs. $<1\%$, platinum chemotherapy, and smoking status) and imputation to replace missing data, the analysis demonstrated a statistically significant difference in change in HRQoL between baseline and 12 and 21 weeks.”²⁴⁶ Mean utility values at baseline, week 12, week 21, and changes from baseline in both the pembrolizumab combination therapy and control group were confidential.
- Results:
 - “The most plausible ICERs for pembrolizumab combination compared with pemetrexed plus carboplatin or cisplatin are highly uncertain”²⁴⁵ “The committee considered the incremental cost-effectiveness ratios (ICERs) presented by the company which included the commercial arrangement for pembrolizumab. The ERG also incorporated the commercial arrangement for pemetrexed maintenance therapy. The exact ICERs cannot be reported because the commercial arrangements are confidential. ... The results of the ERG's preferred base case, ... gave an ICER below £50,000 per QALY gained. ... The committee was concerned that because the trial data are immature and overall survival has not been reached in the pembrolizumab combination arm ... it could not, with any certainty, conclude that the most plausible ICER is below £50,000 per QALY gained without further evidence.”²⁴⁵
 - “The most plausible ICERs for pembrolizumab combination compared with chemotherapy plus carboplatin or cisplatin are highly uncertain”²⁴⁵ “Using the ERG's preferred assumptions ... the ICERs ranged from below £50,000 per QALY gained for the comparison with gemcitabine plus carboplatin or cisplatin and above £50,000 per QALY gained for the comparison with vinorelbine plus carboplatin or cisplatin. ... The committee was aware that the results are not generated from a direct comparison The committee could not, with any certainty, conclude that the most plausible ICER is below £50,000 per QALY gained without further evidence.”²⁴⁵
 - “The most plausible ICERs for pembrolizumab combination compared with pembrolizumab monotherapy for people whose tumours express at least a 50% tumour proportion score are uncertain”²⁴⁵ In “ERG's base case, using the confidential commercial arrangements for pembrolizumab and pemetrexed maintenance therapy the ICER was below £30,000 per QALY gained. ... The committee was aware that the results are not generated from a direct comparison and more data on overall survival from KEYNOTE-189 would help to address some of this uncertainty. The committee could not, with any certainty, conclude that the most plausible ICER is below £30,000 per QALY gained without further evidence.”²⁴⁵



- Uncertainty/sensitivity:
 - “the best treatment duration with pembrolizumab combination was unknown and therefore a 2-year treatment stopping rule in line with the clinical and cost-effectiveness evidence is acceptable.”²⁴⁵
 - “The committee concluded that because of the short median duration of follow-up in the trial ..., they could not with any certainty, choose the most appropriate method for extrapolating the overall survival data.”²⁴⁵
- Conclusions:
 - “The committee considered that the ICERs were not all clearly within the range usually considered a cost-effective use of resources. The committee concluded not to recommend pembrolizumab combination for routine use in adults with untreated, metastatic, non-squamous NSCLC whose tumours have no EGFR- or ALK- positive mutations.”²⁴⁵
 - “The current cost-effectiveness results were very uncertain but some scenarios were within the range considered a cost-effective use of NHS resources. It agreed that with longer follow-up data on overall survival, pembrolizumab combination has the potential to be cost effective. The committee concluded that pembrolizumab combination met the criteria to be considered for inclusion in the Cancer Drugs Fund. It recommended pembrolizumab combination for use within the Cancer Drugs Fund as an option for untreated, metastatic, nonsquamous NSCLC, in adults whose tumours have no EGFR- or ALK- positive mutations, if treatment does not exceed 2 years and the conditions in the managed access agreement are followed.”²⁴⁵
- (Confidential) prices:
 - Pembrolizumab is available to the NHS with a discount. The size of the discount is commercial in confidence.²⁴⁵
 - The results presented in the report “include the agreed and tentative commercial access agreements (CAAs) for pembrolizumab. They do not include existing agreements for comparators.”²⁴⁶



Reference Costs (list prices & remarks)	Population, Intervention & comparator IC, IE and ICERs	Remarks on use of generic utility instrument (e.g. EQ- 5D) to measure impact on QoL in economic evaluations	Most uncertain variables or important variables in sensitivity analysis
Pembrolizumab			
NICE, TA557 (2019) ²⁴⁵ Griffin (2018) ²⁴⁶	Patients with untreated, metastatic, non-squamous non-small-cell lung cancer (NSCLC) whose tumours have no epidermal growth factor receptor (EGFR)- or anaplastic lymphoma kinase (ALK)-positive mutations. Pembrolizumab with pemetrexed and carboplatin or cisplatin (pembrolizumab combination) In comparison with: 1) Pemetrexed in combination with a platinum drug (carboplatin or cisplatin) = main comparison; 2) Chemotherapy (vinorelbine, gemcitabine, docetaxel, or paclitaxel) in combination with a platinum drug (carboplatin or cisplatin); 3) Pembrolizumab monotherapy.		
List prices, negotiated discounts are hidden.	ERG base case results: This includes the agreed and tentative commercial access agreements (CAAs) for pembrolizumab. They do not include existing agreements for comparators:	EQ-5D VAS used in the underlying KEYNOTE-189 trial. High levels of missing data. HRQoL values kept confidential.	Extrapolation of overall survival data. Optimal treatment duration pembrolizumab.
Drug costs per administration (assuming no wastage):	A) Whole population, main comparison (deterministic)		
	Costs IC QALYs IE ICER		
Pembrolizumab (3w): £5260	PC £86 863	2.35	
Docetaxel (3w): £25.01	SoC £44 409 £42 454	1.22 1.13	£37 622
Gemcitabine (3w): £35.07	B) Whole population, other comparisons		
Paclitaxel (3w): £23.75	Costs IC QALYs IE ICER		
Vinorelbine (1w): £15.08	PC £86 863	2.35	
Carboplatin (3w): £30.13	Plat. + Gem. £27 292 £59 571	0.93 1.43	£41 710
Cisplatin (3w): £12.16	Plat. + Vin. £28 917 £57 946	1.35 1.00	£57 939
Pemetrexed (3w): £1448	Plat. + Doc. £28 662 £58 201	1.10 1.26	£46 337
	Plat. + Pacl. £25 937 £60 926	0.83 1.52	£40 096
	C) TPS>=50% sub-population, vs. pembrolizumab monotherapy		
	Costs IC QALYs IE ICER		
	PC £106 292	3.11	
	Pemb. mono. £75 796 £30 496	2.25 0.86	£35 695

1w: 1 week; 3w: 3 weeks; PC: Pembrolizumab combination; Pemb. mono.: Pembrolizumab monotherapy; Plat. + Doc.: Platinum + Docetaxel; Plat. + Gem.: Platinum + Gemcitabine; Plat. + Pacl.: Platinum + Paclitaxel; Plat. + Vin.: Platinum + Vinorelbine; SoC: Standard of Care



Appendix 9.4.2.14. NICE, TA531 (2018): pembrolizumab

- QoL:
 - “The committee discussed the utility data used in the company model. It noted that EQ-5D data were collected in KEYNOTE-024; these data are the preferred measure of health-related quality of life in adults. The utility values for pembrolizumab and standard care were pooled (adjusted for age) and divided into 4 groups based on time to death (from less than 30 days to at least 360 days).”²⁴⁷ “The ERG highlighted that the utilities derived from KEYNOTE-024 were also implausibly high; the values at 360 days before death were higher than the UK population norm for people of the same age.”²⁴⁷
- Results:
 - “The decision-making ICERs cannot be presented because they include the commercial access agreement reduction for pemetrexed. ... [The committee] agreed that the ICERs, ranging from £30,000 per QALY gained to less than £50,000 per QALY gained, on which it was basing its decision were associated with uncertainty, particularly for overall survival and the duration of treatment effect. The committee concluded that all the scenarios presented were plausible. Therefore, the most plausible cost-effectiveness estimate was likely to be between the ranges presented by the company and the ERG.”²⁴⁷
 - In the underlying report,²⁴⁸ information on costs, QALYs, incremental costs, incremental QALYs and ICERs per QALY gained are kept confidential.
- Uncertainty/sensitivity:
 - “The committee noted that the most plausible cost-effectiveness estimates were associated with uncertainty, particularly for overall survival and the duration of treatment effect.”²⁴⁷
 - “The committee noted that in the company's sensitivity analyses, the most influential parameter in the cost-effectiveness analysis was the extrapolation of overall survival in the pembrolizumab and standard care arms. ... The utility values for long-term survivors were the second most influential parameter in the cost-effectiveness analysis.”²⁴⁷
- Conclusions:
 - “The committee agreed that the most plausible ICER for pembrolizumab compared with standard care was likely to be within the range normally considered to be a cost-effective use of NHS resources. Therefore, it concluded that pembrolizumab could be recommended for routine use as an option for people with untreated PD-L1-positive metastatic NSCLC (with at least a 50% tumour proportion score) and no EGFR- or ALK-positive tumour mutations, only if pembrolizumab is stopped at 2 years of uninterrupted treatment, or earlier in the event of disease progression, and if the company provides pembrolizumab according to the commercial access agreement.”²⁴⁷
- (Confidential) prices:
 - The company has a commercial arrangement. This makes pembrolizumab available to the NHS with a discount. The size of the discount is commercial in confidence.



Reference Costs (list prices & remarks)	Population, Intervention & comparator IC, IE and ICERs	Remarks on use of generic utility instrument (e.g. EQ- 5D) to measure impact on QoL in economic evaluations	Most uncertain variables or important variables in sensitivity analysis
Pembrolizumab			
NICE, TA531 (2018) ²⁴⁷ Beale (2018) ²⁴⁸	Patients with untreated PD-L1-positive metastatic non-small-cell lung cancer. Pembrolizumab compared with standard care. Standard care therapies included platinum-based combinations with either gemcitabine or paclitaxel, and a platinum-based combination with pemetrexed.		
List prices, negotiated discounts are hidden. Pembrolizumab: the average cost of a course of treatment is £84 002 based on the list price.	The company's base-case ICER was £30 244 per QALY gained. The company also explored alternative assumptions about the period of treatment benefit associated with pembrolizumab treatment; these scenarios gave ICERs ranging from £30 244 to £44 483 per QALY gained. The decision-making ICERs cannot be presented because they include the commercial access agreement reduction for pemetrexed.	EQ-5D data were collected in KEYNOTE-024.	Overall survival Duration of treatment effect Utility values.

**Appendix 9.4.2.15. NICE, TA428 (2017): pembrolizumab**

- QoL:
 - We did not identify a full HTA report with further details on QoL. “The committee concluded that the KEYNOTE-010 utility data were the most appropriate to inform decision-making and including a disutility for adverse events was appropriate.”²⁵⁹
- Results:
 - “the ICERs are sensitive to a continued treatment effect after stopping treatment, with a range when using the company's preferred assumptions of £61,954 to £44,490 per QALY gained ..., but concluded that within the uncertainties and with implementation of a 2-year stopping rule, the majority of plausible ICERs are below the range usually considered to be a cost-effective use of NHS resources.”²⁵⁹
- Uncertainty/sensitivity:
 - The key drivers of cost-effectiveness were the treatment duration and long-term treatment effect.²⁵⁹
- Conclusions:
 - “Pembrolizumab is recommended as an option for treating locally advanced or metastatic PD-L1-positive non-small-cell lung cancer in adults who have had at least one chemotherapy (and targeted treatment if they have an epidermal growth factor receptor [EGFR]- or anaplastic lymphoma kinase [ALK]-positive tumour), only if: [1] pembrolizumab is stopped at 2 years of uninterrupted treatment and no documented disease progression, and [2] the company provides pembrolizumab with the discount agreed in the patient access scheme revised in the context of this appraisal.”²⁵⁹
- (Confidential) prices:
 - “After guidance publication in January 2017, the company agreed a commercial access agreement with NHS England that replaces the patient access scheme on equivalent terms. The financial terms of the agreement are commercial in confidence.”²⁵⁹

Reference Costs (list prices & remarks)	Population, Intervention & comparator IC, IE and ICERs	Remarks on use of generic utility instrument (e.g. EQ-5D) to measure impact on QoL in economic evaluations	Most uncertain variables or important variables in sensitivity analysis
Pembrolizumab			
NICE, TA428 (2017) ²⁵⁹	Patients with PD-L1-positive non-small-cell lung cancer who received chemotherapy. Pembrolizumab compared with docetaxel.		
List prices, negotiated discounts are hidden. No full HTA report with further details was identified.	No full HTA report with further details was identified. The ICERs are sensitive to a continued treatment effect after stopping treatment, with a range when using the company's preferred assumptions of £61,954 to £44,490 per QALY gained.	No full HTA report with further details was identified.	Treatment duration Long-term treatment effect.



APPENDIX 10. OVARIAN CANCER

Appendix 10.1. BCR data

Appendix 10.1.1. Descriptive statistics

Appendix 10.1.1.1. Epithelial Ovarian Cancer, exploration

Table 135 – Epithelial ovarian cancer (2004-2017): Frequency table of patient and tumour characteristics

Characteristic	Total	Incidence period		
		2004-2008	2009-2013	2014-2017
Overall	11,206	4,363	3,846	2,997
Gender				
Female	11,206 (100.0)	4,363 (100.0)	3,846 (100.0)	2,997 (100.0)
Age at diagnosis (year)				
<50 years	1,295 (11.6)	555 (12.7)	419 (10.9)	321 (10.7)
50-59 years	2,119 (18.9)	897 (20.6)	708 (18.4)	514 (17.2)
60-69 years	2,773 (24.7)	1,033 (23.7)	980 (25.5)	760 (25.4)
70-79 years	3,019 (26.9)	1,203 (27.6)	1,019 (26.5)	797 (26.6)
80+ years	2,000 (17.8)	675 (15.5)	720 (18.7)	605 (20.2)
WHO - Performance Status				
0 – Asymptomatic	1,660 (14.8)	552 (12.7)	564 (14.7)	544 (18.2)
1 – Symptomatic but completely ambulatory	5,782 (51.6)	1,840 (42.2)	2,203 (57.3)	1,739 (58.0)
2 – Symptomatic, <50% in bed during the day	1,049 (9.4)	426 (9.8)	327 (8.5)	296 (9.9)
3 – Symptomatic, >50% in bed, but not bedbound	367 (3.3)	163 (3.7)	114 (3.0)	90 (3.0)
4 – Bedbound	95 (0.8)	40 (0.9)	35 (0.9)	20 (0.7)
Not reported	2,253 (20.1)	1,342 (30.8)	603 (15.7)	308 (10.3)
Combined stage				
0	16 (0.1)	0 (0.0)	7 (0.2)	9 (0.3)
I	1,859 (16.6)	683 (15.7)	630 (16.4)	546 (18.2)



II	601 (5.4)	238 (5.5)	217 (5.6)	146 (4.9)
IIIA/B	1,165 (10.4)	400 (9.2)	390 (10.1)	375 (12.5)
IIIC	2,015 (18.0)	679 (15.6)	732 (19.0)	604 (20.2)
IV	2,340 (20.9)	705 (16.2)	856 (22.3)	779 (26.0)
X/NA	3,210 (28.6)	1,658 (38.0)	1,014 (26.4)	538 (18.0)

Note: the values between parentheses are column percentages.

Table 136 – Epithelial ovarian cancer (2004-2017): Frequency table of patient and tumour characteristics (cut-off point: 2012)

Characteristic	Total	Incidence period	
		2004-2011	2013-2017
Overall	10 463	6 735	3 728
Gender			
Female	10 463 (100.0)	6 735 (100.0)	3 728 (100.0)
Age at diagnosis (year)			
<50 years	1 209 (11.6)	811 (12.1)	397 (10.6)
50-59 years	1 971 (18.8)	1 318 (19.6)	653 (17.5)
60-69 years	2 587 (24.7)	1 631 (24.2)	956 (25.6)
70-79 years	2 836 (27.1)	1 856 (27.6)	980 (26.3)
80+ years	1 860 (17.8)	1 118 (16.6)	742 (19.9)
WHO - Performance Status			
0 – Asymptomatic	1 544 (14.8)	894 (13.3)	650 (17.4)
1 – Symptomatic but completely ambulatory	5 346 (51.1)	3 163 (47.0)	2 183 (58.6)
2 – Symptomatic, <50% in bed during the day	1 002 (9.6)	639 (9.5)	363 (9.7)
3 – Symptomatic, >50% in bed, but not bedbound	367 (3.3)	163 (3.7)	114 (3.0)
4 – Bedbound	92 (0.9)	64 (1.0)	28 (0.8)
Not reported	2 137 (20.4)	1 743 (25.9)	394 (10.6)
Combined stage			
0	14 (0.1)	2 (0.0)	12 (0.3)
I	1 726 (16.5)	1 026 (15.2)	700 (18.8)
II	555 (5.3)	355 (5.3)	200 (5.4)



IIIA/B	1 088 (10.4)	628 (9.3)	460 (12.3)
IIIC	1 881 (18.0)	1 111 (16.5)	770 (20.7)
IV	2 177 (20.8)	1 212 (18.0)	965 (25.9)
X/NA	3 022 (28.9)	2 401 (35.6)	621 (16.7)

Note: the values between parentheses are column percentages.

Table 137 – Epithelial ovarian cancer (2004-2017), Combined stage I, Frequency table of patient and tumour characteristics

Characteristic	Total	Incidence period		
		2004-2008	2009-2013	2014-2017
Overall	1,859	683	630	546
Gender				
Female	1,859 (100.0)	683 (100.0)	630 (100.0)	546 (100.0)
Age at diagnosis (year)				
<50 years	368 (19.8)	134 (19.6)	123 (19.5)	111 (20.3)
50-59 years	482 (25.9)	188 (27.5)	170 (27.0)	124 (22.7)
60-69 years	455 (24.5)	148 (21.7)	148 (23.5)	159 (29.1)
70-79 years	349 (18.8)	143 (20.9)	107 (17.0)	99 (18.1)
80+ years	205 (11.0)	70 (10.2)	82 (13.0)	53 (9.7)
WHO - Performance Status				
0 – Asymptomatic	448 (24.1)	141 (20.6)	159 (25.2)	148 (27.1)
1 – Symptomatic but completely ambulatory	988 (53.1)	311 (45.5)	355 (56.3)	322 (59.0)
2 – Symptomatic, <50% in bed during the day	80 (4.3)	33 (4.8)	23 (3.7)	24 (4.4)
3 – Symptomatic, >50% in bed, but not bedbound	17 (0.9)	7 (1.0)	3 (0.5)	7 (1.3)
4 – Bedbound	1 (0.1)	0 (0.0)	1 (0.2)	0 (0.0)
Not reported	325 (17.5)	191 (28.0)	89 (14.1)	45 (8.2)

Note: the values between parentheses are column percentages.

**Table 138 – Epithelial ovarian cancer (2004-2017), Combined stage I, Frequency table of patient and tumour characteristics (cut-off point: 2012)**

Characteristic	Total	Incidence period	
		2004-2011	2013-2017
Overall	1 726	1 026	700
Gender			
Female	1 726 (100.0)	1 026 (100.0)	700 (100.0)
Age at diagnosis (year)			
<50 years	346 (20.0)	199 (19.4)	147 (21.0)
50-59 years	443 (25.7)	283 (27.6)	160 (22.9)
60-69 years	419 (24.3)	218 (21.2)	201 (28.7)
70-79 years	325 (18.8)	204 (19.9)	121 (17.3)
80+ years	193 (11.2)	122 (11.9)	71 (10.1)
WHO - Performance Status			
0 – Asymptomatic	413 (23.9)	229 (22.3)	184 (26.3)
1 – Symptomatic but completely ambulatory	916 (53.1)	504 (49.1)	412 (58.9)
2 – Symptomatic, <50% in bed during the day	77 (4.5)	47 (4.6)	30 (4.3)
3 – Symptomatic, >50% in bed, but not bedbound	16 (0.9)	8 (0.8)	8 (1.1)
4 – Bedbound	0 (0.0)	0 (0.0)	0 (0.0)
Not reported	304 (17.6)	238 (23.2)	66 (9.4)

Note: the values between parentheses are column percentages.



Table 139 – Epithelial ovarian cancer (2004-2017), Combined stage II, Frequency table of patient and tumour characteristics

Characteristic	Total	Incidence period		
		2004-2008	2009-2013	2014-2017
Overall	601	238	217	146
Gender				
Female	601 (100.0)	238 (100.0)	217 (100.0)	146 (100.0)
Age at diagnosis (year)				
<50 years	65 (10.8)	27 (11.3)	20 (9.2)	18 (12.3)
50-59 years	137 (22.8)	55 (23.1)	49 (22.6)	33 (22.6)
60-69 years	156 (26.0)	62 (26.1)	61 (28.1)	33 (22.6)
70-79 years	163 (27.1)	66 (27.7)	61 (28.1)	36 (24.7)
80+ years	80 (13.3)	28 (11.8)	26 (12.0)	26 (17.8)
WHO - Performance Status				
0 – Asymptomatic	97 (16.1)	34 (14.3)	35 (16.1)	28 (19.2)
1 – Symptomatic but completely ambulatory	348 (57.9)	118 (49.6)	136 (62.7)	94 (64.4)
2 – Symptomatic, <50% in bed during the day	33 (5.5)	22 (9.2)	5 (2.3)	6 (4.1)
3 – Symptomatic, >50% in bed, but not bedbound	17 (2.8)	7 (2.9)	7 (3.2)	3 (2.1)
4 – Bedbound	1 (0.2)	1 (0.4)	0 (0.0)	0 (0.0)
Not reported	105 (17.5)	56 (23.5)	34 (15.7)	15 (10.3)

Note: the values between parentheses are column percentages.

**Table 140 – Epithelial ovarian cancer (2004-2017), Combined stage II, Frequency table of patient and tumour characteristics (cut-off point: 2012)**

Characteristic	Total	Incidence period	
		2004-2011	2013-2017
Overall	555	355	200
Gender			
Female	555 (100.0)	355 (100.0)	200 (100.0)
Age at diagnosis (year)			
<50 years	62 (11.2)	39 (11.0)	23 (11.5)
50-59 years	124 (22.3)	79 (22.3)	45 (22.5)
60-69 years	144 (25.9)	98 (27.6)	46 (23.0)
70-79 years	153 (27.6)	97 (27.3)	56 (28.0)
80+ years	72 (13.0)	42 (11.8)	30 (15.0)
WHO - Performance Status			
0 – Asymptomatic	88 (15.9)	54 (15.2)	34 (17.0)
1 – Symptomatic but completely ambulatory	319 (57.5)	188 (53.0)	131 (65.5)
2 – Symptomatic, <50% in bed during the day	33 (5.9)	25 (7.0)	8 (4.0)
3 – Symptomatic, >50% in bed, but not bedbound	17 (3.1)	14 (3.9)	3 (1.5)
4 – Bedbound	1 (0.2)	1 (0.3)	0 (0.0)
Not reported	97 (17.5)	73 (20.6)	24 (12.0)

Note: the values between parentheses are column percentages.



Table 141 – Epithelial ovarian cancer (2004-2017), Combined stage IIIA/B, Frequency table of patient and tumour characteristics

Characteristic	Total	Incidence period		
		2004-2008	2009-2013	2014-2017
Overall	1,165	400	390	375
Gender				
Female	1,165 (100.0)	400 (100.0)	390 (100.0)	375 (100.0)
Age at diagnosis (year)				
<50 years	136 (11.7)	49 (12.3)	44 (11.3)	43 (11.5)
50-59 years	204 (17.5)	76 (19.0)	60 (15.4)	68 (18.1)
60-69 years	313 (26.9)	105 (26.3)	121 (31.0)	87 (23.2)
70-79 years	342 (29.4)	109 (27.3)	113 (29.0)	120 (32.0)
80+ years	170 (14.6)	61 (15.3)	52 (13.3)	57 (15.2)
WHO - Performance Status				
0 – Asymptomatic	183 (15.7)	51 (12.8)	60 (15.4)	72 (19.2)
1 – Symptomatic but completely ambulatory	677 (58.1)	207 (51.8)	241 (61.8)	229 (61.1)
2 – Symptomatic, <50% in bed during the day	103 (8.8)	31 (7.8)	34 (8.7)	38 (10.1)
3 – Symptomatic, >50% in bed, but not bedbound	39 (3.3)	19 (4.8)	11 (2.8)	9 (2.4)
4 – Bedbound	8 (0.7)	4 (1.0)	1 (0.3)	3 (0.8)
Not reported	155 (13.3)	88 (22.0)	43 (11.0)	24 (6.4)

Note: the values between parentheses are column percentages.


Table 142 – Epithelial ovarian cancer (2004-2017), Combined stage IIIA/B, Frequency table of patient and tumour characteristics (cut-off point: 2012)

Characteristic	Total	Incidence period	
		2004-2011	2013-2017
Overall	1 088	628	460
Gender			
Female	1 088 (100.0)	628 (100.0)	460 (100.0)
Age at diagnosis (year)			
<50 years	126 (11.6)	75 (11.9)	51 (11.1)
50-59 years	192 (17.6)	109 (17.4)	83 (18.0)
60-69 years	292 (26.8)	175 (27.9)	117 (25.4)
70-79 years	317 (29.1)	178 (28.3)	139 (30.2)
80+ years	161 (14.8)	91 (14.5)	70 (15.2)
WHO - Performance Status			
0 – Asymptomatic	169 (15.5)	83 (13.2)	86 (18.7)
1 – Symptomatic but completely ambulatory	632 (58.1)	354 (56.4)	278 (60.4)
2 – Symptomatic, <50% in bed during the day	98 (9.0)	49 (7.8)	49 (10.7)
3 – Symptomatic, >50% in bed, but not bedbound	37 (3.4)	25 (4.0)	12 (2.6)
4 – Bedbound	8 (0.7)	5 (0.8)	3 (0.7)
Not reported	144 (13.2)	112 (17.8)	32 (7.0)

Note: the values between parentheses are column percentages.



Table 143 – Epithelial ovarian cancer (2004-2017), Combined stage IIIC, Frequency table of patient and tumour characteristics

Characteristic	Total	Incidence period		
		2004-2008	2009-2013	2014-2017
Overall	2,015	679	732	604
Gender				
Female	2,015 (100.0)	679 (100.0)	732 (100.0)	604 (100.0)
Age at diagnosis (year)				
<50 years	216 (10.7)	81 (11.9)	76 (10.4)	59 (9.8)
50-59 years	454 (22.5)	170 (25.0)	162 (22.1)	122 (20.2)
60-69 years	539 (26.7)	175 (25.8)	199 (27.2)	165 (27.3)
70-79 years	531 (26.4)	178 (26.2)	191 (26.1)	162 (26.8)
80+ years	275 (13.6)	75 (11.0)	104 (14.2)	96 (15.9)
WHO - Performance Status				
0 – Asymptomatic	323 (16.0)	105 (15.5)	101 (13.8)	117 (19.4)
1 – Symptomatic but completely ambulatory	1,214 (60.2)	346 (51.0)	487 (66.5)	381 (63.1)
2 – Symptomatic, <50% in bed during the day	184 (9.1)	72 (10.6)	52 (7.1)	60 (9.9)
3 – Symptomatic, >50% in bed, but not bedbound	41 (2.0)	21 (3.1)	13 (1.8)	7 (1.2)
4 – Bedbound	9 (0.4)	3 (0.4)	6 (0.8)	0 (0.0)
Not reported	244 (12.1)	132 (19.4)	73 (10.0)	39 (6.5)

Note: the values between parentheses are column percentages.

**Table 144 – Epithelial ovarian cancer (2004-2017), Combined stage IIIC, Frequency table of patient and tumour characteristics (cut-off point: 2012)**

Characteristic	Total	Incidence period	
		2004-2011	2013-2017
Overall	1 881	1 111	770
Gender			
Female	1 881 (100.0)	1 111 (100.0)	770 (100.0)
Age at diagnosis (year)			
<50 years	200 (10.6)	129 (11.6)	71 (9.2)
50-59 years	422 (22.4)	260 (23.4)	162 (21.0)
60-69 years	505 (26.8)	291 (26.2)	214 (27.8)
70-79 years	500 (26.6)	304 (27.4)	196 (25.5)
80+ years	254 (13.5)	127 (11.4)	127 (16.5)
WHO - Performance Status			
0 – Asymptomatic	300 (15.9)	164 (14.8)	136 (17.7)
1 – Symptomatic but completely ambulatory	1 122 (59.6)	619 (55.7)	503 (65.3)
2 – Symptomatic, <50% in bed during the day	174 (9.3)	103 (9.3)	71 (9.2)
3 – Symptomatic, >50% in bed, but not bedbound	39 (2.1)	28 (2.5)	11 (1.4)
4 – Bedbound	9 (0.5)	8 (0.7)	1 (0.1)
Not reported	237 (12.6)	189 (17.0)	48 (6.2)

Note: the values between parentheses are column percentages.



Table 145 – Epithelial ovarian cancer (2004-2017), Combined stage IV, Frequency table of patient and tumour characteristics

Characteristic	Total	Incidence period		
		2004-2008	2009-2013	2014-2017
Overall	2,340	705	856	779
Gender				
Female	2,340 (100.0)	705 (100.0)	856 (100.0)	779 (100.0)
Age at diagnosis (year)				
<50 years	174 (7.4)	56 (7.9)	69 (8.1)	49 (6.3)
50-59 years	355 (15.2)	114 (16.2)	135 (15.8)	106 (13.6)
60-69 years	610 (26.1)	183 (26.0)	222 (25.9)	205 (26.3)
70-79 years	711 (30.4)	212 (30.1)	260 (30.4)	239 (30.7)
80+ years	490 (20.9)	140 (19.9)	170 (19.9)	180 (23.1)
WHO - Performance Status				
0 – Asymptomatic	290 (12.4)	73 (10.4)	115 (13.4)	102 (13.1)
1 – Symptomatic but completely ambulatory	1,271 (54.3)	320 (45.4)	481 (56.2)	470 (60.3)
2 – Symptomatic, <50% in bed during the day	344 (14.7)	123 (17.4)	121 (14.1)	100 (12.8)
3 – Symptomatic, >50% in bed, but not bedbound	143 (6.1)	62 (8.8)	42 (4.9)	39 (5.0)
4 – Bedbound	34 (1.5)	14 (2.0)	12 (1.4)	8 (1.0)
Not reported	258 (11.0)	113 (16.0)	85 (9.9)	60 (7.7)

Note: the values between parentheses are column percentages.

**Table 146 – Epithelial ovarian cancer (2004-2017), Combined stage IV, Frequency table of patient and tumour characteristics (cut-off point: 2012)**

Characteristic	Total	Incidence period	
		2004-2011	2013-2017
Overall	2 177	1 212	965
Gender			
Female	2 177 (100.0)	1 212 (100.0)	965 (100.0)
Age at diagnosis (year)			
<50 years	156 (7.2)	96 (7.9)	60 (6.2)
50-59 years	325 (14.9)	188 (15.5)	137 (14.2)
60-69 years	568 (26.1)	314 (25.9)	254 (26.3)
70-79 years	672 (30.9)	372 (30.7)	300 (31.1)
80+ years	456 (20.9)	242 (20.0)	214 (22.2)
WHO - Performance Status			
0 – Asymptomatic	265 (12.2)	138 (11.4)	127 (13.2)
1 – Symptomatic but completely ambulatory	1 175 (54.0)	596 (49.2)	579 (60.0)
2 – Symptomatic, <50% in bed during the day	330 (15.2)	203 (16.7)	127 (13.2)
3 – Symptomatic, >50% in bed, but not bedbound	136 (6.2)	92 (7.6)	44 (4.6)
4 – Bedbound	32 (1.5)	22 (1.8)	10 (1.0)
Not reported	239 (11.0)	161 (13.3)	78 (8.1)
Debulking			
No	1 333 (61.2)	815 (67.2)	518 (53.7)
Yes	844 (38.8)	397 (32.8)	447 (46.3)

Note: the values between parentheses are column percentages.


Table 147 – Epithelial ovarian cancer (2004-2017): Combined stage IV - no debulking, Frequency table of patient and tumour characteristics

Characteristic	Total	Incidence period		
		2004-2008	2009-2013	2014-2017
Overall	1,406	556	425	425
Gender				
Female	1,406 (100.0)	556 (100.0)	425 (100.0)	425 (100.0)
Age at diagnosis (year)				
<50 years	82 (5.8)	40 (7.2)	26 (6.1)	16 (3.8)
50-59 years	145 (10.3)	77 (13.8)	34 (8.0)	34 (8.0)
60-69 years	293 (20.8)	130 (23.4)	79 (18.6)	84 (19.8)
70-79 years	446 (31.7)	176 (31.7)	137 (32.2)	133 (31.3)
80+ years	440 (31.3)	133 (23.9)	149 (35.1)	158 (37.2)
WHO - Performance Status				
0 – Asymptomatic	129 (9.2)	55 (9.9)	41 (9.6)	33 (7.8)
1 – Symptomatic but completely ambulatory	659 (46.9)	233 (41.9)	194 (45.6)	232 (54.6)
2 – Symptomatic, <50% in bed during the day	265 (18.8)	104 (18.7)	87 (20.5)	74 (17.4)
3 – Symptomatic, >50% in bed, but not bedbound	133 (9.5)	59 (10.6)	37 (8.7)	37 (8.7)
4 – Bedbound	34 (2.4)	14 (2.5)	12 (2.8)	8 (1.9)
Not reported	186 (13.2)	91 (16.4)	54 (12.7)	41 (9.6)

Note: the values between parentheses are column percentages.



Table 148 – Epithelial ovarian cancer (2004-2017): Combined stage IV - no debulking, Frequency table of patient and tumour characteristics (cut-off point: 2012)

Characteristic	Total	Incidence period	
		2004-2011	2013-2017
Overall	1 333	815	518
Gender			
Female	1 333 (100.0)	815 (100.0)	518 (100.0)
Age at diagnosis (year)			
<50 years	76 (5.7)	55 (6.7)	21 (4.1)
50-59 years	136 (10.2)	98 (12.0)	38 (7.3)
60-69 years	281 (21.1)	178 (21.8)	103 (19.9)
70-79 years	430 (32.3)	262 (32.1)	168 (32.4)
80+ years	410 (30.8)	222 (27.2)	188 (36.3)
WHO - Performance Status			
0 – Asymptomatic	123 (9.2)	82 (10.1)	41 (7.9)
1 – Symptomatic but completely ambulatory	621 (46.6)	341 (41.8)	280 (54.1)
2 – Symptomatic, <50% in bed during the day	255 (19.1)	160 (19.6)	95 (18.3)
3 – Symptomatic, >50% in bed, but not bedbound	127 (9.5)	85 (10.4)	42 (8.1)
4 – Bedbound	32 (2.4)	22 (2.7)	10 (1.9)
Not reported	175 (13.1)	125 (15.3)	50 (9.7)

Note: the values between parentheses are column percentages.



Table 149 – Epithelial ovarian cancer (2004-2017): Combined stage IV - debulking, Frequency table of patient and tumour characteristics

Characteristic	Total	Incidence period		
		2004-2008	2009-2013	2014-2017
Overall	934	149	431	354
Gender				
Female	934 (100.0)	149 (100.0)	431 (100.0)	354 (100.0)
Age at diagnosis (year)				
<50 years	92 (9.9)	16 (10.7)	43 (10.0)	33 (9.3)
50-59 years	210 (22.5)	37 (24.8)	101 (23.4)	72 (20.3)
60-69 years	317 (33.9)	53 (35.6)	143 (33.2)	121 (34.2)
70-79 years	265 (28.4)	36 (24.2)	123 (28.5)	106 (29.9)
80+ years	50 (5.4)	7 (4.7)	21 (4.9)	22 (6.2)
WHO - Performance Status				
0 – Asymptomatic	161 (17.2)	18 (12.1)	74 (17.2)	69 (19.5)
1 – Symptomatic but completely ambulatory	612 (65.5)	87 (58.4)	287 (66.6)	238 (67.2)
2 – Symptomatic, <50% in bed during the day	79 (8.5)	19 (12.8)	34 (7.9)	26 (7.3)
3 – Symptomatic, >50% in bed, but not bedbound	10 (1.1)	3 (2.0)	5 (1.2)	2 (0.6)
Not reported	72 (7.7)	22 (14.8)	31 (7.2)	19 (5.4)

Note: the values between parentheses are column percentages.



Table 150 – Epithelial ovarian cancer (2004-2017): Combined stage IV - debulking, Frequency table of patient and tumour characteristics (cut-off point: 2012)

Characteristic	Total	2004-2011	2013-2017
Overall	844	397	447
Gender			
Female	844 (100.0)	397 (100.0)	447 (100.0)
Age at diagnosis (year)			
<50 years	80 (9.5)	41 (10.3)	39 (8.7)
50-59 years	189 (22.4)	90 (22.7)	99 (22.1)
60-69 years	287 (34.0)	136 (34.3)	151 (33.8)
70-79 years	242 (28.7)	110 (27.7)	132 (29.5)
80+ years	46 (5.5)	20 (5.0)	26 (5.8)
WHO - Performance Status			
0 – Asymptomatic	142 (16.8)	56 (14.1)	86 (19.2)
1 – Symptomatic but completely ambulatory	554 (65.6)	255 (64.2)	299 (66.9)
2 – Symptomatic, <50% in bed during the day	75 (8.9)	43 (10.8)	32 (7.2)
3 – Symptomatic, >50% in bed, but not bedbound	9 (1.1)	7 (1.8)	2 (0.4)
Not reported	64 (7.6)	36 (9.1)	28 (6.3)

Note: the values between parentheses are column percentages.



Appendix 10.1.1.2. Epithelial ovarian cancer, Observed and Relative Survival graphs

Epithelial Ovarian Cancer (2004-2017)

Figure 234 – Epithelial ovarian cancer (2004-2017), Kaplan-Meier graphs observed survival by incidence period

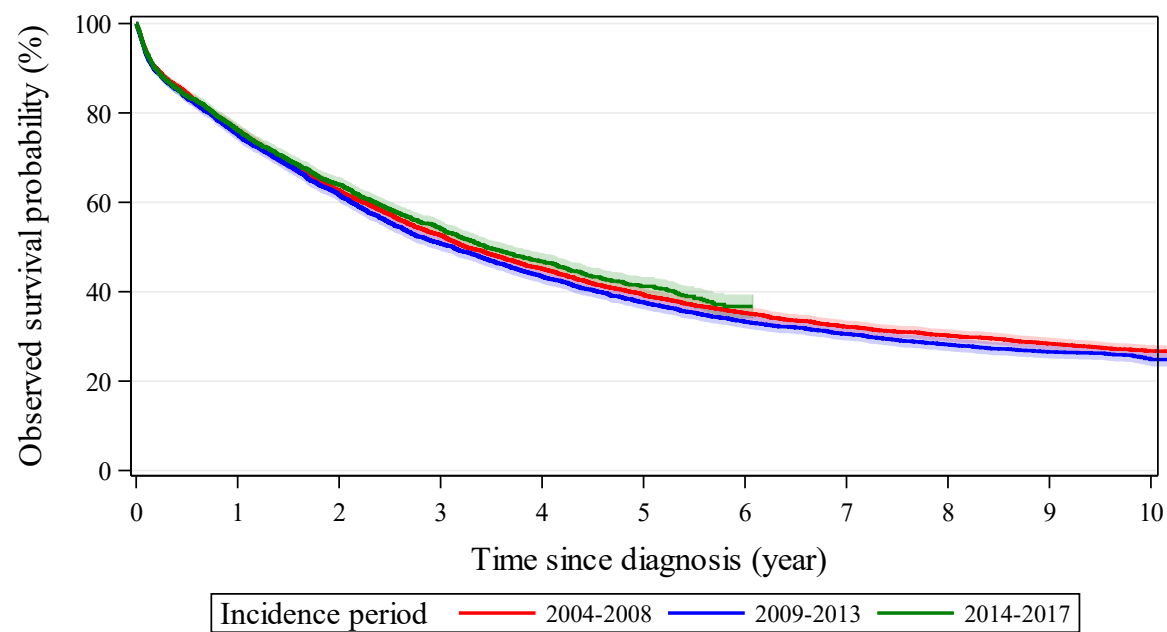




Figure 235 – Epithelial ovarian cancer (2004-2017), Kaplan-Meier graphs observed survival by incidence period (cut-off point: 2012)

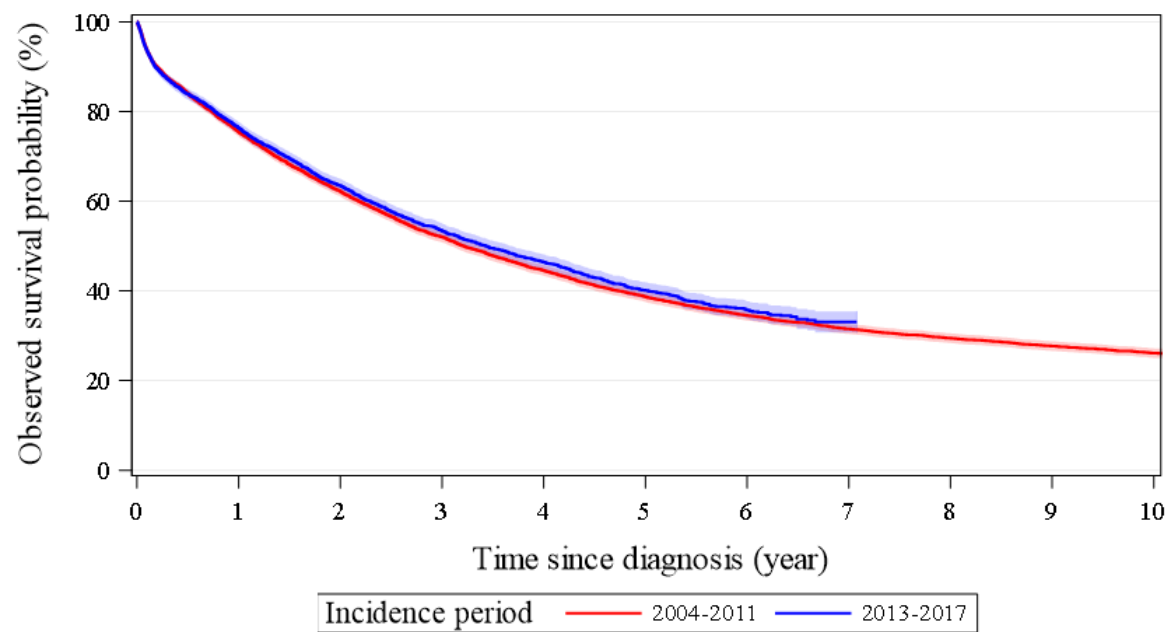




Figure 236 – Epithelial ovarian cancer (2004-2017), relative survival graphs by incidence period

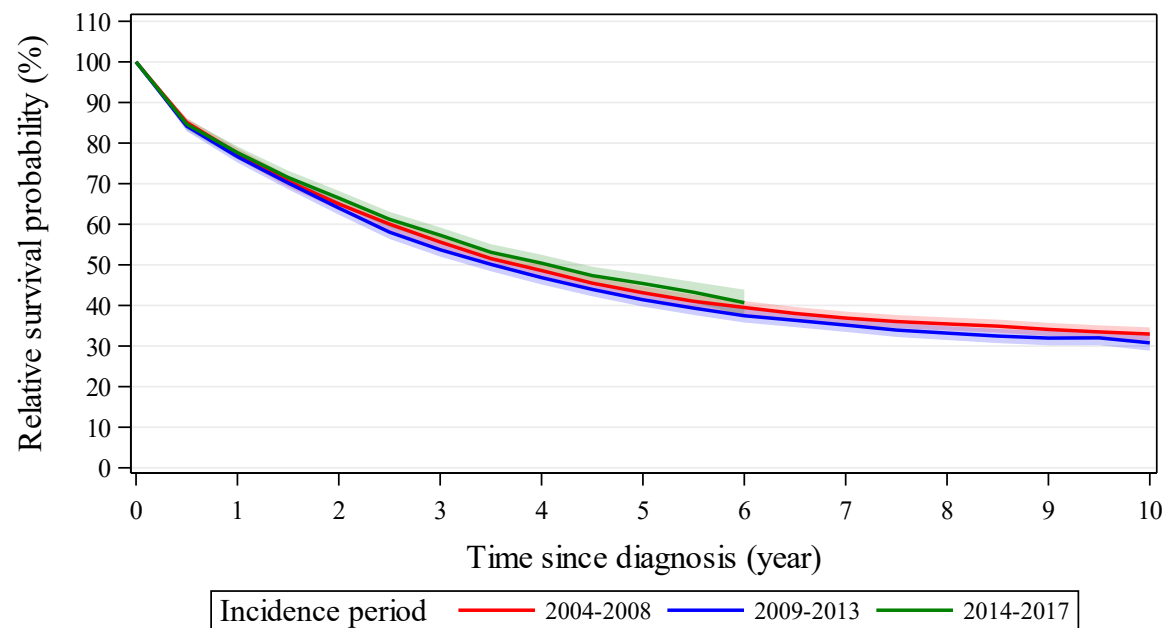
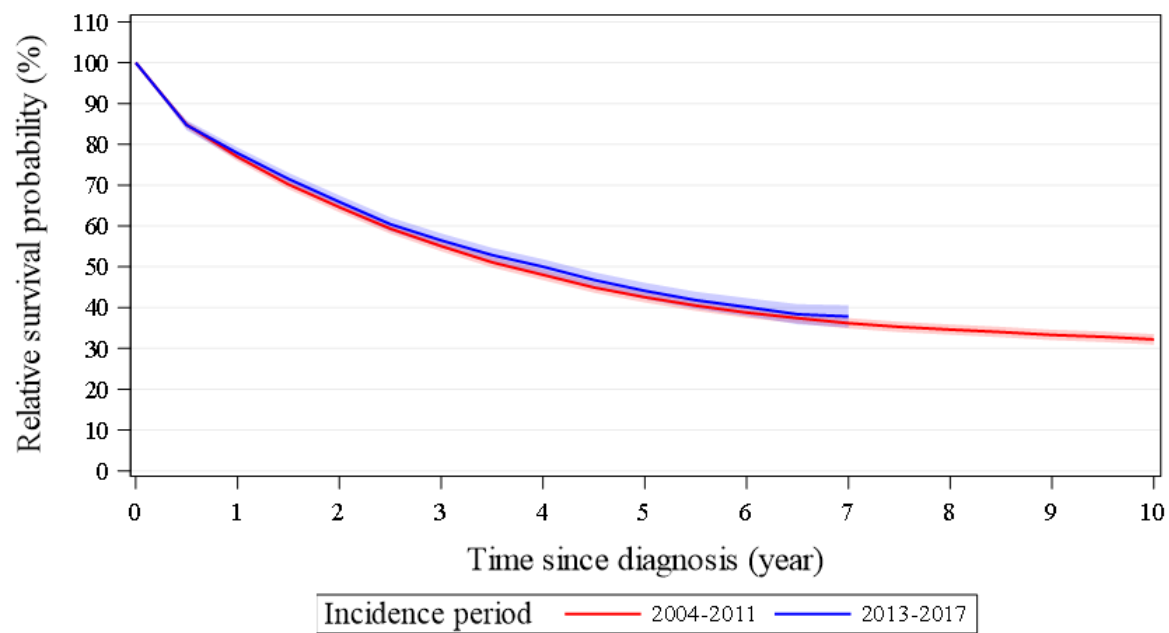


Figure 237 – Epithelial ovarian cancer (2004-2017), relative survival graphs by incidence period (cut-off point: 2012)



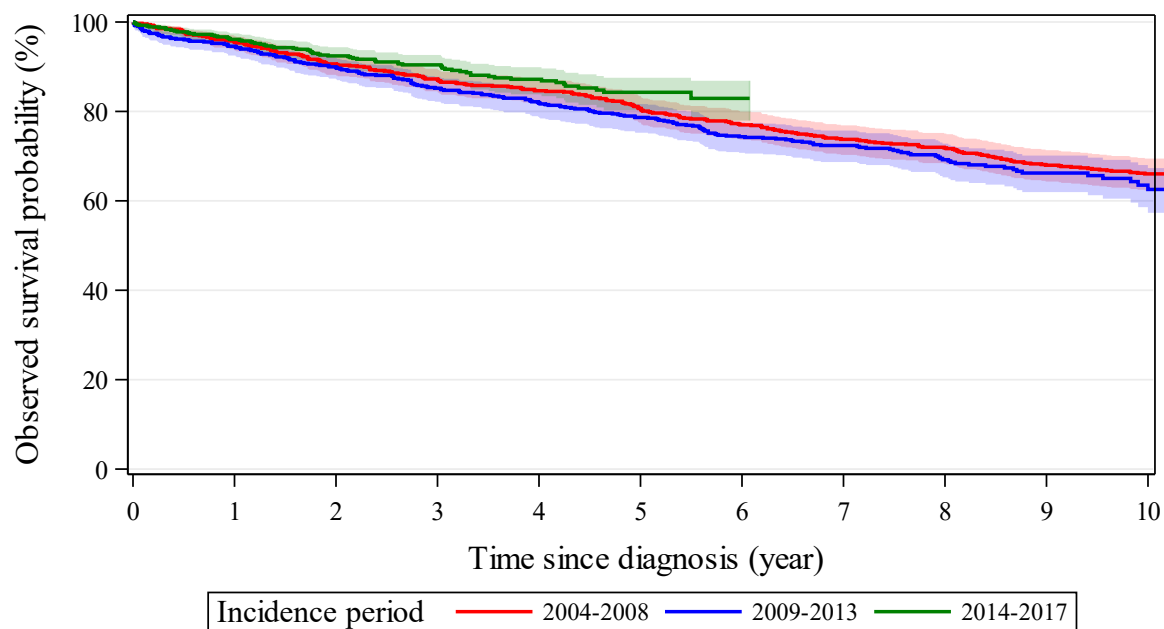
**Epithelial Ovarian Cancer, combined stage I (2004-2017)****Figure 238 – Epithelial ovarian cancer (2004-2017), combined stage I, Kaplan-Meier graphs observed survival by incidence period**



Figure 239 – Epithelial ovarian cancer (2004-2017), combined stage I, Kaplan-Meier graphs observed survival by incidence period (cut-off point: 2012)

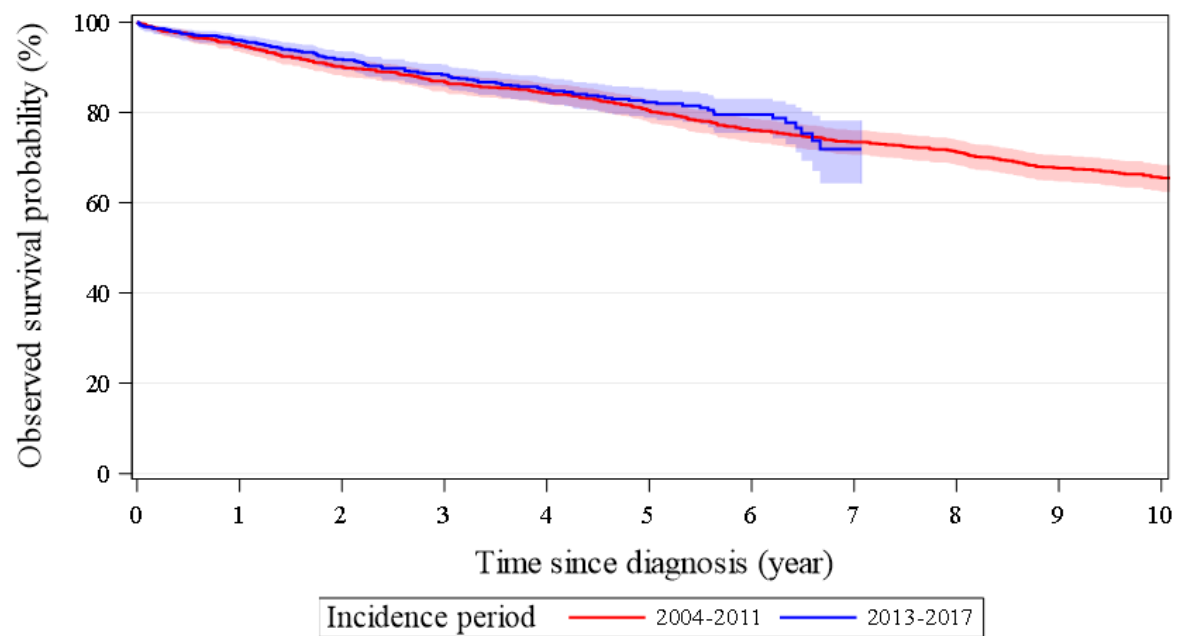




Figure 240 – Epithelial ovarian cancer (2004-2017), combined stage I, relative survival graphs by incidence period

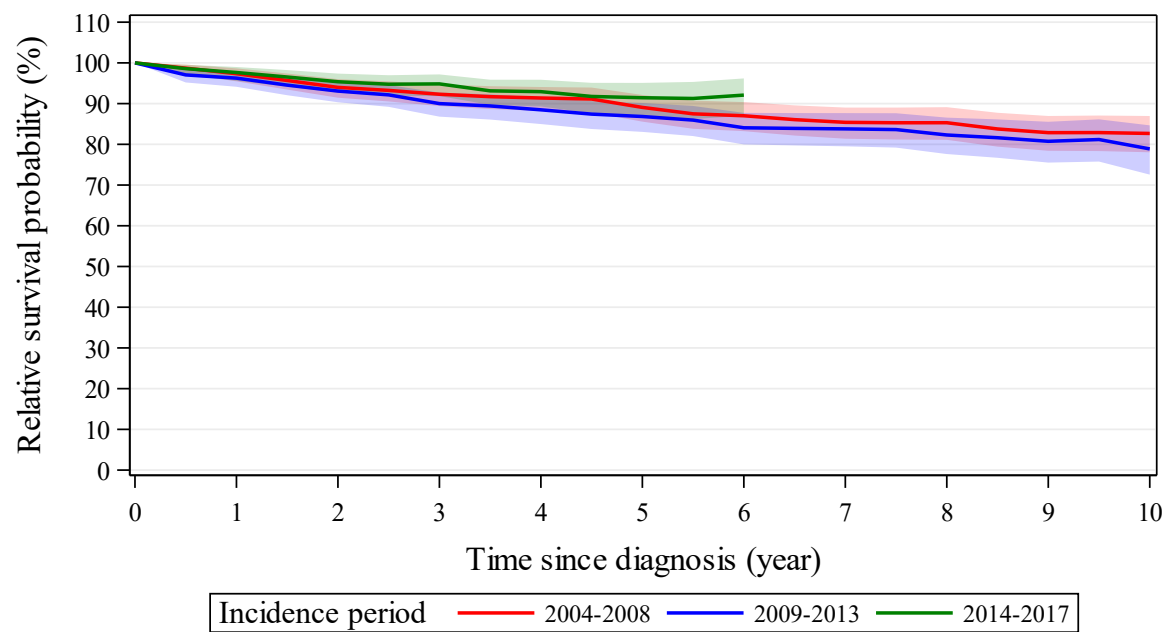
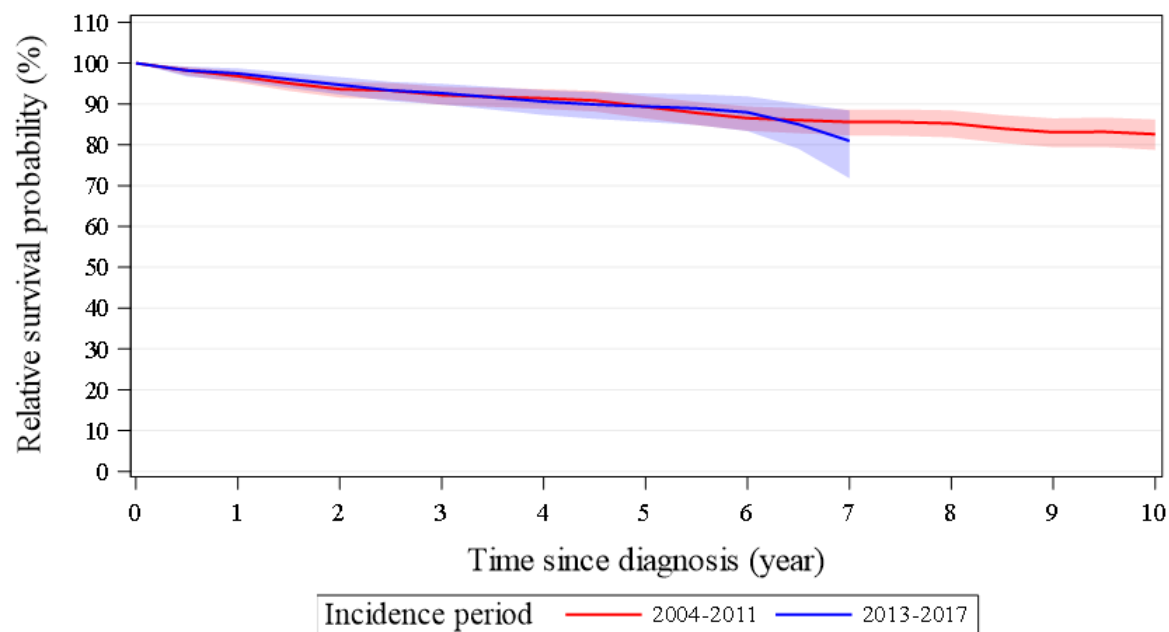




Figure 241 – Epithelial ovarian cancer (2004-2017), combined stage I, relative survival graphs by incidence period (cut-off point: 2012)



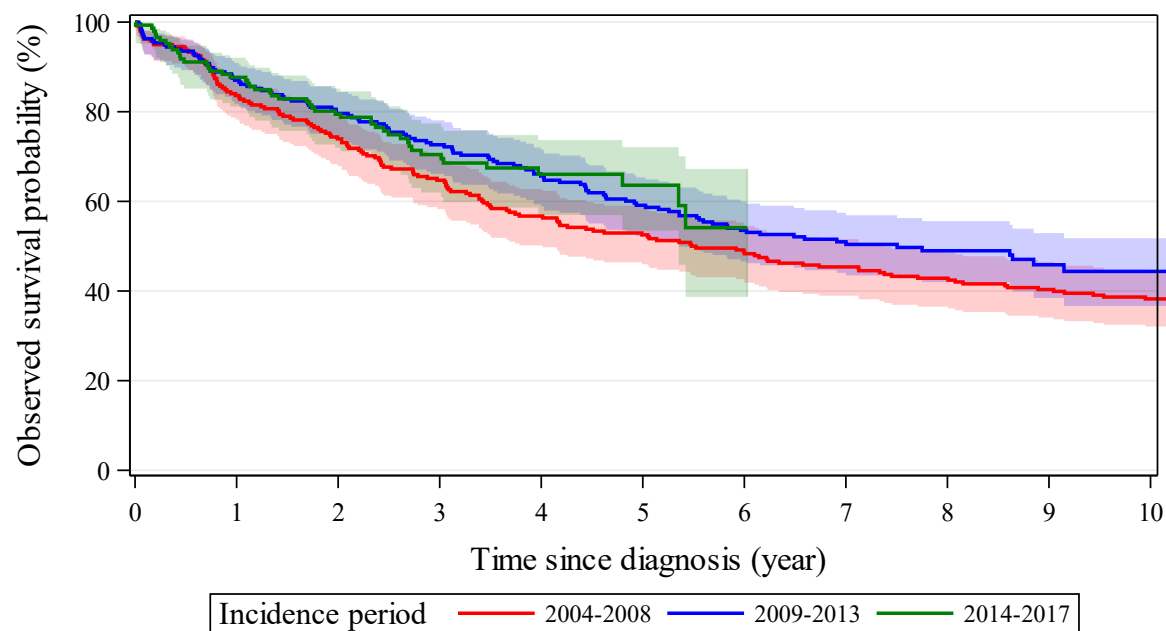
**Epithelial Ovarian Cancer, combined stage II (2004-2017)****Figure 242 – Epithelial ovarian cancer (2004-2017), combined stage II, Kaplan-Meier graphs observed survival by incidence period**



Figure 243 – Epithelial ovarian cancer (2004-2017), combined stage II, Kaplan-Meier graphs observed survival by incidence period

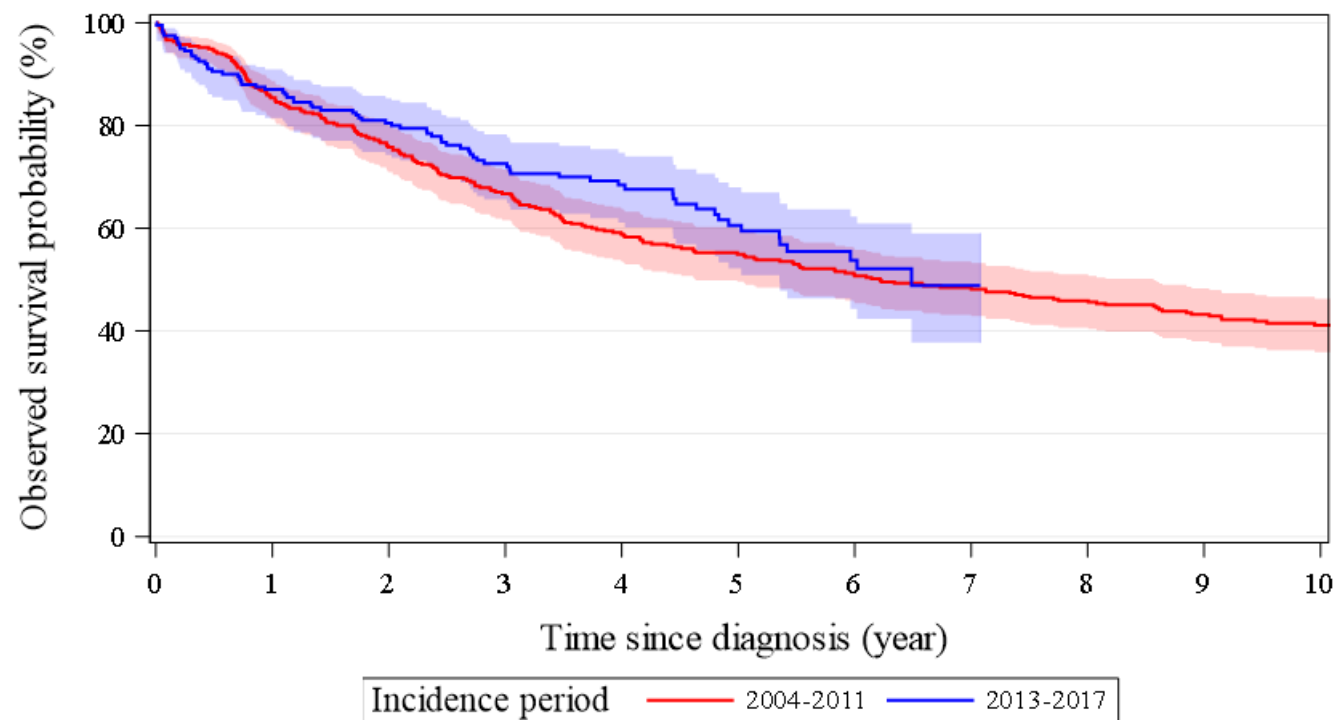




Figure 244 – Epithelial ovarian cancer (2004-2017), combined stage II, relative survival graphs by incidence period

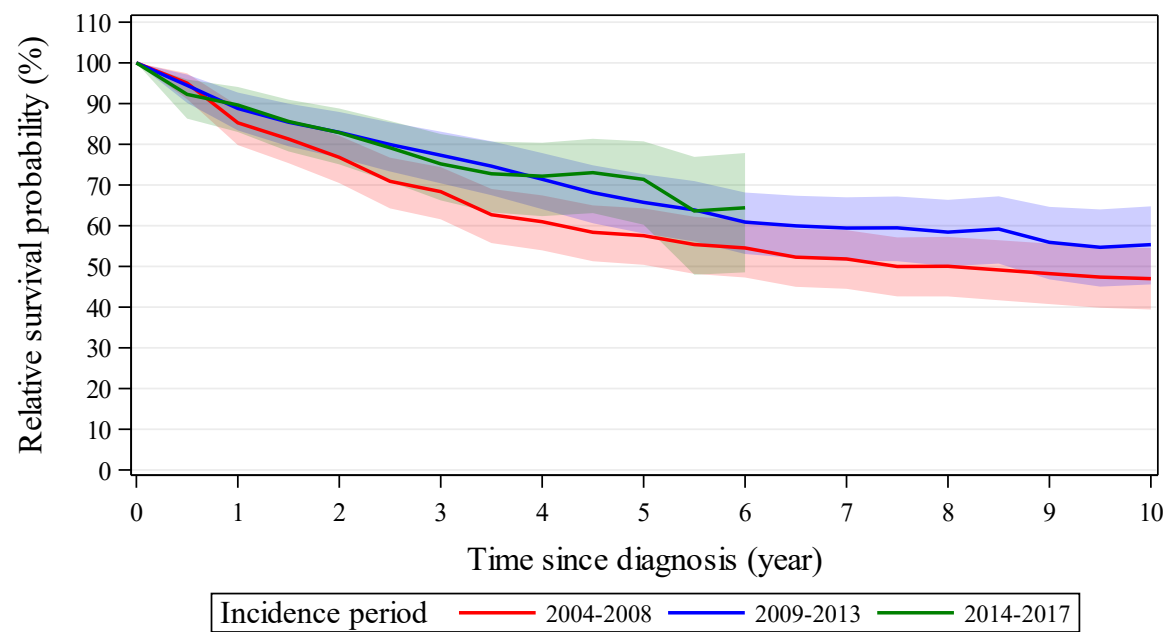
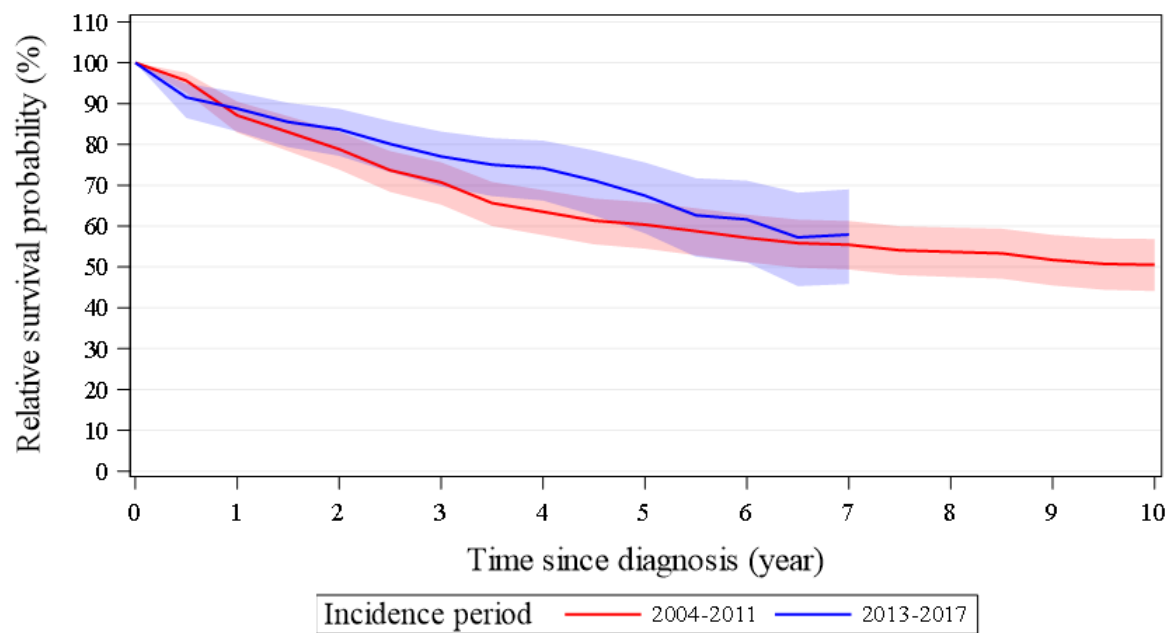




Figure 245 – Epithelial ovarian cancer (2004-2017), combined stage II, relative survival graphs by incidence period (cut-off point: 2012)



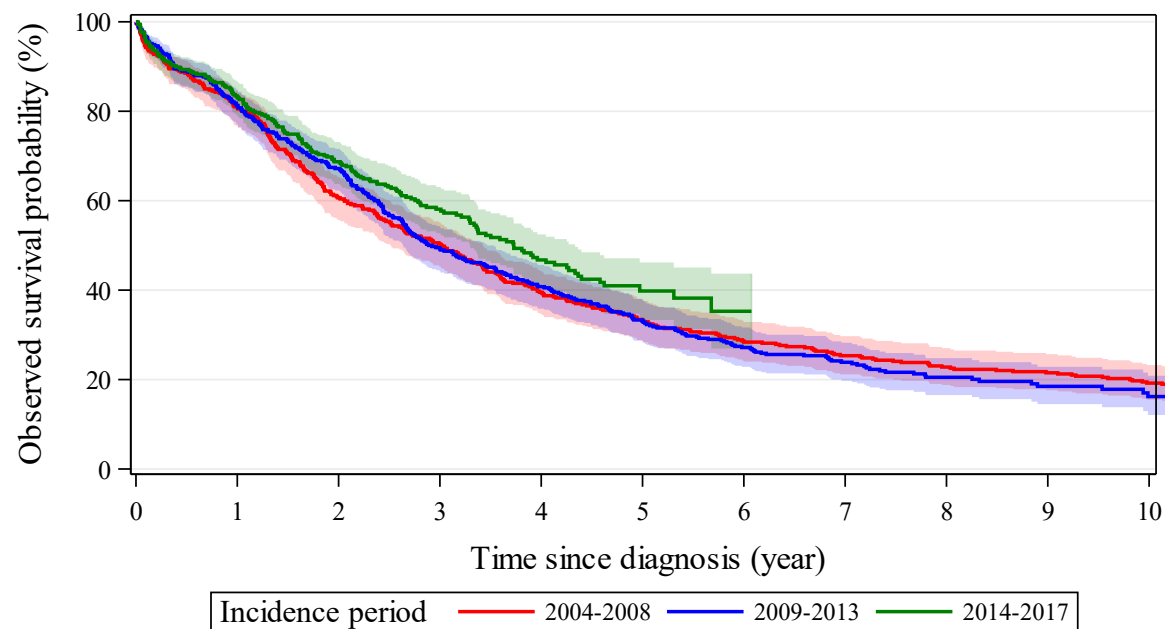
**Epithelial Ovarian Cancer, combined stage IIIA/B (2004-2017)****Figure 246 – Epithelial ovarian cancer (2004-2017), combined stage IIIA/B, Kaplan-Meier graphs observed survival by incidence period**

Figure 247 – Epithelial ovarian cancer (2004-2017), combined stage IIIA/B, Kaplan-Meier graphs observed survival by incidence period (cut-off point: 2012)

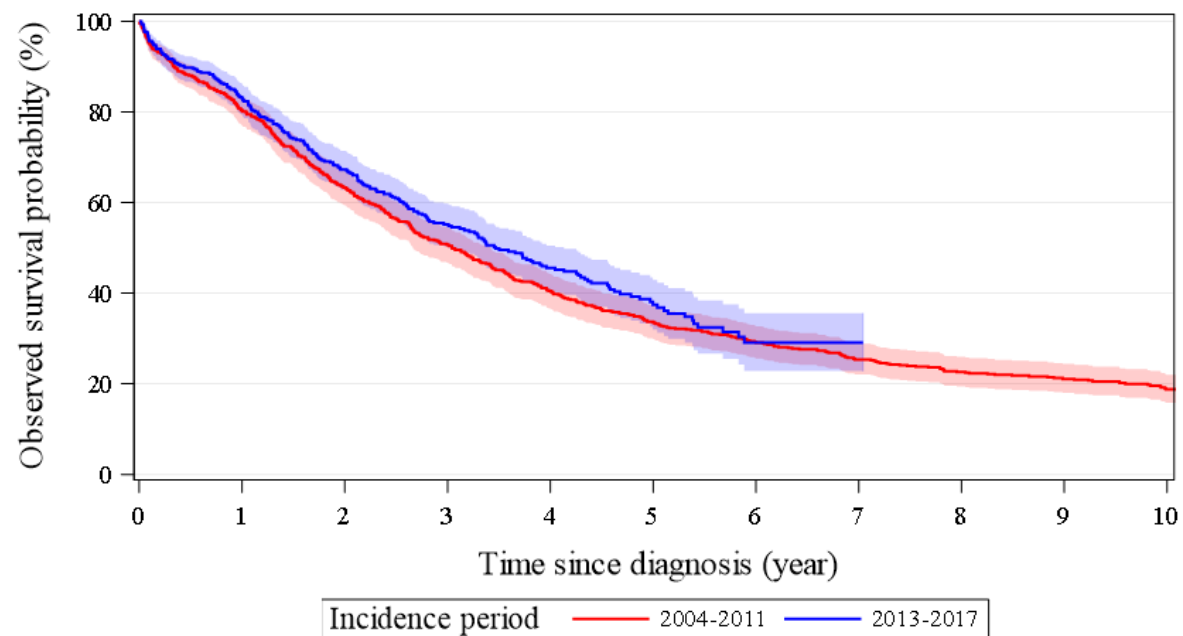




Figure 248 – Epithelial ovarian cancer (2004-2017), combined stage IIIA/B, relative survival graphs by incidence period

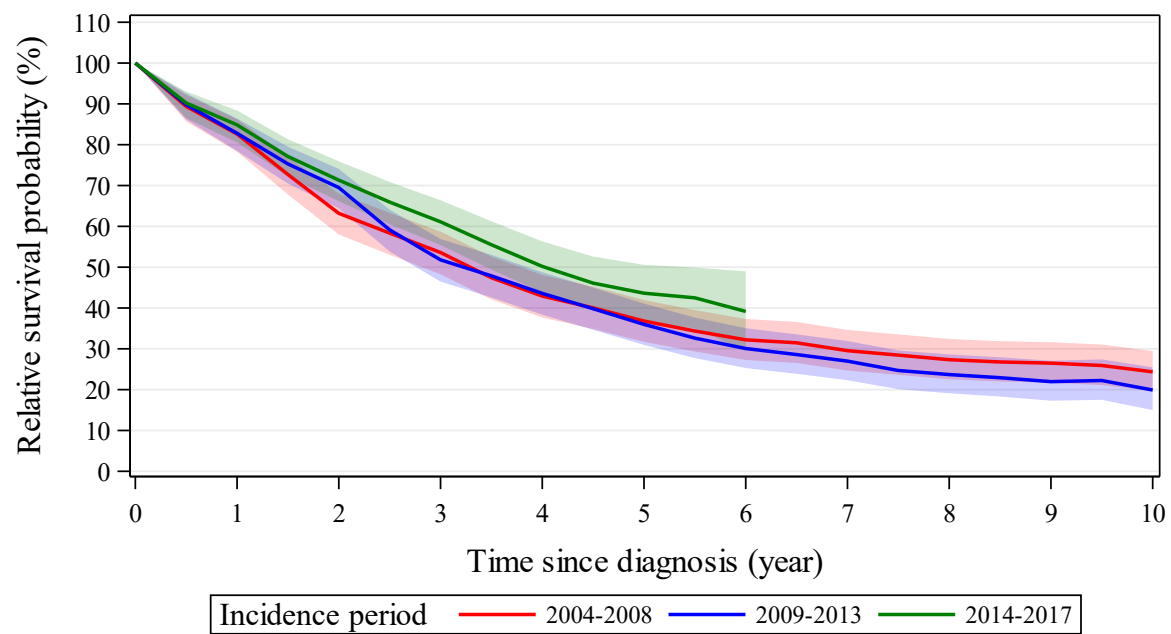
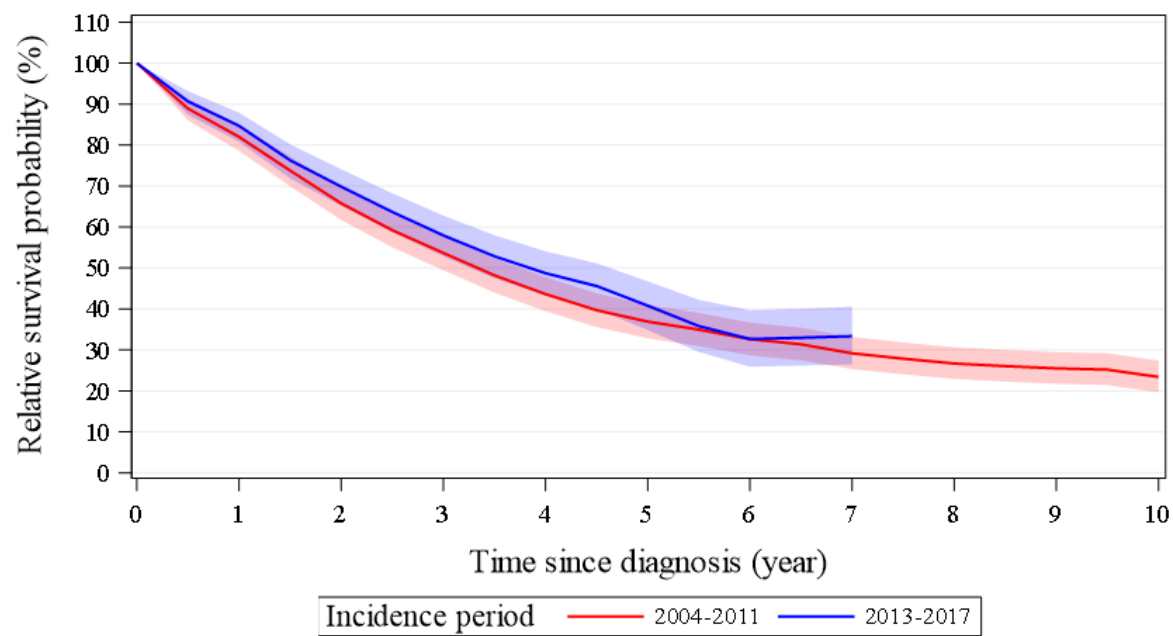




Figure 249 – Epithelial ovarian cancer (2004-2017), combined stage IIIA/B, relative survival graphs by incidence period (cut-off point: 2012)



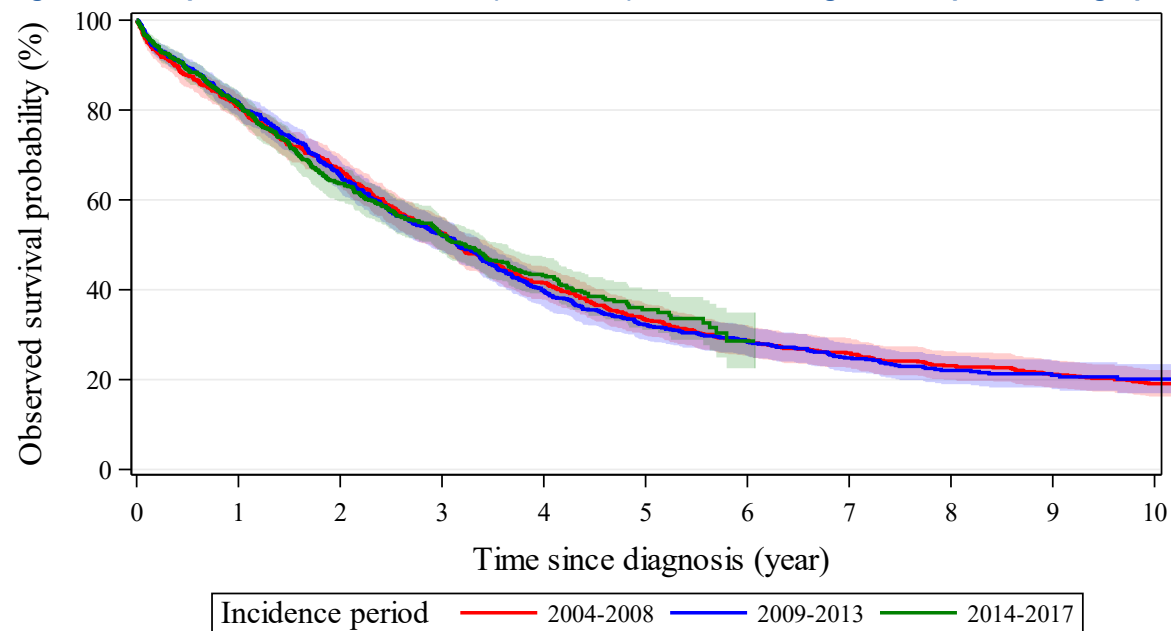
**Epithelial Ovarian Cancer, combined stage IIIC (2004-2017)****Figure 250 – Epithelial ovarian cancer (2004-2017), combined stage IIIC, Kaplan-Meier graphs observed survival by incidence period**



Figure 251 – Epithelial ovarian cancer (2004-2017), combined stage IIIC, Kaplan-Meier graphs observed survival by incidence period (cut-off point: 2012)

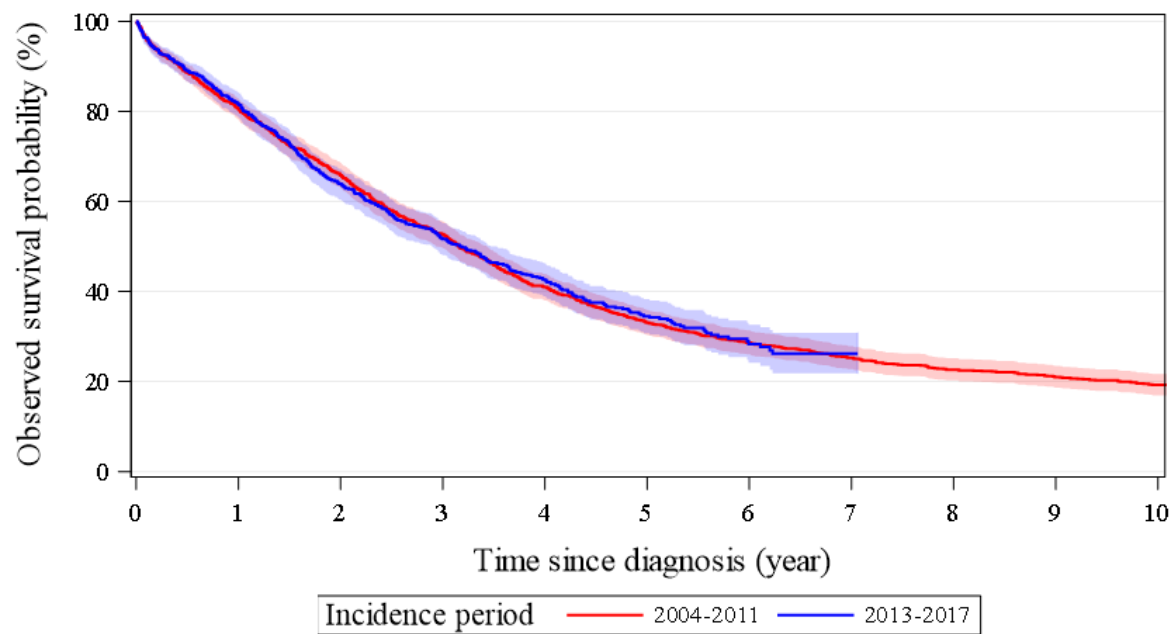




Figure 252 – Epithelial ovarian cancer (2004-2017), combined stage IIIC, relative survival graphs by incidence period

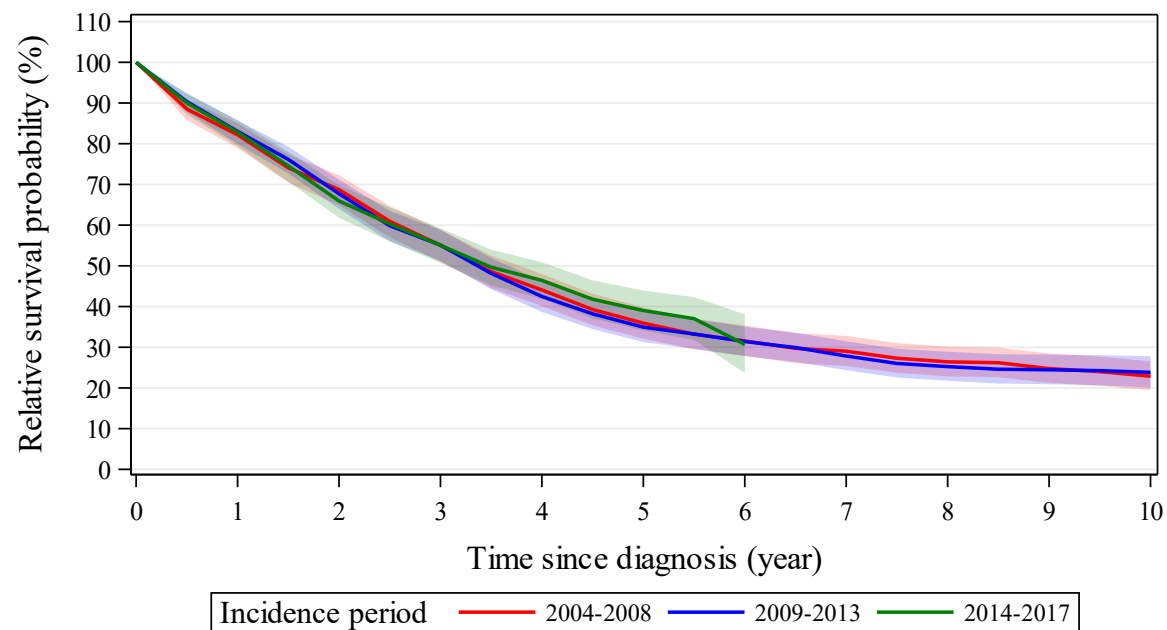
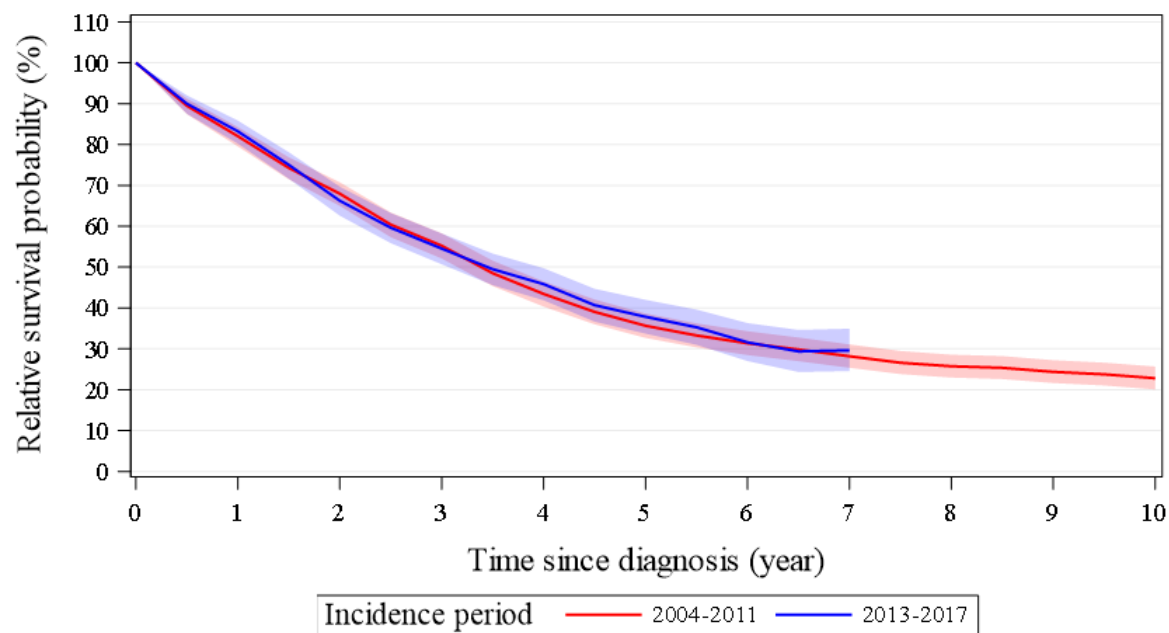


Figure 253 – Epithelial ovarian cancer (2004-2017), combined stage IIIC, relative survival graphs by incidence period (cut-off point: 2012)



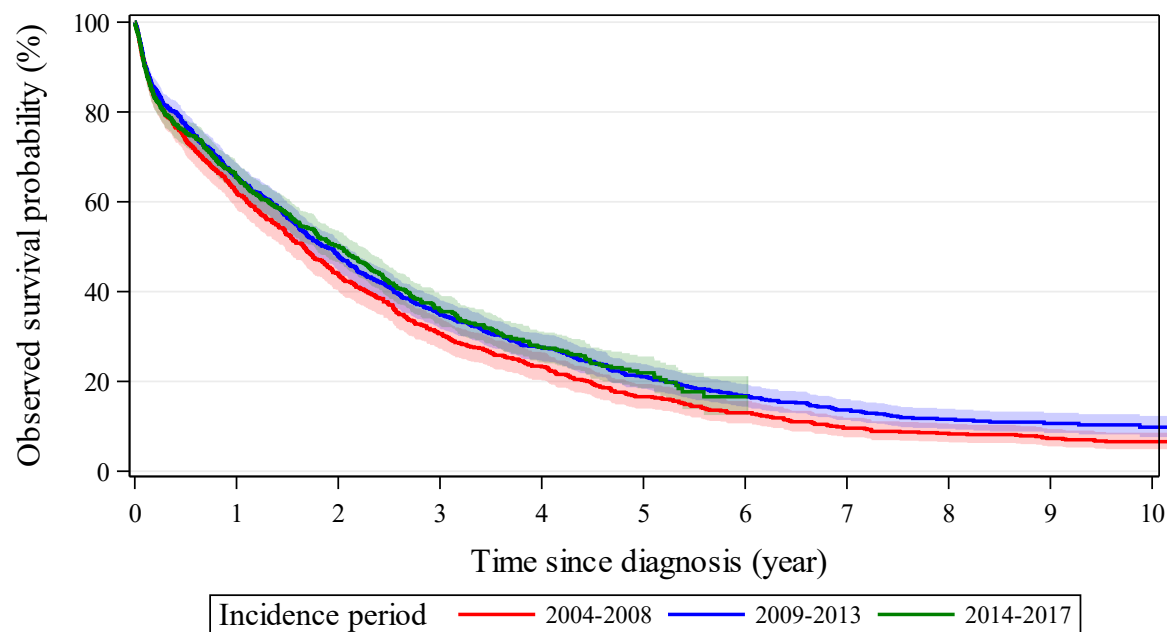
**Epithelial Ovarian Cancer, combined stage IV (2004-2017)****Figure 254 – Epithelial ovarian cancer (2004-2017), combined stage IV, Kaplan-Meier graphs observed survival by incidence period**

Figure 255 – Epithelial ovarian cancer (2004-2017), combined stage IV, Kaplan-Meier graphs observed survival by incidence period (cut-off point: 2012)

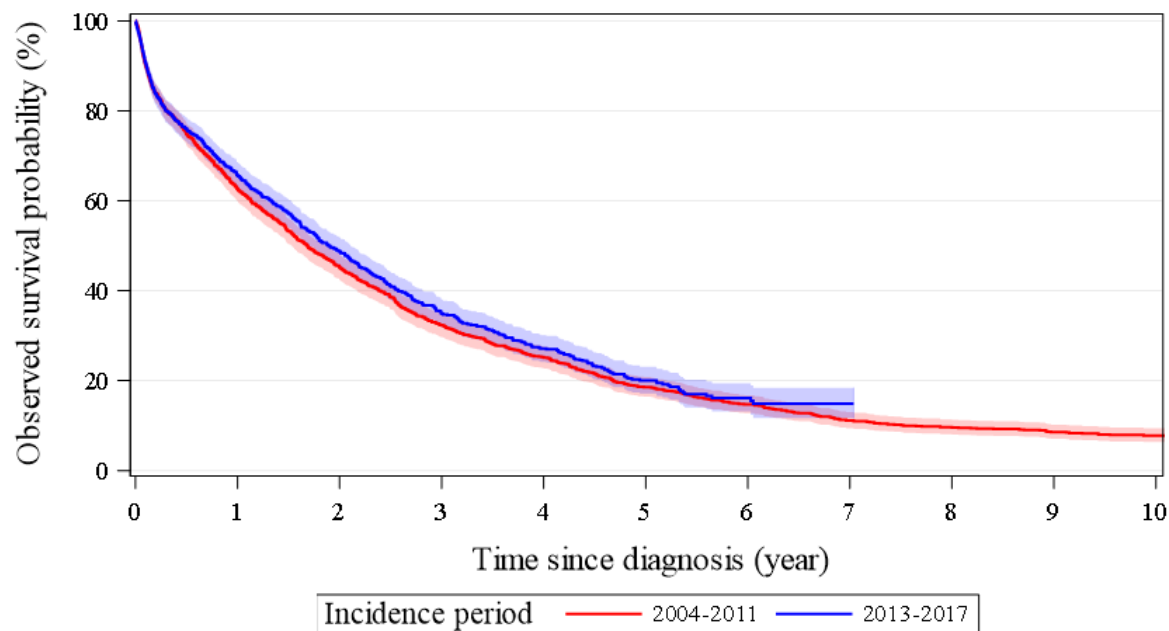




Figure 256 – Epithelial ovarian cancer (2004-2017), combined stage IV, relative survival graphs by incidence period

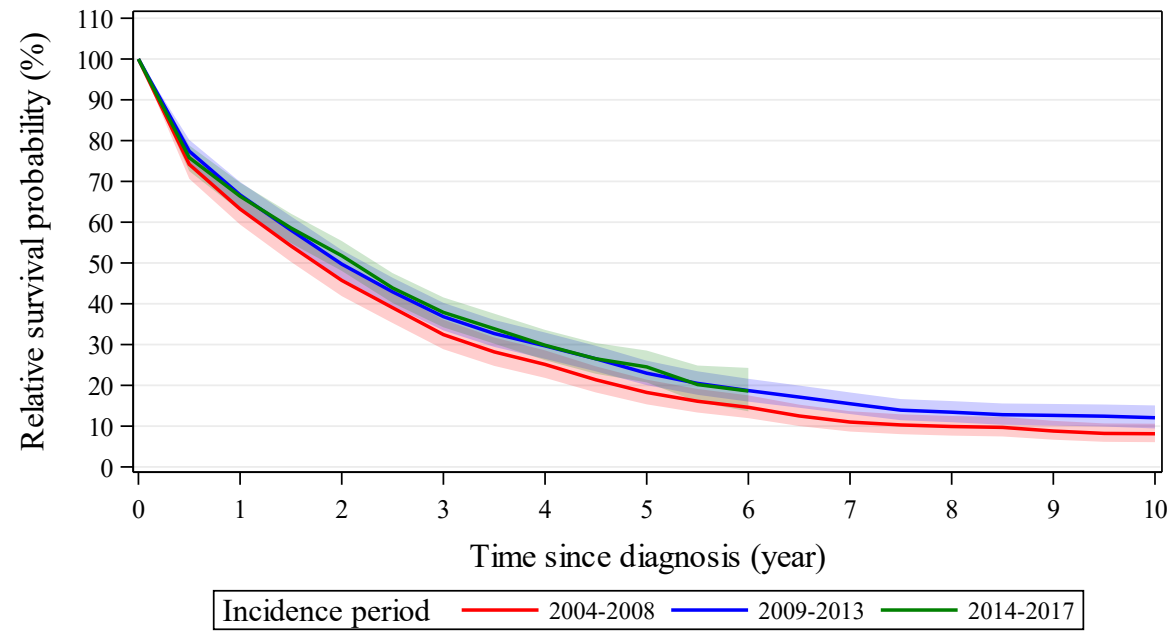




Figure 257 – Epithelial ovarian cancer (2004-2017), combined stage IV, relative survival graphs by incidence period (cut-off point: 2012)

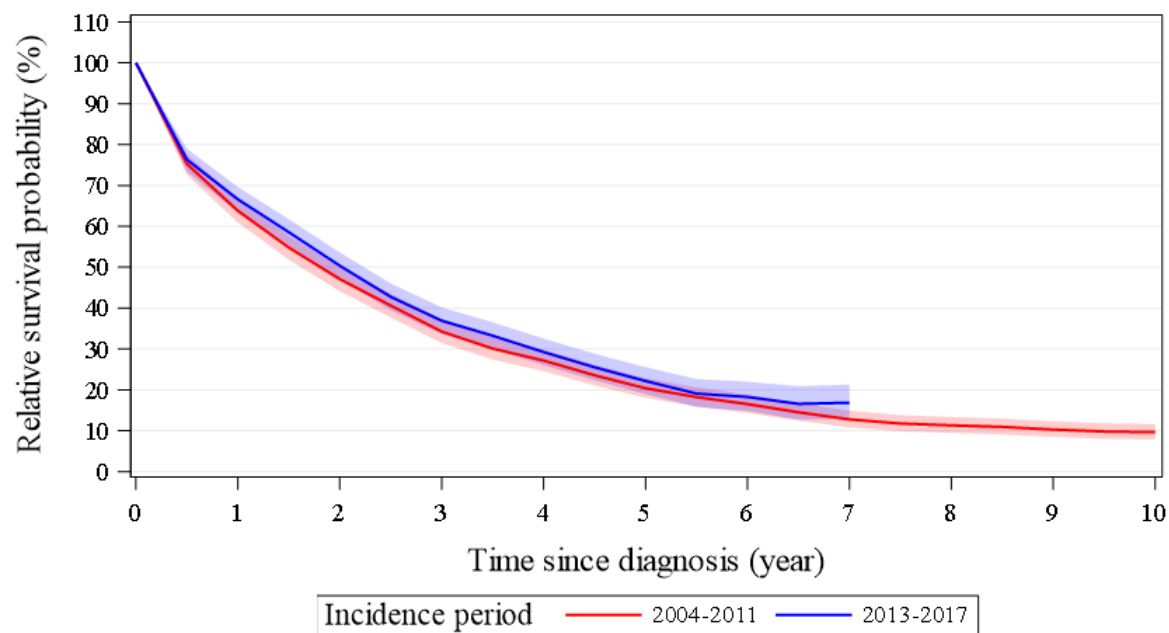




Figure 258 – Epithelial ovarian cancer (2004-2017), combined stage IV, Kaplan-Meier graphs observed survival by debulking status

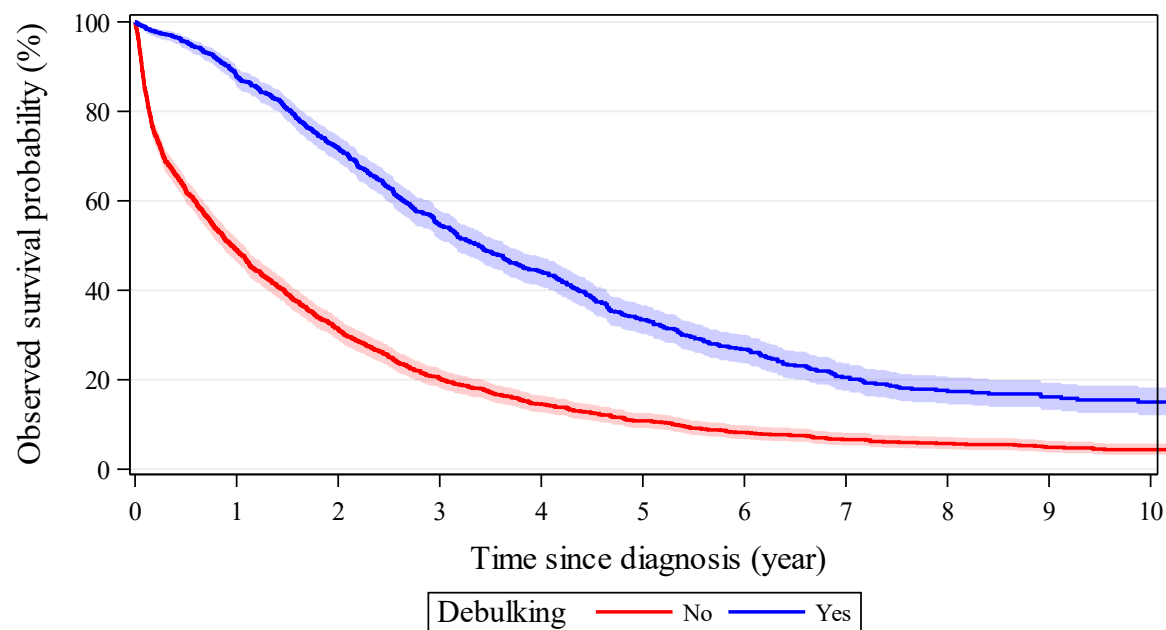




Figure 259 – Epithelial ovarian cancer (2004-2017), combined stage IV, Kaplan-Meier graphs observed survival by debulking status (cut-off point: 2012)

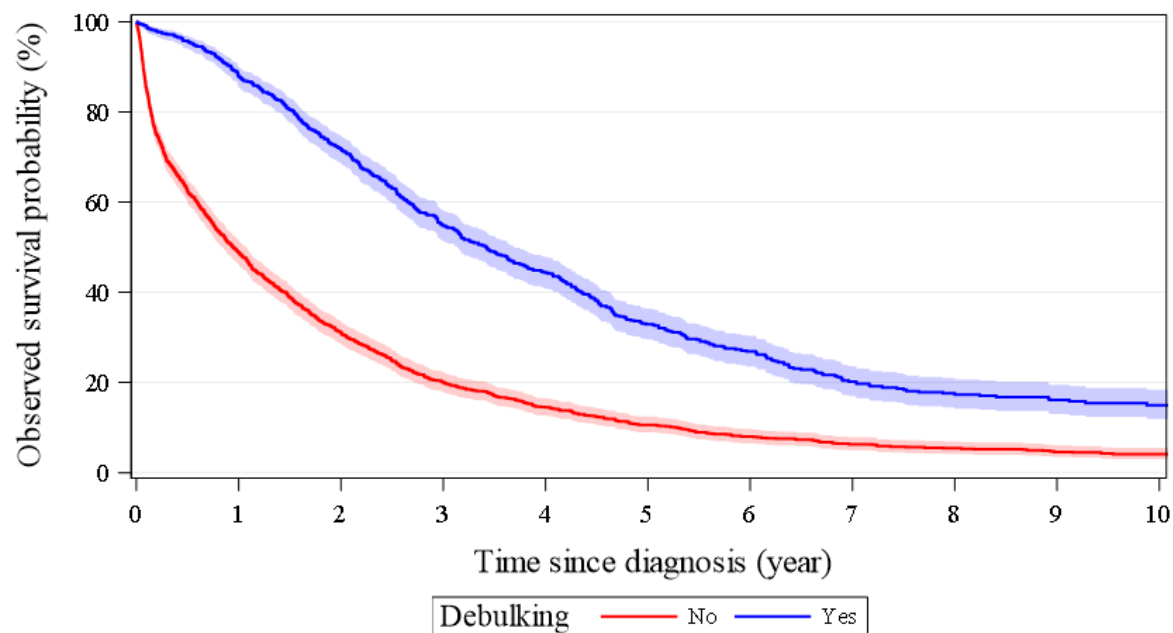




Figure 260 – Epithelial ovarian cancer (2004-2017), combined stage IV, relative survival graphs by debulking status

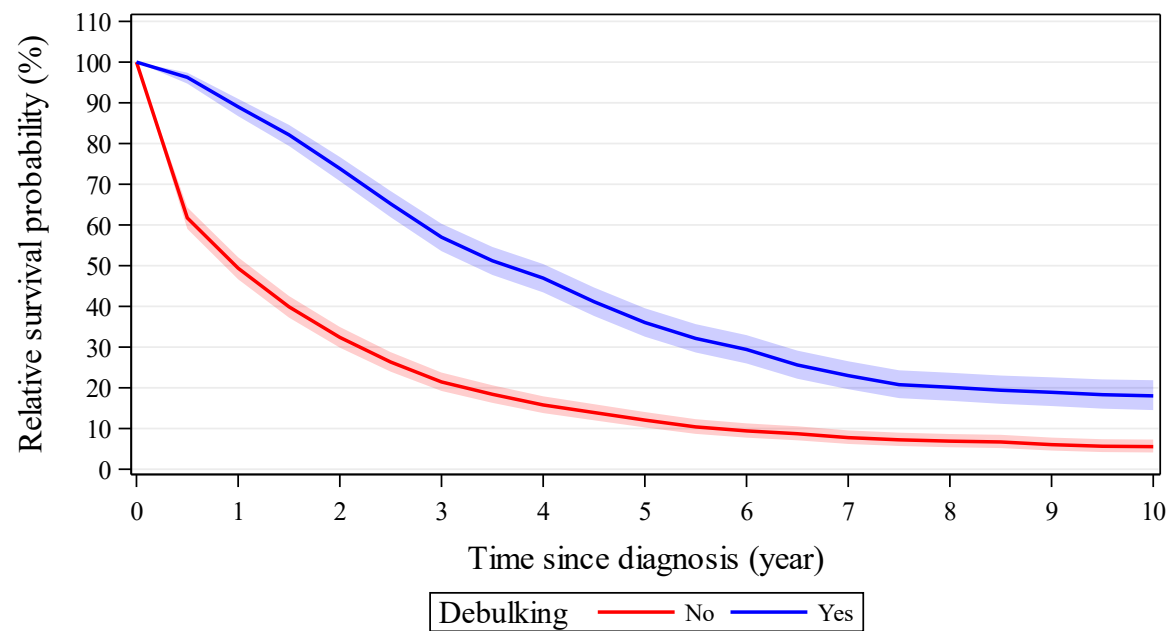
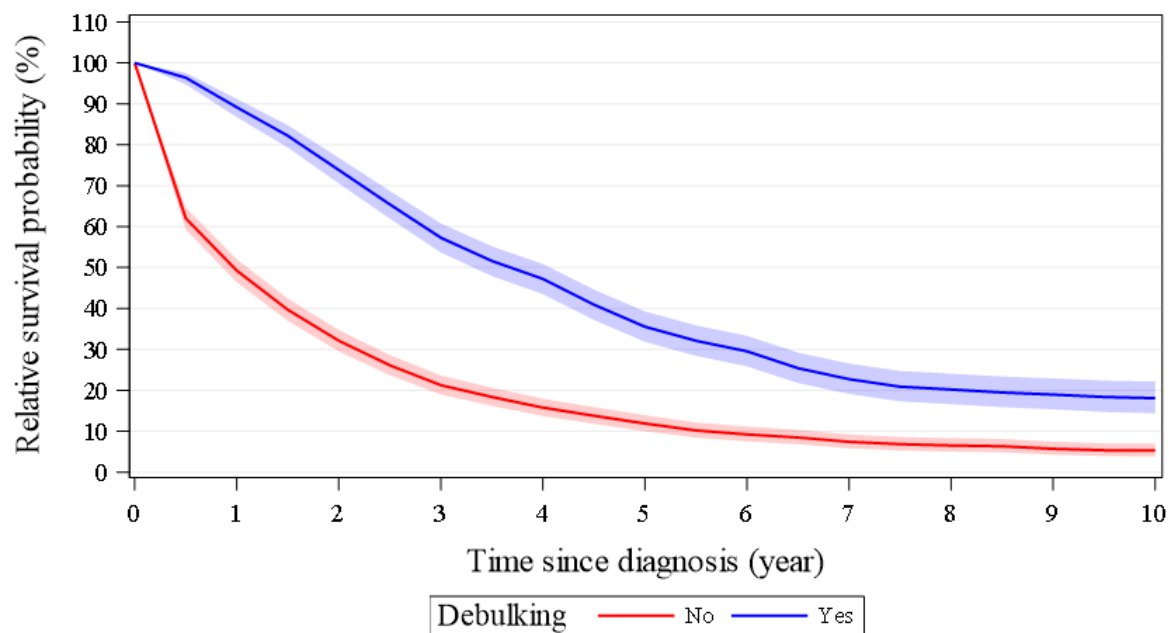




Figure 261 – Epithelial ovarian cancer (2004-2017), combined stage IV, relative survival graphs by debulking status (cut-off point: 2012)



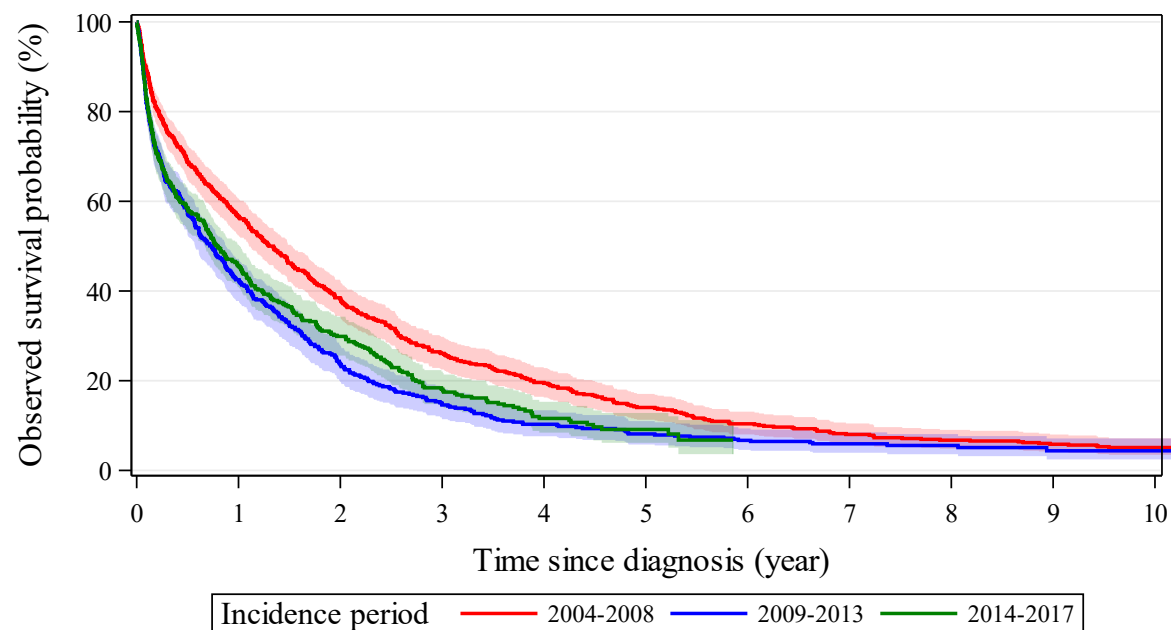
**Epithelial Ovarian Cancer, combined stage IV - no debulking (2004-2017)****Figure 262 – Epithelial ovarian cancer (2004-2017), combined stage IV - no debulking, Kaplan-Meier graphs observed survival by incidence period**

Figure 263 – Epithelial ovarian cancer (2004-2017), combined stage IV - no debulking, Kaplan-Meier graphs observed survival by incidence period (cut-off point: 2012)

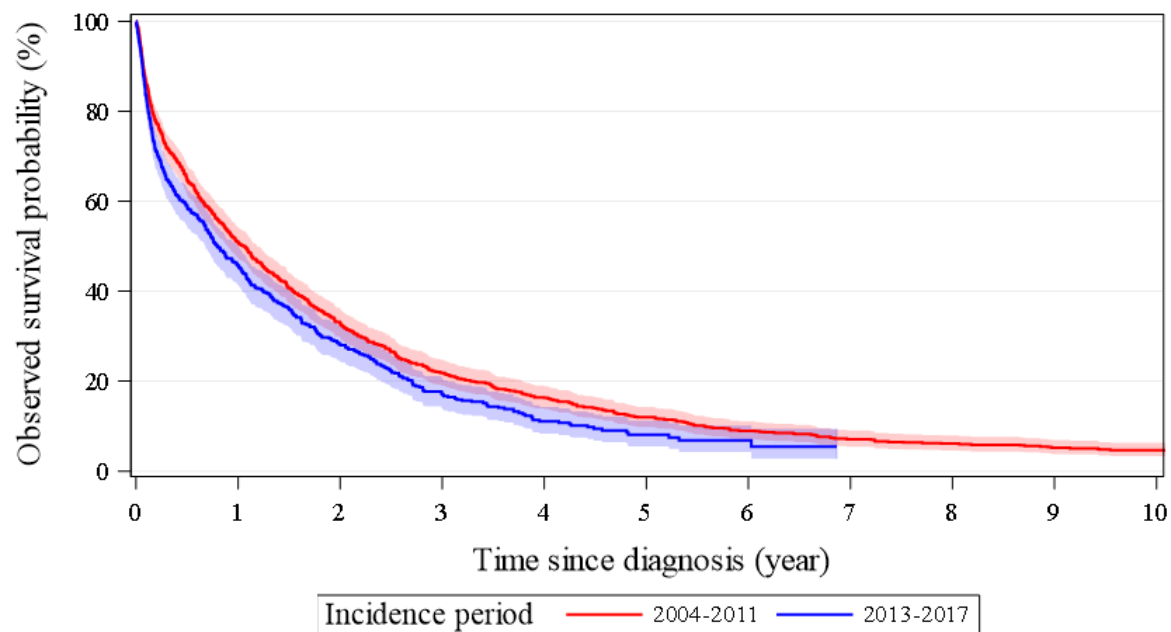




Figure 264 – Epithelial ovarian cancer (2004-2017), combined stage IV - no debulking, relative survival graphs by incidence period

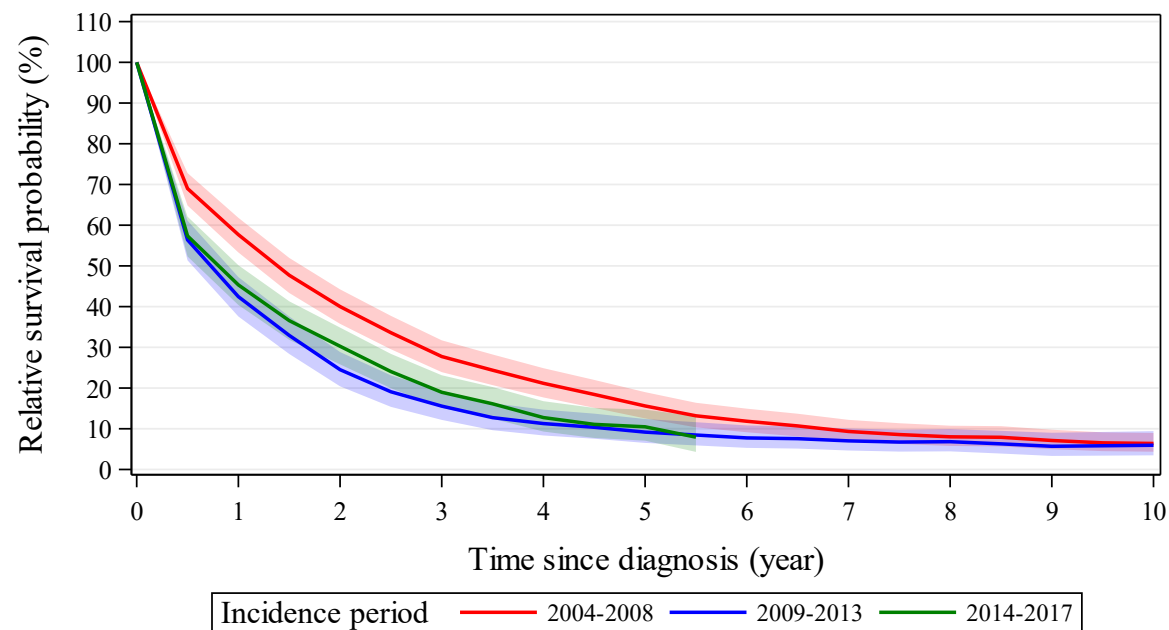
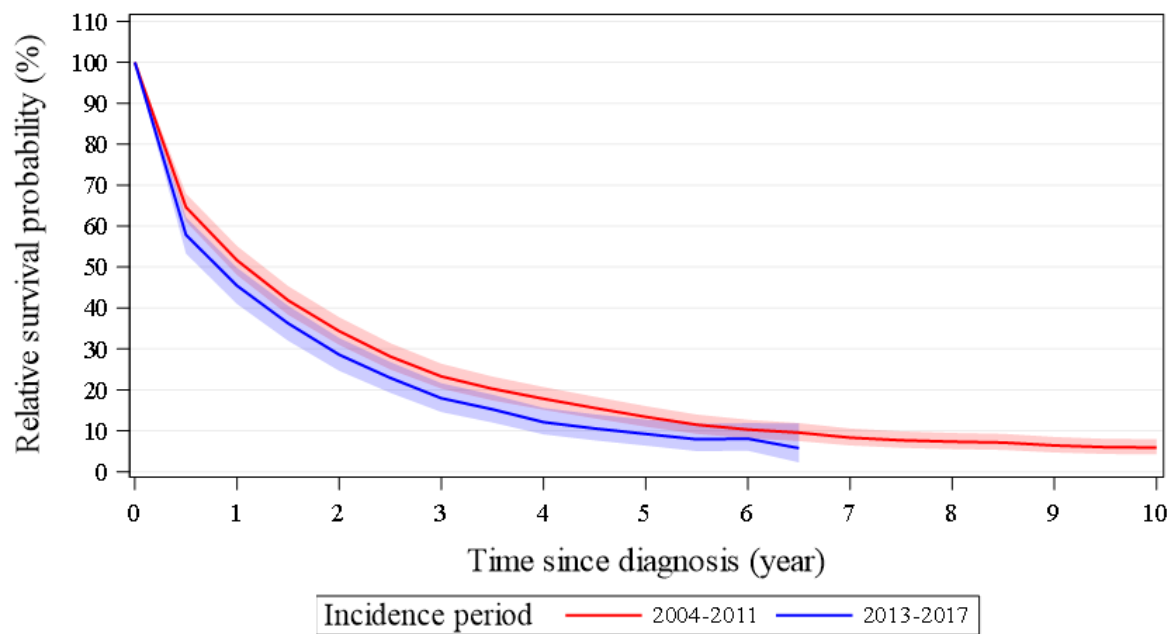


Figure 265 – Epithelial ovarian cancer (2004-2017), combined stage IV - no debulking, relative survival graphs by incidence period (cut-off point: 2012)



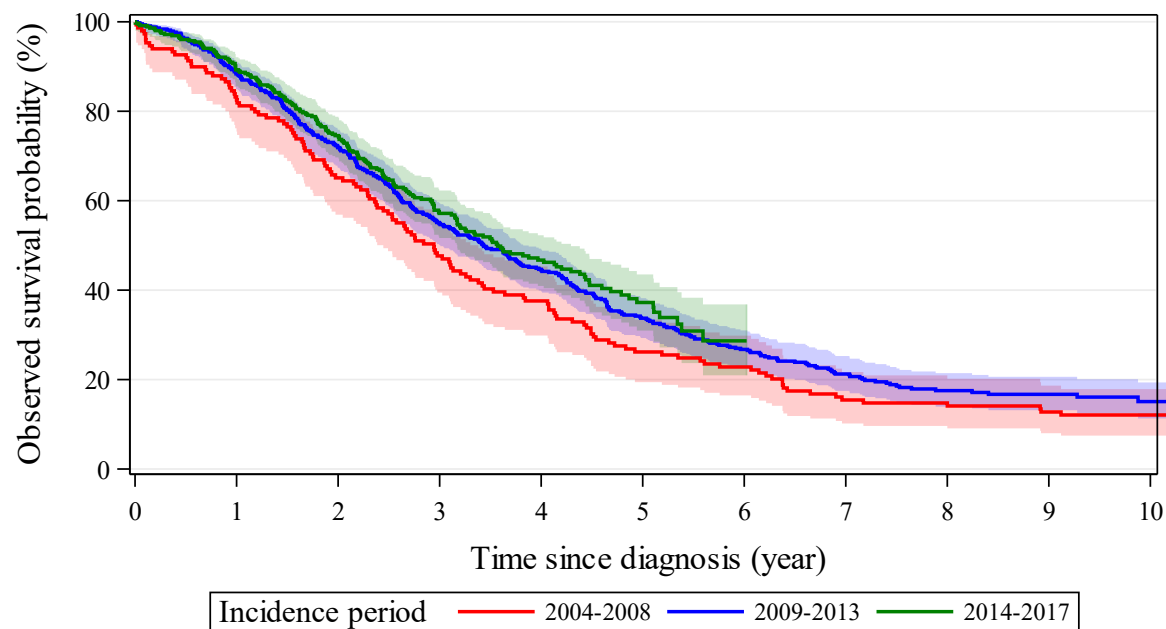
**Epithelial Ovarian Cancer, combined stage IV - debulking (2004-2017)****Figure 266 – Epithelial ovarian cancer (2004-2017), combined stage IV - debulking, Kaplan-Meier graphs observed survival by incidence period**



Figure 267 – Epithelial ovarian cancer (2004-2017), combined stage IV - debulking, Kaplan-Meier graphs observed survival by incidence period (cut-off point: 2012)

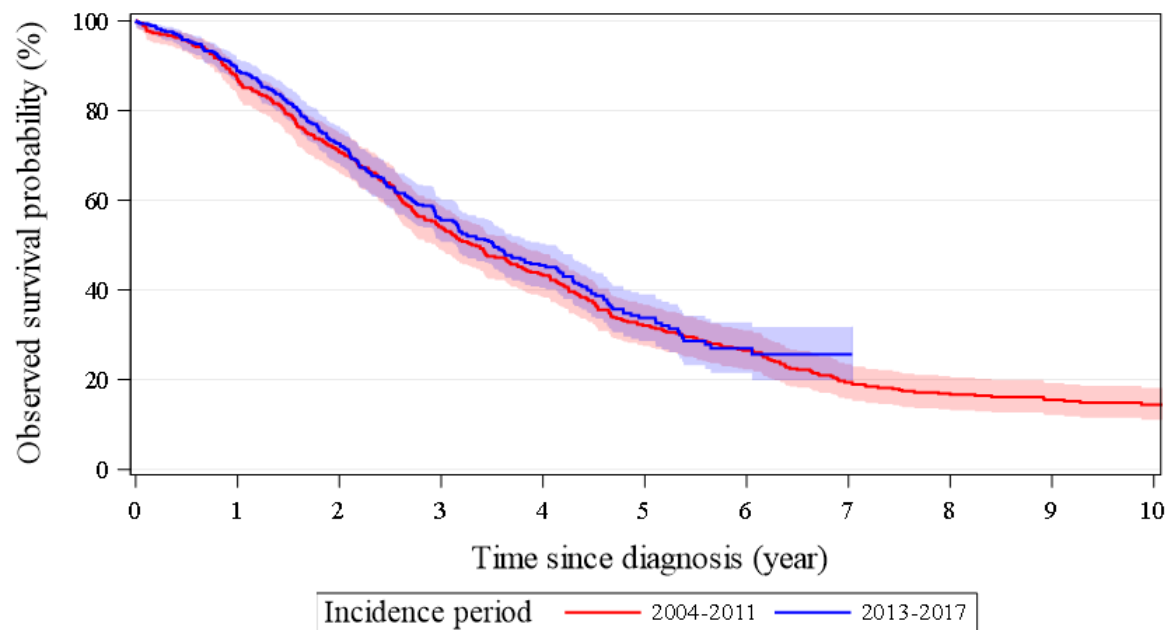




Figure 268 – Epithelial ovarian cancer (2004-2017), combined stage IV - debulking, relative survival graphs by incidence period

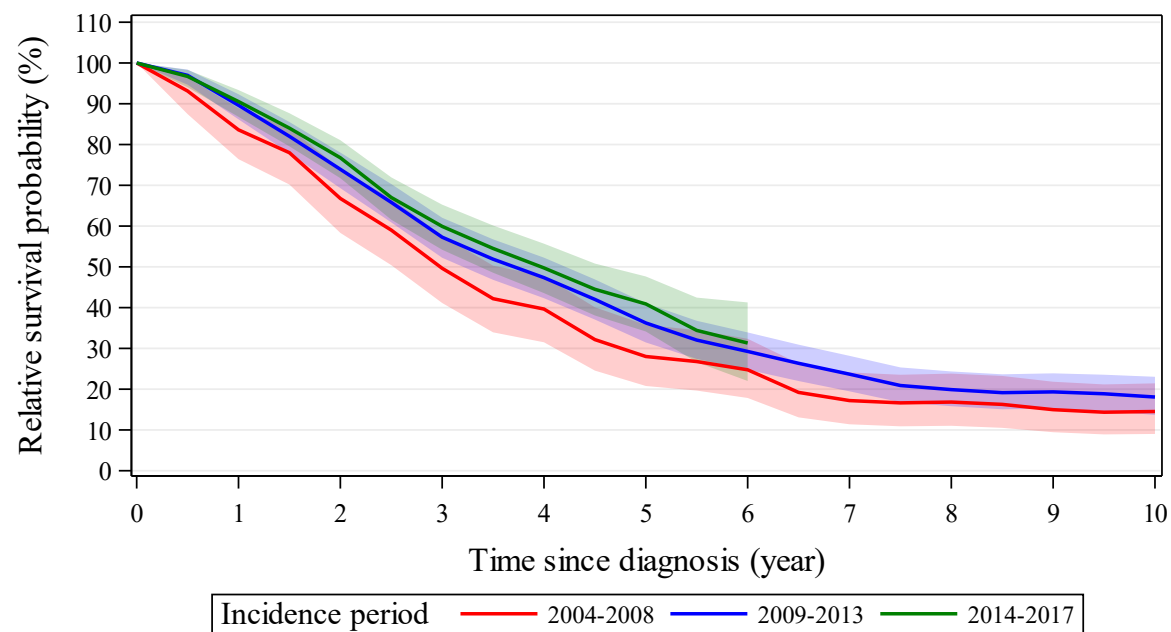
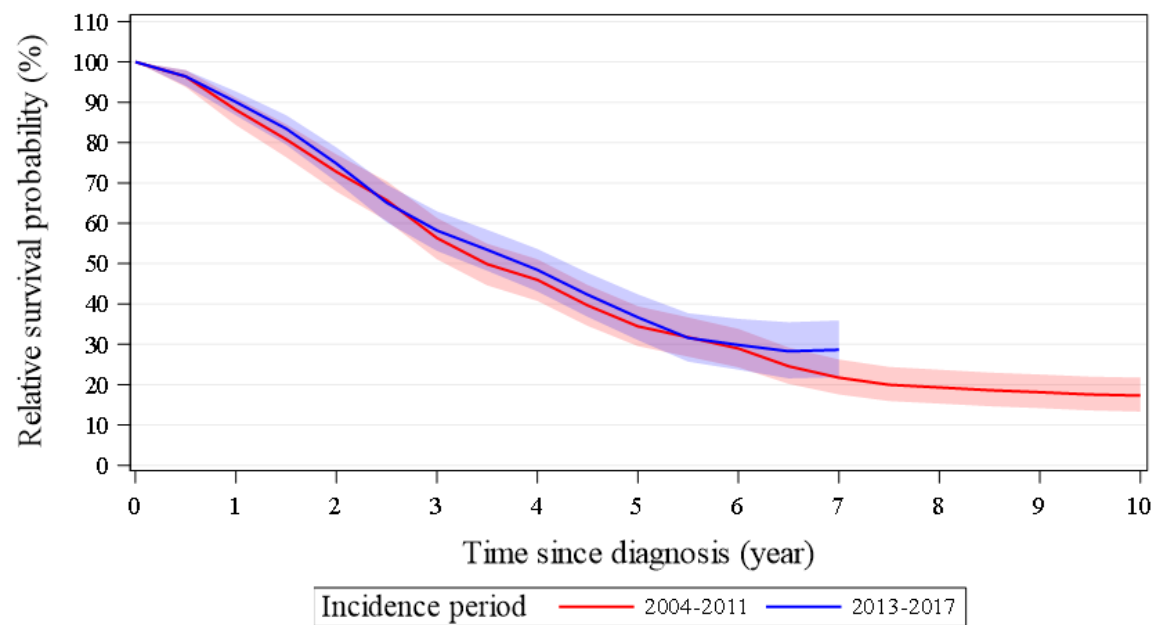




Figure 269 – Epithelial ovarian cancer (2004-2017), combined stage IV - debulking, relative survival graphs by incidence period (cut-off point: 2012)

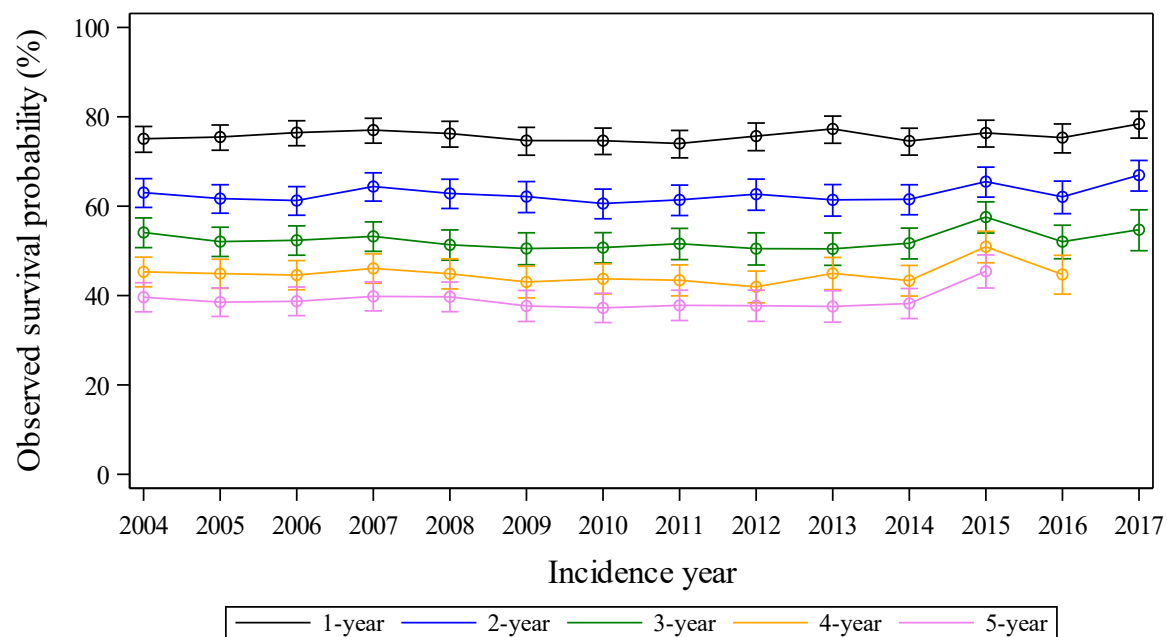




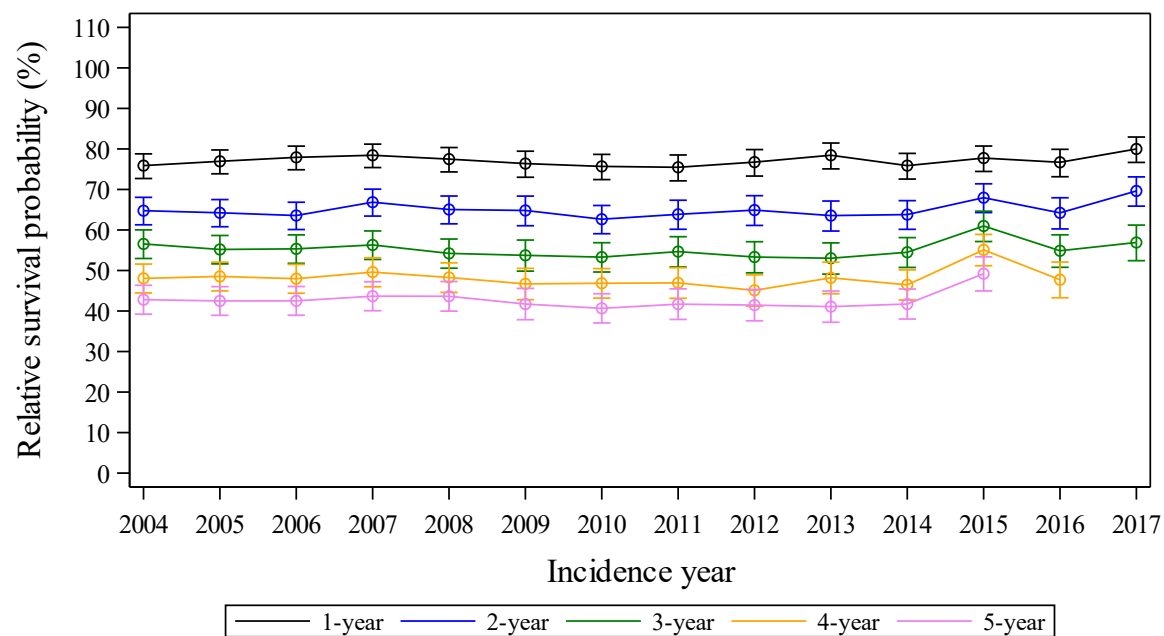
Appendix 10.1.1.3. Epithelial Ovarian Cancer, time trend Observed and Relative Survival

Epithelial Ovarian Cancer (2004-2017)

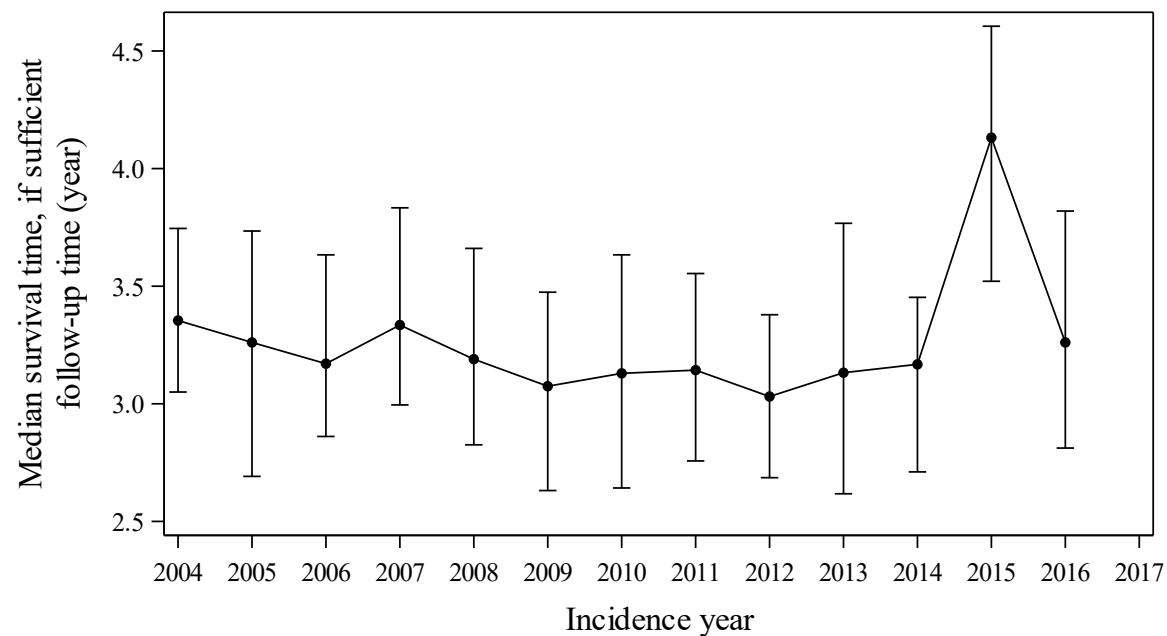
Figure 270 – Epithelial ovarian cancer (2004-2017), time trend observed survival with incidence year



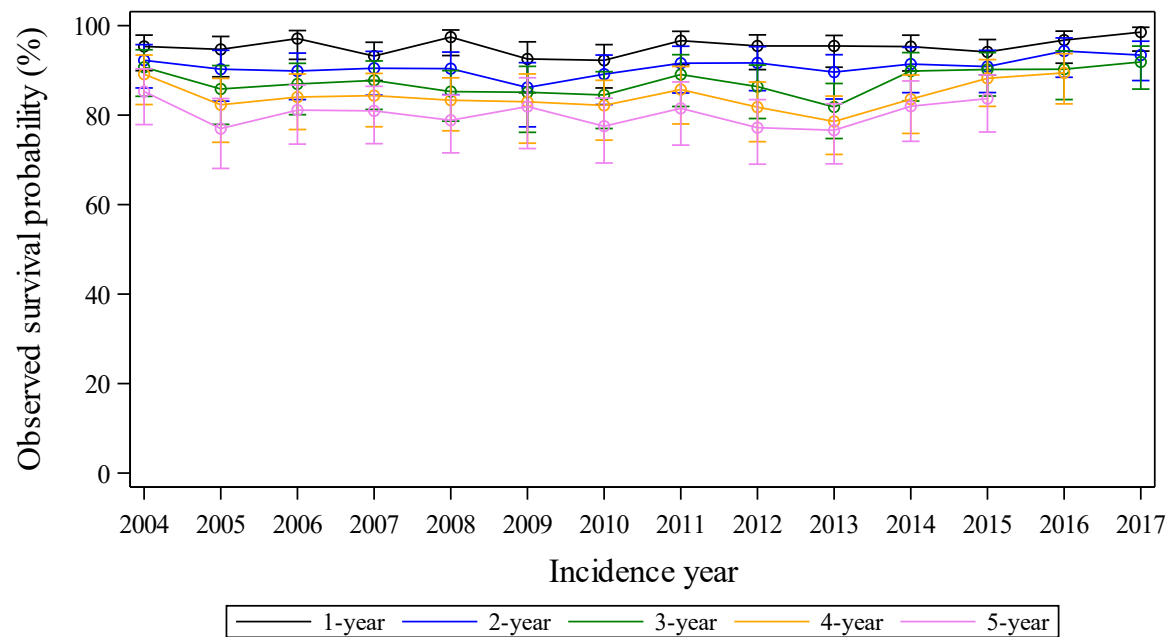
Note: the error bars represent the 95% CI.

**Figure 271 – Epithelial ovarian cancer (2004-2017), time trend relative survival with incidence year**

Note: the error bars represent the 95% CI.

**Figure 272 – Epithelial ovarian cancer (2004-2017), Median time observed survival**

Note: the error bars represent the 95% CI. When the upper error is not plotted, the upper limit could not be determined with the follow-up available.

**Epithelial Ovarian Cancer, combined stage I (2004-2017)****Figure 273 – Epithelial ovarian cancer (2004-2017), combined stage I, time trend observed survival with incidence year**

Note: the error bars represent the 95% CI.



Figure 274 – Epithelial ovarian cancer (2004-2017), combined stage I, time trend relative survival with incidence year

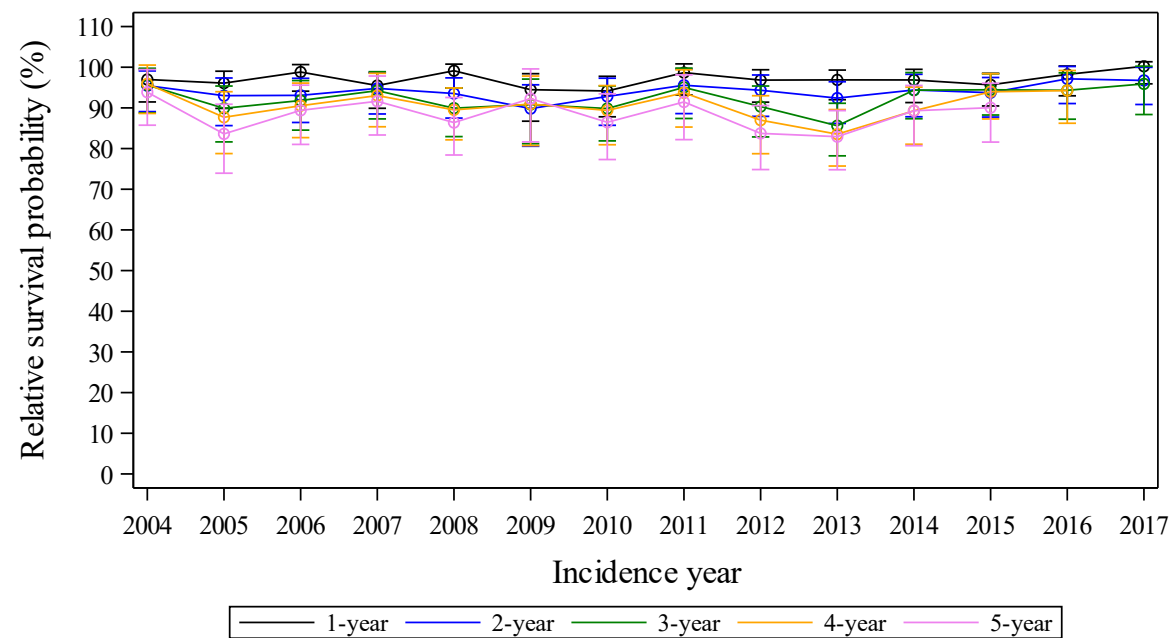
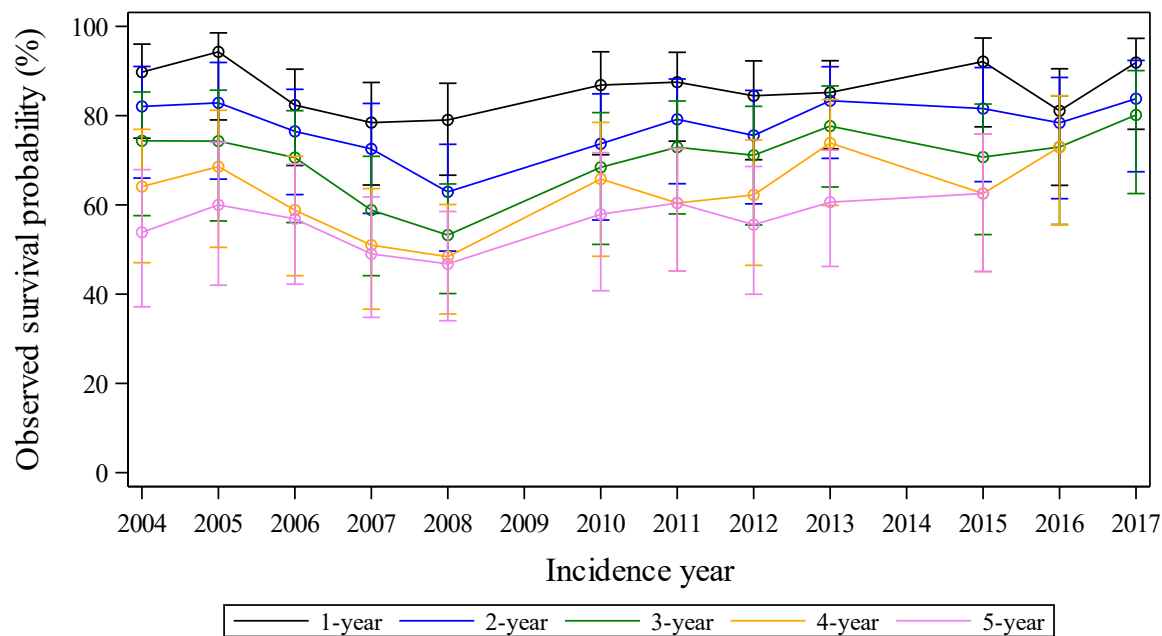
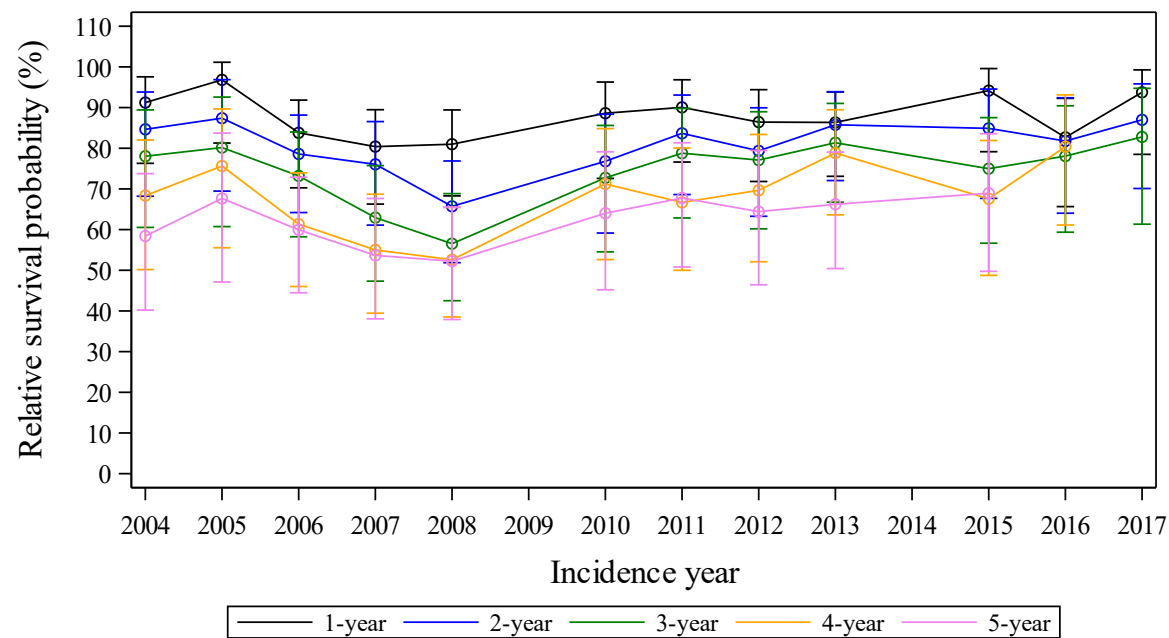


**Figure 275 – Epithelial ovarian cancer (2004-2017), combined stage I, median time observed survival**

No data points to plot, as survival curves remain above 50% and the median survival time can therefore not be determined.

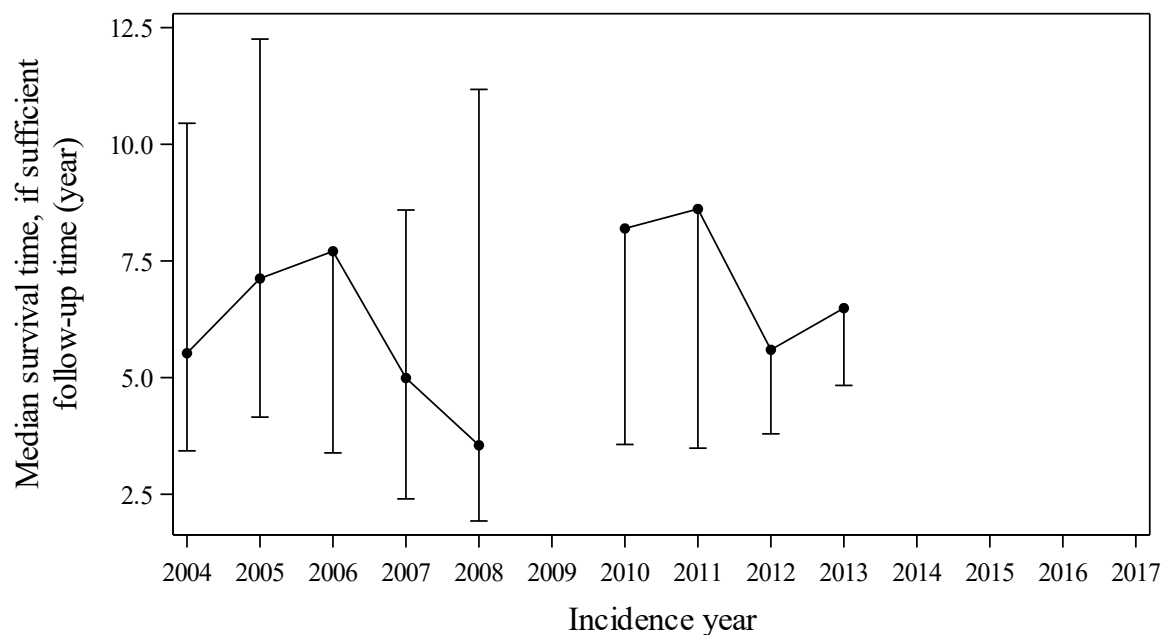
Epithelial Ovarian Cancer, combined stage II (2004-2017)**Figure 276 – Epithelial ovarian cancer (2004-2017), combined stage II, time trend observed survival with incidence year**

Note: the error bars represent the 95% CI.

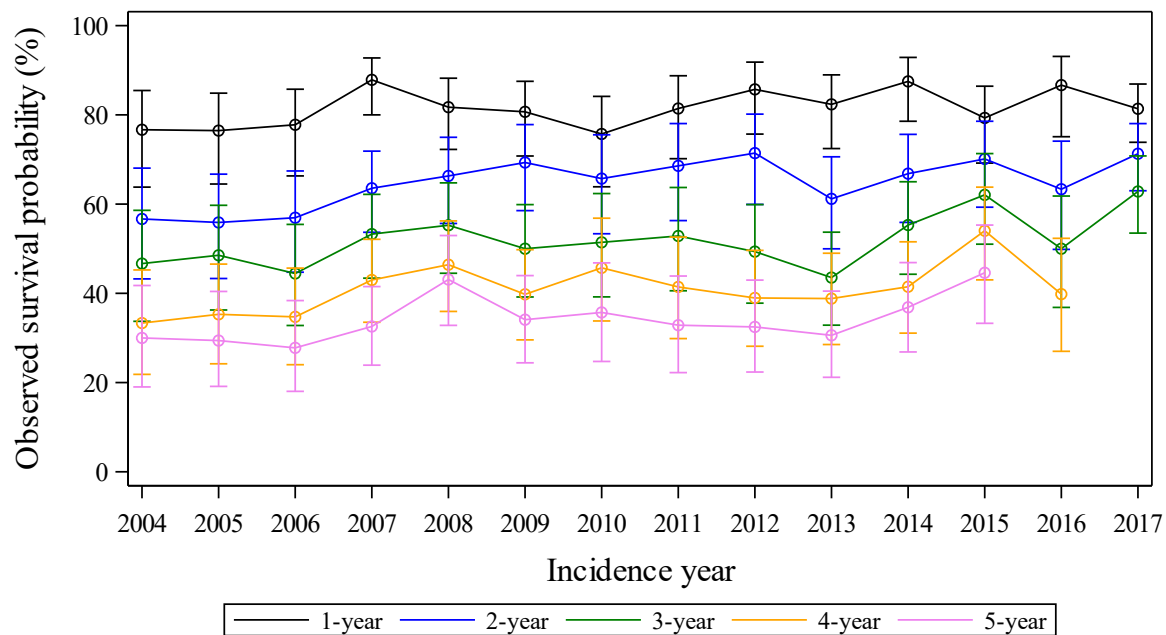
**Figure 277 – Epithelial ovarian cancer (2004-2017), combined stage II, time trend relative survival with incidence year**

Note: the error bars represent the 95% CI.

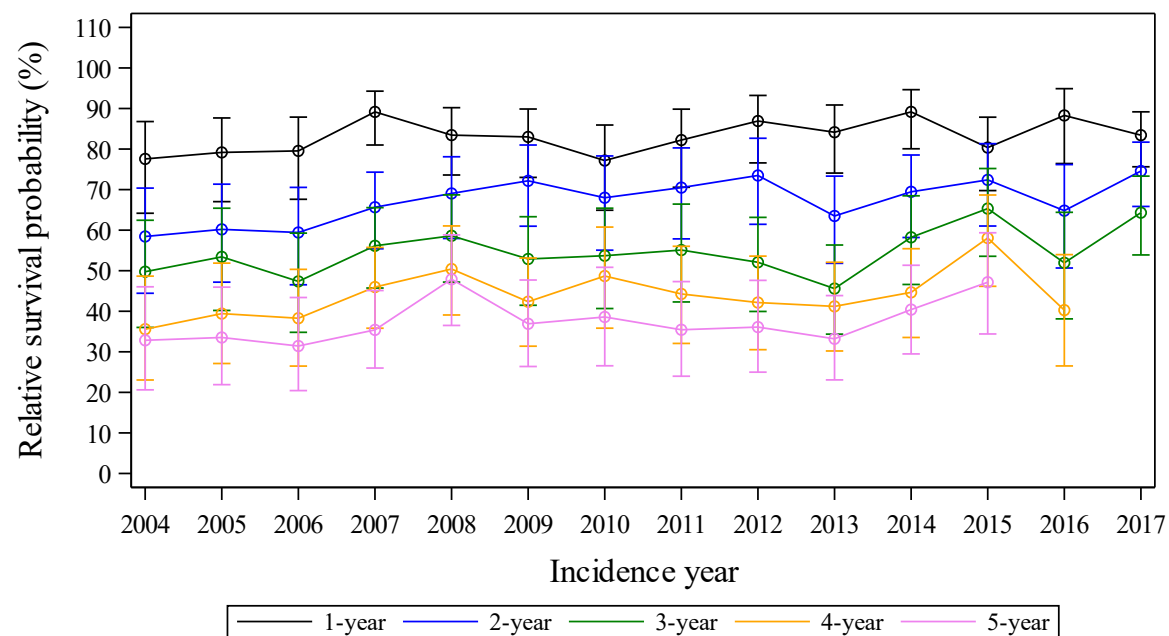
Figure 278 – Epithelial ovarian cancer (2004-2017), combined stage II, median time observed survival



Note: the error bars represent the 95% CI. When the upper error is not plotted, the upper limit could not be determined with the follow-up available. Survival results based on small number of persons initially at risk ($N < 35$) can be too variable to be practically meaningful and are therefore not reported.

**Epithelial Ovarian Cancer, combined stage IIIA/B (2004-2017)****Figure 279 – Epithelial ovarian cancer (2004-2017), combined stage IIIA/B, time trend observed survival with incidence year**

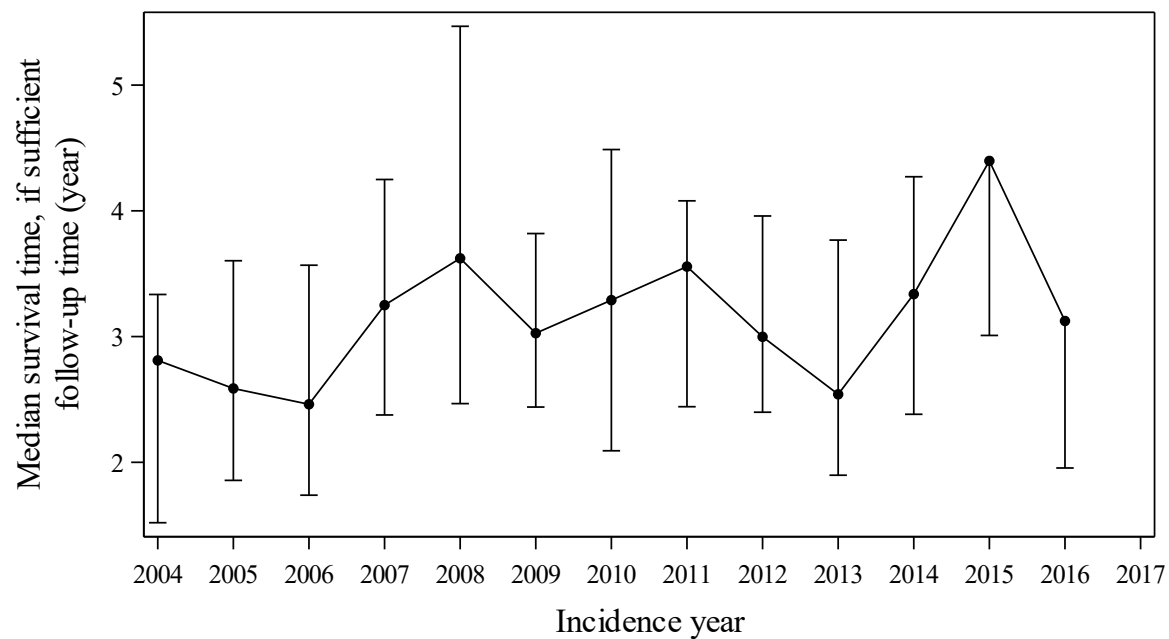
Note: the error bars represent the 95% CI.

**Figure 280 – Epithelial ovarian cancer (2004-2017), combined stage IIIA/B, time trend relative survival with incidence year**

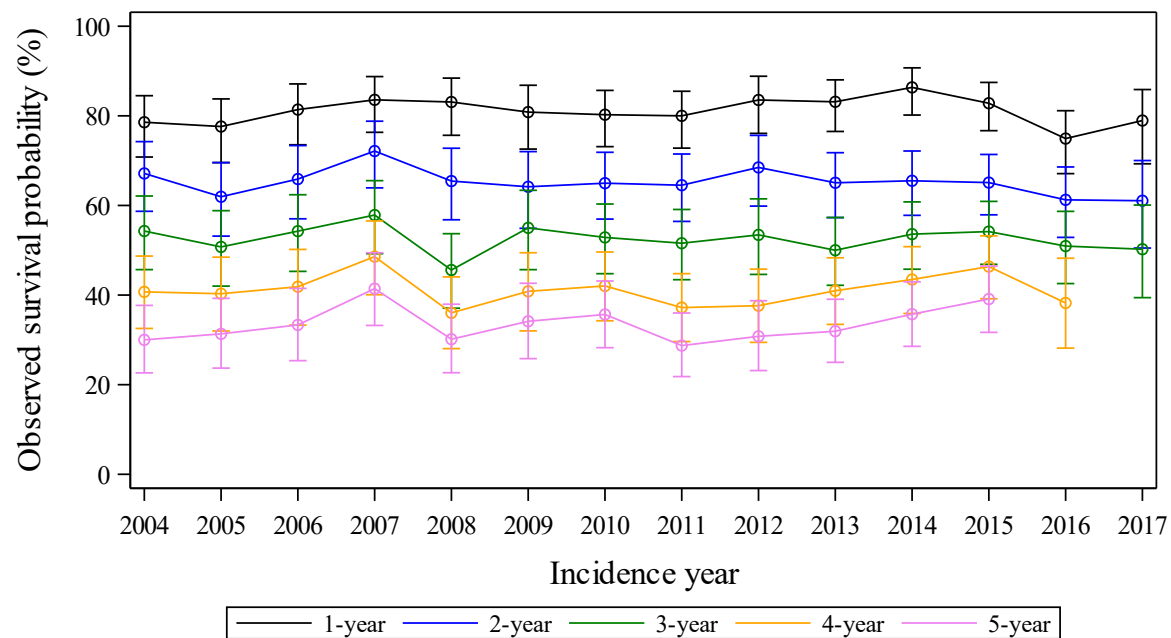
Note: the error bars represent the 95% CI.



Figure 281 – Epithelial ovarian cancer (2004-2017), combined stage IIIA/B, median time observed survival



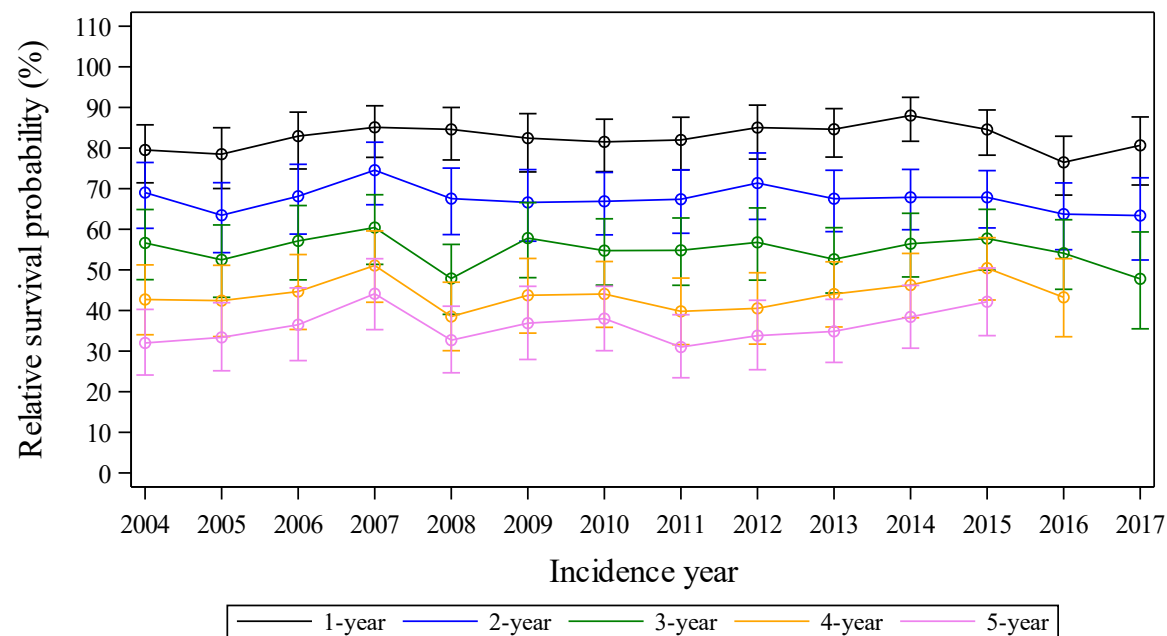
Note: the error bars represent the 95% CI. When the upper error is not plotted, the upper limit could not be determined with the follow-up available.

**Epithelial Ovarian Cancer, combined stage IIIC (2004-2017)****Figure 282 – Epithelial ovarian cancer (2004-2017), combined stage IIIC, time trend observed survival with incidence year**

Note: the error bars represent the 95% CI.

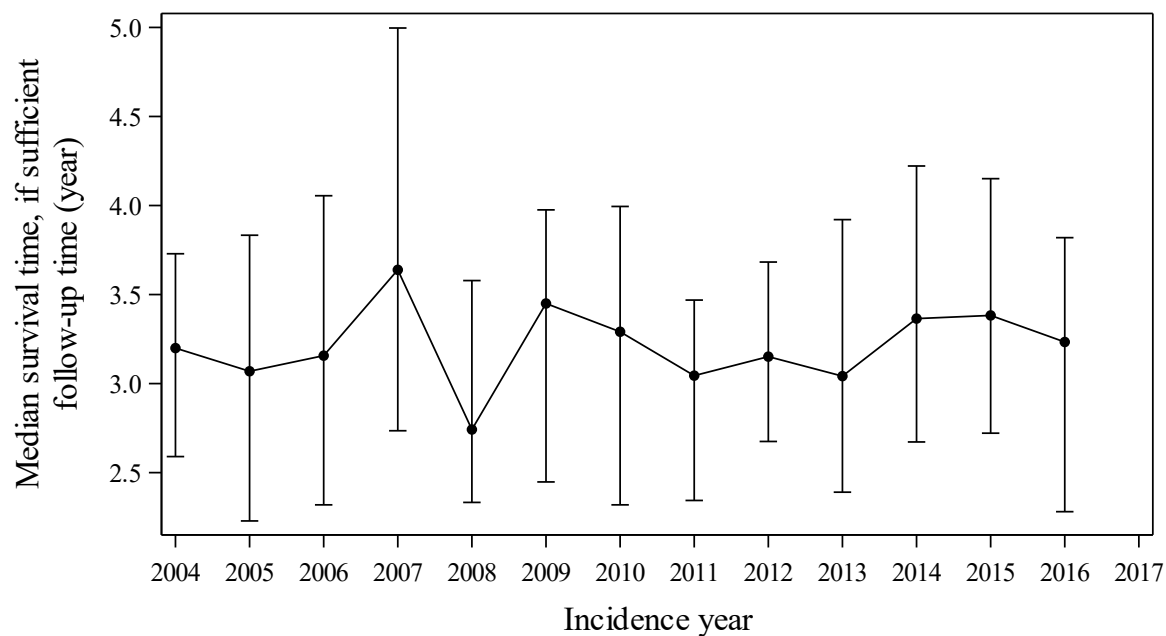


Figure 283 – Epithelial ovarian cancer (2004-2017), combined stage IIIC, time trend relative survival with incidence year

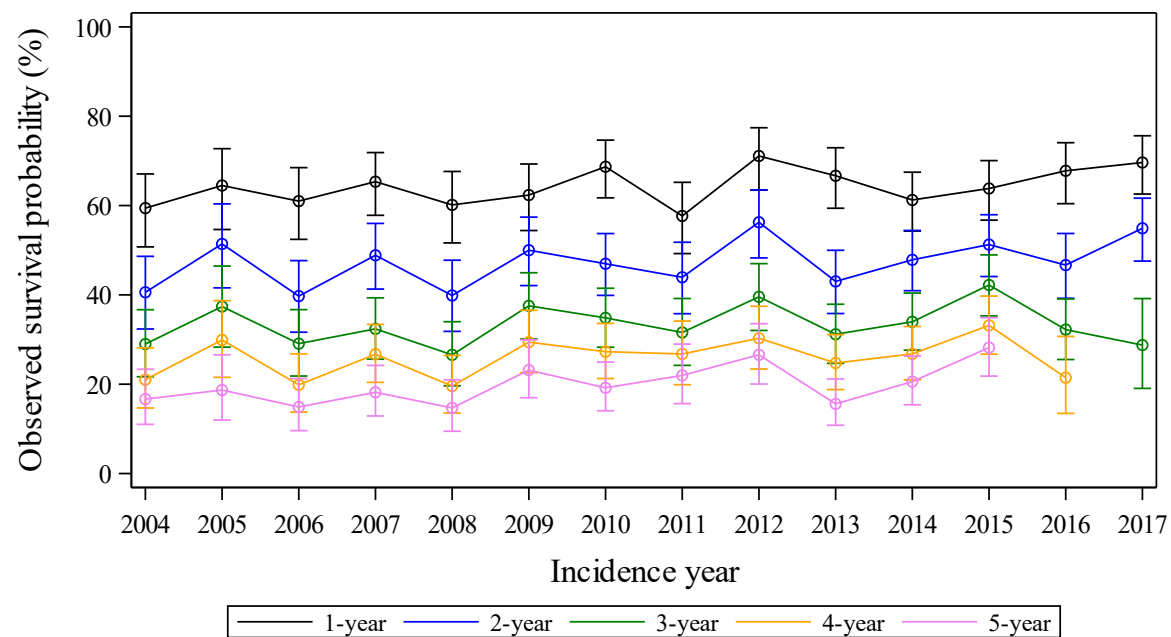


Note: the error bars represent the 95% CI.

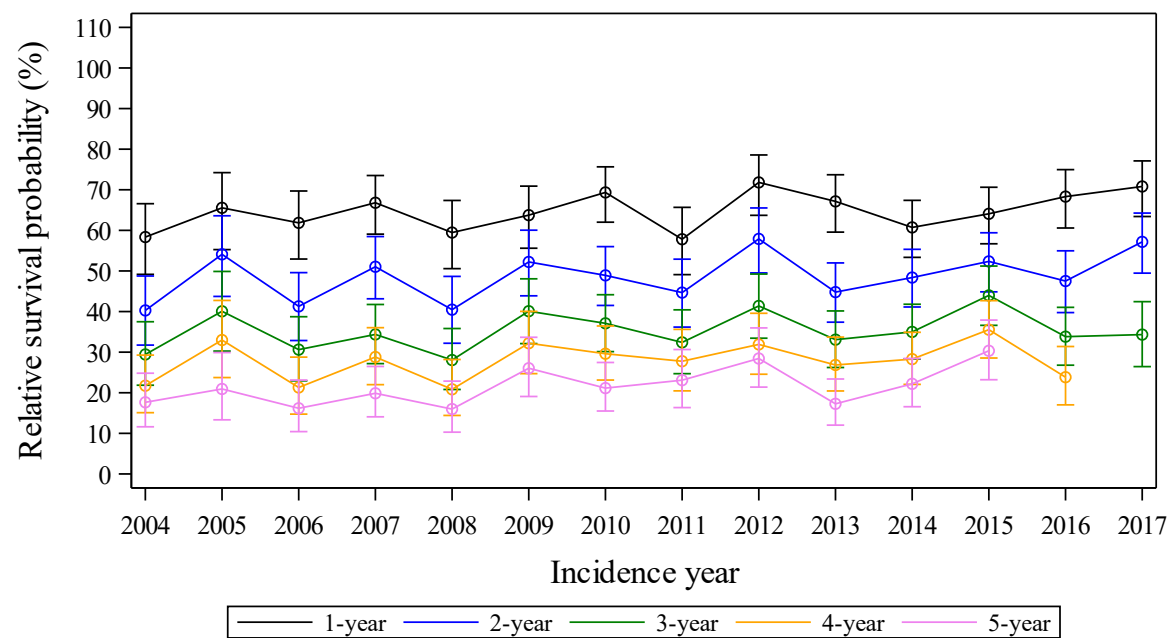
Figure 284 – Epithelial ovarian cancer (2004-2017), combined stage IIIC, median time observed survival



Note: the error bars represent the 95% CI. When the upper error is not plotted, the upper limit could not be determined with the follow-up available.

**Epithelial Ovarian Cancer, combined stage IV (2004-2017)****Figure 285 – Epithelial ovarian cancer (2004-2017), combined stage IV, time trend observed survival with incidence year**

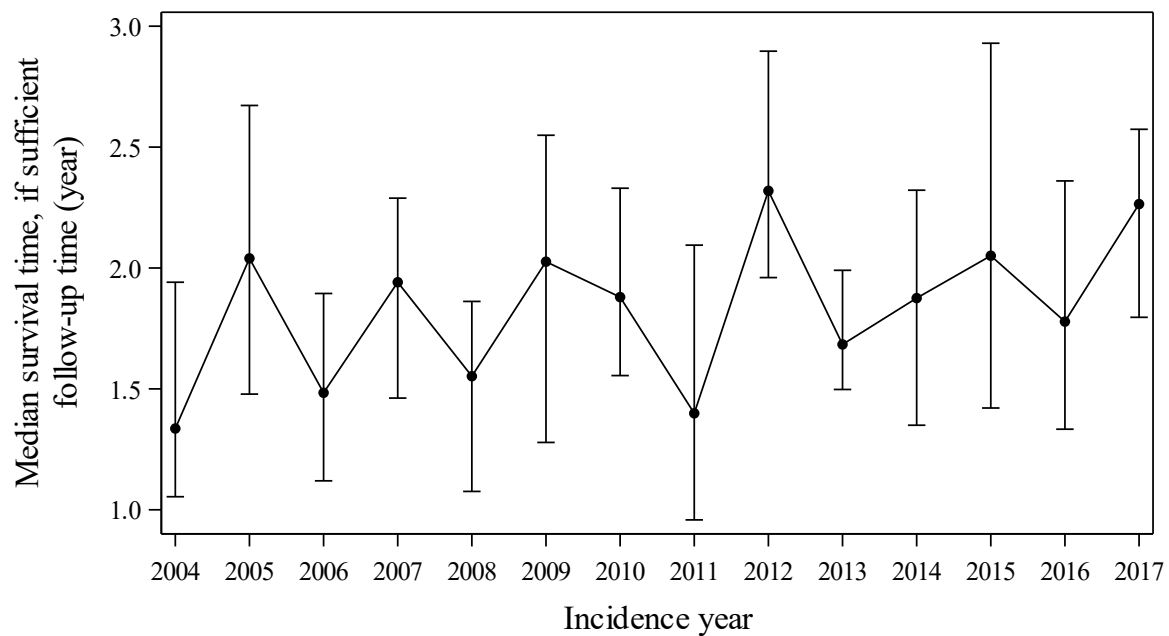
Note: the error bars represent the 95% CI.

**Figure 286 – Epithelial ovarian cancer (2004-2017), combined stage IV, time trend relative survival with incidence year**

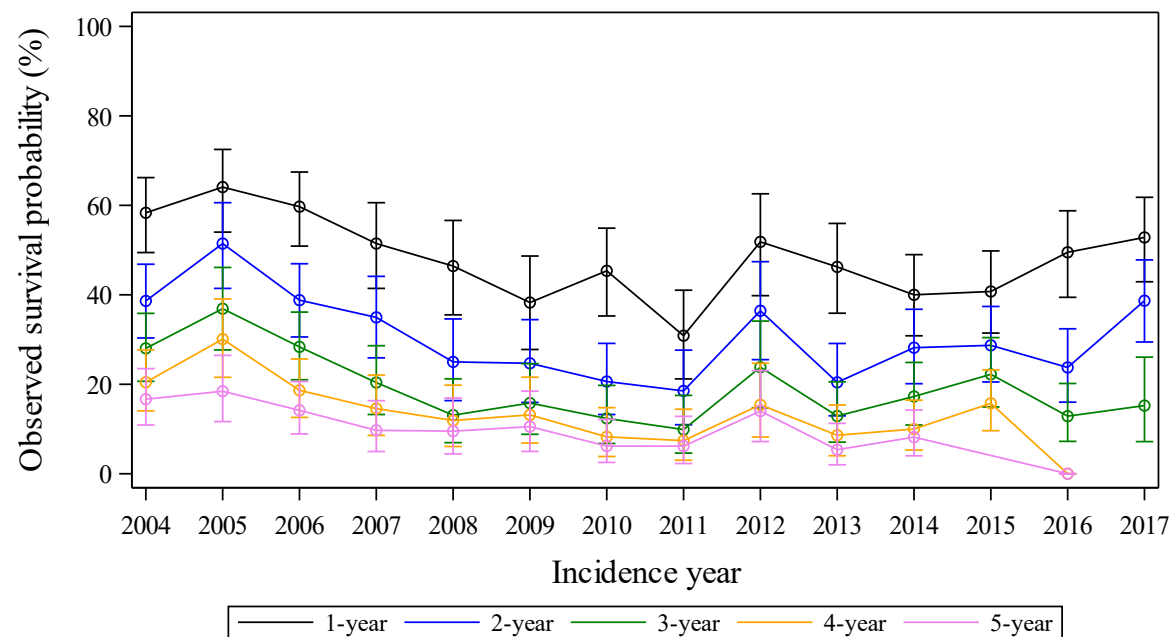
Note: the error bars represent the 95% CI.



Figure 287 – Epithelial ovarian cancer (2004-2017), combined stage IV, median time observed survival



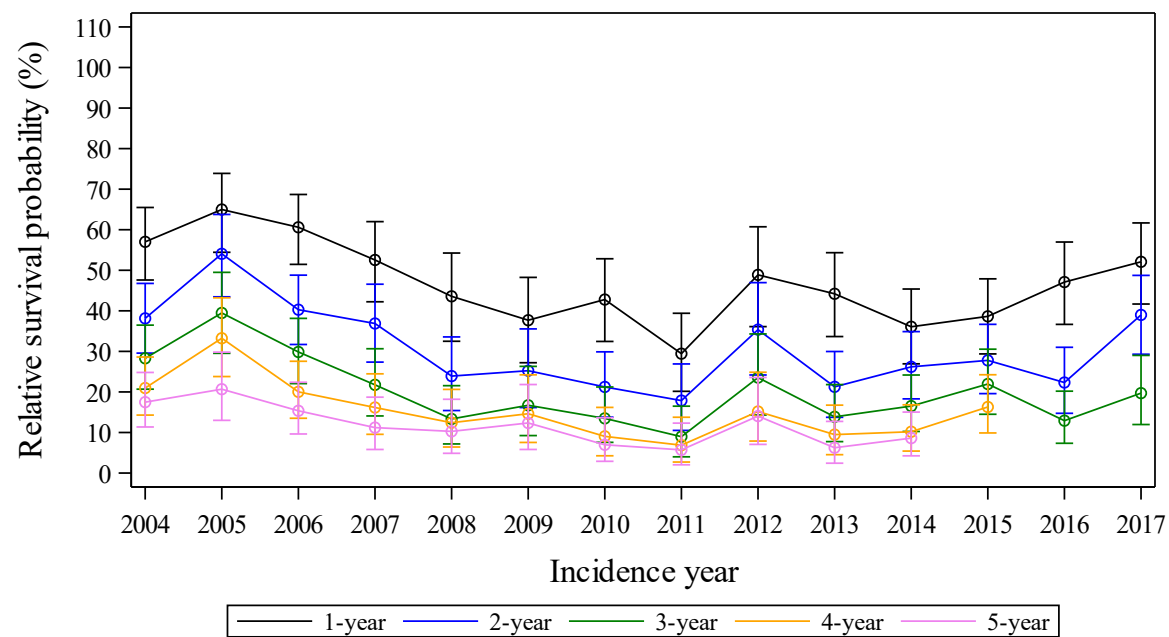
Note: the error bars represent the 95% CI. When the upper error is not plotted, the upper limit could not be determined with the follow-up available.

**Epithelial Ovarian Cancer, combined stage IV - no debulking (2004-2017)****Figure 288 – Epithelial ovarian cancer (2004-2017), combined stage IV - no debulking, time trend observed survival with incidence year**

Note: the error bars represent the 95% CI.

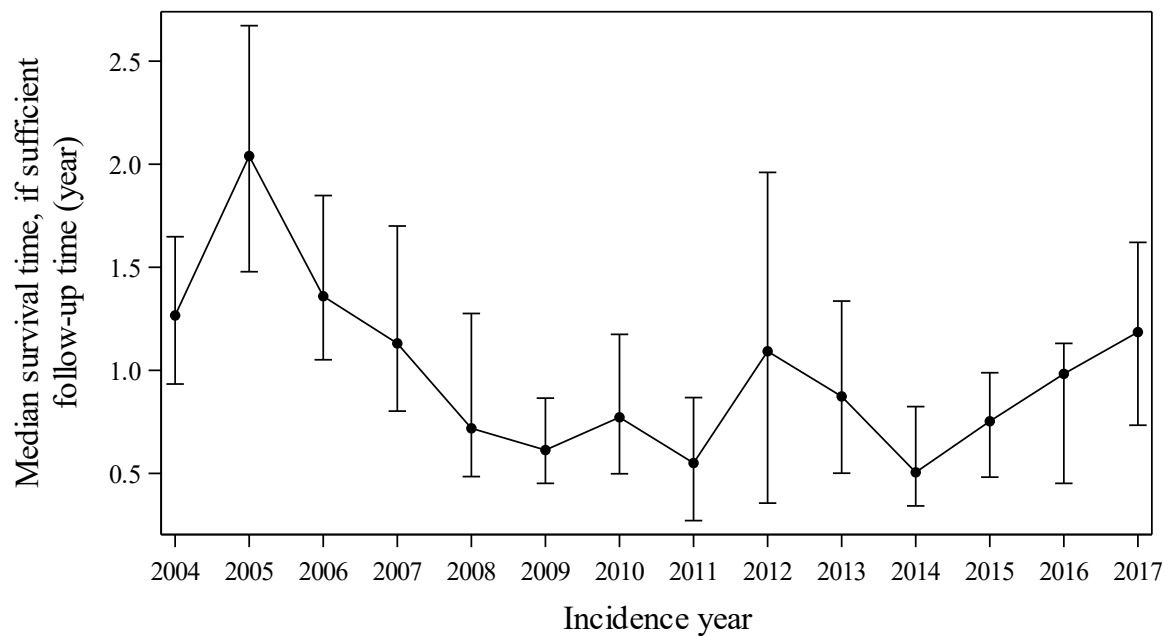


Figure 289 – Epithelial ovarian cancer (2004-2017), combined stage IV - no debulking, time trend relative survival with incidence year

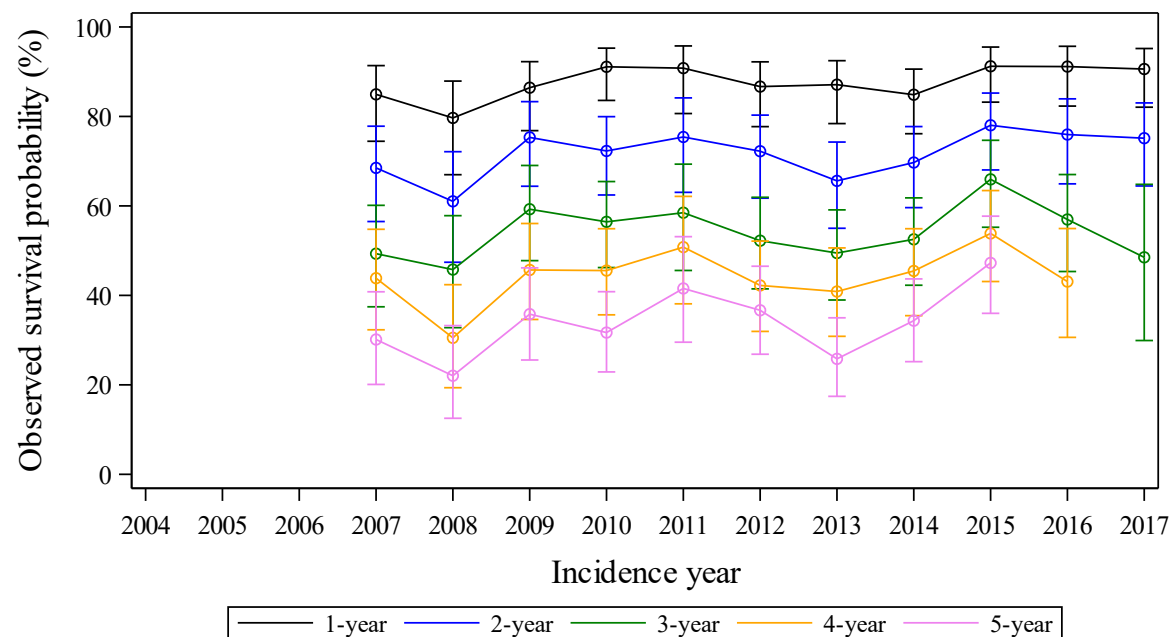


Note: the error bars represent the 95% CI.

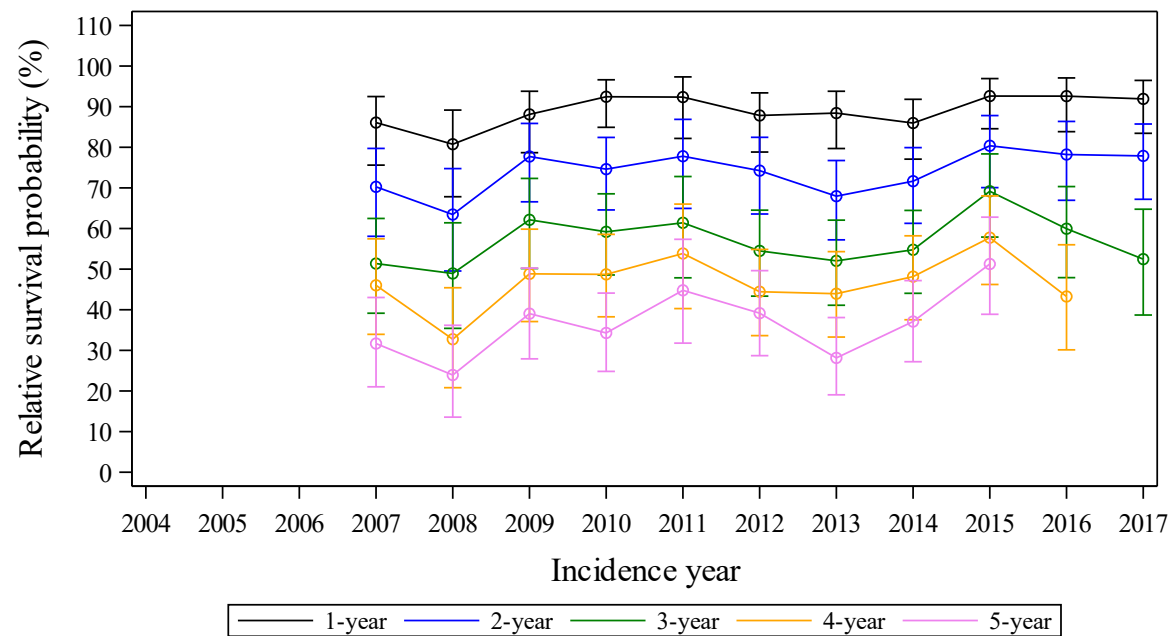
Figure 290 – Epithelial ovarian cancer (2004-2017), combined stage IV - no debulking, median time observed survival



Note: the error bars represent the 95% CI. When the upper error is not plotted, the upper limit could not be determined with the follow-up available.

**Epithelial Ovarian Cancer, combined stage IV - debulking (2004-2017)****Figure 291 – Epithelial ovarian cancer (2004-2017) - combined stage IV, debulking, time trend observed survival with incidence year**

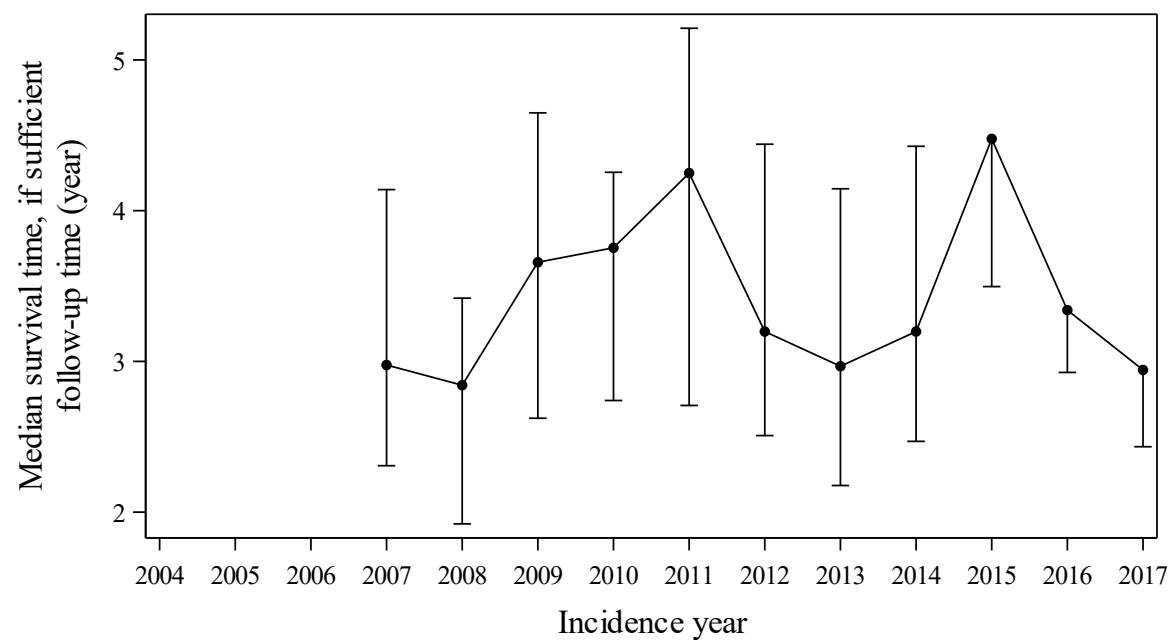
Note: the error bars represent the 95% CI.

**Figure 292 – Epithelial ovarian cancer (2004-2017) - combined stage IV, debulking, time trend relative survival with incidence year**

Note: the error bars represent the 95% CI.



Figure 293 – Epithelial ovarian cancer (2004-2017) - combined stage IV, debulking, median time observed survival



Note: the error bars represent the 95% CI. When the upper error is not plotted, the upper limit could not be determined with the follow-up available.



Appendix 10.1.1.4. Epithelial Ovarian Cancer, time trend tables Observed and Relative Survival

Table 151 – Epithelial ovarian cancer (2004-2017), time trend observed survival with incidence year

Unadjusted observed survival, %													
Characteristic	N at risk	1 year		2 year		3 year		4 year		5 year		Median survival time (year)	
		%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI	T	95% CI
All													
2004	863	75.1	[72.1, 77.8]	63.0	[59.7, 66.2]	54.1	[50.7, 57.4]	45.3	[42.0, 48.6]	39.6	[36.4, 42.9]	3.4	[3.1, 3.7]
2005	893	75.5	[72.5, 78.2]	61.7	[58.4, 64.8]	52.1	[48.7, 55.3]	44.9	[41.6, 48.1]	38.5	[35.3, 41.7]	3.3	[2.7, 3.7]
2006	888	76.5	[73.5, 79.1]	61.3	[58.0, 64.4]	52.4	[49.0, 55.6]	44.6	[41.3, 47.8]	38.7	[35.5, 41.9]	3.2	[2.9, 3.6]
2007	880	77.0	[74.1, 79.7]	64.4	[61.1, 67.5]	53.2	[49.9, 56.5]	46.1	[42.8, 49.3]	39.8	[36.6, 43.0]	3.3	[3.0, 3.8]
2008	838	76.3	[73.2, 79.0]	62.9	[59.5, 66.0]	51.4	[47.9, 54.7]	44.9	[41.5, 48.2]	39.7	[36.4, 43.0]	3.2	[2.8, 3.7]
2009	751	74.7	[71.4, 77.6]	62.1	[58.6, 65.5]	50.5	[46.9, 54.0]	43.0	[39.5, 46.6]	37.7	[34.2, 41.1]	3.1	[2.6, 3.5]
2010	833	74.7	[71.6, 77.5]	60.6	[57.2, 63.8]	50.7	[47.3, 54.1]	43.7	[40.4, 47.1]	37.2	[34.0, 40.5]	3.1	[2.6, 3.6]
2011	788	74.0	[70.8, 76.9]	61.4	[57.9, 64.7]	51.6	[48.0, 55.0]	43.4	[39.9, 46.9]	37.8	[34.4, 41.2]	3.1	[2.8, 3.6]
2012	743	75.7	[72.4, 78.6]	62.7	[59.1, 66.1]	50.5	[46.8, 54.0]	41.9	[38.4, 45.5]	37.7	[34.2, 41.2]	3.0	[2.7, 3.4]
2013	731	77.3	[74.1, 80.2]	61.4	[57.8, 64.8]	50.4	[46.8, 54.0]	45.0	[41.3, 48.5]	37.6	[34.1, 41.1]	3.1	[2.6, 3.8]
2014	807	74.6	[71.4, 77.4]	61.5	[58.1, 64.8]	51.7	[48.2, 55.1]	43.3	[39.9, 46.7]	38.2	[34.9, 41.6]	3.2	[2.7, 3.5]
2015	771	76.4	[73.2, 79.2]	65.5	[62.0, 68.7]	57.6	[54.0, 61.0]	50.9	[47.3, 54.4]	45.4	[41.7, 49.1]	4.1	[3.5, 4.6]
2016	683	75.3	[71.9, 78.4]	62.1	[58.3, 65.6]	52.1	[48.2, 55.7]	44.7	[40.3, 49.0]	no FU	—	3.3	[2.8, 3.8]
2017	728	78.4	[75.2, 81.2]	66.9	[63.4, 70.2]	54.7	[50.0, 59.2]	no FU	—	no FU	—	>3	
Combined Stage I													
2004	129	95.3	[89.9, 97.9]	92.2	[86.1, 95.8]	90.7	[84.2, 94.6]	89.1	[82.4, 93.4]	85.3	[77.9, 90.3]	>16	
2005	113	94.7	[88.6, 97.6]	90.3	[83.1, 94.5]	85.8	[77.9, 91.1]	82.3	[73.9, 88.2]	77.0	[68.1, 83.7]	>15	
2006	138	97.1	[92.5, 98.9]	89.9	[83.5, 93.9]	87.0	[80.1, 91.6]	84.0	[76.8, 89.2]	81.1	[73.5, 86.7]	>14	
2007	147	93.2	[87.7, 96.3]	90.5	[84.4, 94.2]	87.8	[81.3, 92.1]	84.4	[77.4, 89.3]	81.0	[73.6, 86.4]	>13	



Unadjusted observed survival, %														
		1 year		2 year		3 year		4 year		5 year		Median survival time (year)		
Characteristic	N at risk	%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI	T	95% CI	
2008	156	97.4	[93.3, 99.0]	90.4	[84.6, 94.1]	85.3	[78.7, 89.9]	83.3	[76.5, 88.3]	78.8	[71.6, 84.5]	>12		
2009	94	92.6	[85.0, 96.4]	86.2	[77.4, 91.7]	85.1	[76.2, 90.9]	83.0	[73.7, 89.2]	81.9	[72.5, 88.3]	>11		
2010	129	92.2	[86.1, 95.8]	89.1	[82.4, 93.4]	84.5	[77.0, 89.7]	82.2	[74.4, 87.8]	77.5	[69.3, 83.8]	>10		
2011	120	96.6	[91.3, 98.7]	91.6	[84.9, 95.4]	89.1	[81.9, 93.5]	85.7	[78.0, 90.9]	81.5	[73.3, 87.4]	>9		
2012	133	95.5	[90.2, 97.9]	91.7	[85.5, 95.3]	86.4	[79.2, 91.2]	81.8	[74.1, 87.4]	77.2	[69.0, 83.5]	>8		
2013	154	95.5	[90.7, 97.8]	89.6	[83.6, 93.5]	81.8	[74.8, 87.1]	78.6	[71.2, 84.3]	76.6	[69.1, 82.5]	>7		
2014	128	95.3	[89.9, 97.9]	91.4	[85.0, 95.1]	89.8	[83.2, 94.0]	83.6	[75.9, 89.0]	82.0	[74.1, 87.6]	>6		
2015	153	94.1	[89.0, 96.9]	90.8	[85.0, 94.5]	90.2	[84.3, 94.0]	88.2	[82.0, 92.4]	83.7	[76.2, 89.0]	>5		
2016	124	96.8	[91.6, 98.8]	94.3	[88.5, 97.3]	90.3	[83.5, 94.3]	89.4	[82.5, 93.7]	no FU	—	>4		
2017	138	98.5	[94.3, 99.6]	93.4	[87.7, 96.5]	91.9	[85.8, 95.4]	no FU	—	no FU	—	>3		
Combined Stage II														
2004	39	89.7	[74.9, 96.0]	82.1	[66.0, 91.0]	74.4	[57.6, 85.3]	64.1	[47.0, 76.9]	53.8	[37.2, 67.9]	5.5	[3.4, 10.5]	
2005	35	94.3	[79.0, 98.5]	82.9	[65.8, 91.9]	74.3	[56.4, 85.7]	68.6	[50.5, 81.2]	60.0	[42.0, 74.0]	7.1	[4.2, 12.3]	
2006	51	82.4	[68.8, 90.4]	76.5	[62.3, 85.9]	70.6	[56.0, 81.1]	58.8	[44.1, 70.9]	56.9	[42.2, 69.1]	7.7	[3.4, .]	
2007	51	78.4	[64.4, 87.4]	72.5	[58.1, 82.7]	58.8	[44.1, 70.9]	51.0	[36.6, 63.6]	49.0	[34.8, 61.8]	5.0	[2.4, 8.6]	
2008	62	79.0	[66.6, 87.2]	62.9	[49.7, 73.6]	53.2	[40.1, 64.7]	48.4	[35.5, 60.1]	46.8	[34.0, 58.5]	3.5	[1.9, 11.2]	
2009	31	N<35	—	N<35	—	N<35	—	N<35	—	N<35	—	N<35	—	
2010	38	86.8	[71.2, 94.3]	73.7	[56.6, 84.9]	68.4	[51.1, 80.7]	65.8	[48.5, 78.5]	57.9	[40.8, 71.7]	8.2	[3.6, .]	
2011	48	87.5	[74.3, 94.2]	79.2	[64.7, 88.2]	72.9	[58.0, 83.3]	60.4	[45.2, 72.6]	60.4	[45.2, 72.6]	8.6	[3.5, .]	
2012	46	84.4	[70.1, 92.3]	75.6	[60.2, 85.6]	71.1	[55.5, 82.1]	62.2	[46.5, 74.6]	55.6	[40.0, 68.6]	5.6	[3.8, .]	
2013	54	85.2	[72.6, 92.3]	83.3	[70.4, 91.0]	77.7	[64.0, 86.6]	73.9	[59.9, 83.6]	60.6	[46.2, 72.3]	6.5	[4.8, .]	
2014	34	N<35	—	N<35	—	N<35	—	N<35	—	N<35	—	N<35	—	
2015	38	92.1	[77.5, 97.4]	81.6	[65.2, 90.8]	70.7	[53.3, 82.6]	62.5	[45.1, 75.9]	62.5	[45.1, 75.9]	>5		



Unadjusted observed survival, %													
		1 year		2 year		3 year		4 year		5 year		Median survival time (year)	
Characteristic	N at risk	%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI	T	95% CI
2016	37	81.1	[64.4, 90.5]	78.4	[61.4, 88.5]	73.0	[55.6, 84.4]	73.0	[55.6, 84.4]	no FU	—	>4	
2017	37	91.9	[76.9, 97.3]	83.8	[67.4, 92.4]	80.1	[62.5, 90.1]	no FU	—	no FU	—	>3	
Combined Stage IIIA/B													
2004	60	76.7	[63.8, 85.5]	56.7	[43.2, 68.1]	46.7	[33.7, 58.6]	33.3	[21.8, 45.2]	30.0	[19.0, 41.8]	2.8	[1.5, 3.3]
2005	68	76.5	[64.5, 84.9]	55.9	[43.3, 66.7]	48.5	[36.3, 59.7]	35.3	[24.2, 46.6]	29.4	[19.1, 40.4]	2.6	[1.9, 3.6]
2006	72	77.8	[66.3, 85.7]	56.9	[44.7, 67.4]	44.4	[32.8, 55.4]	34.7	[24.0, 45.7]	27.8	[18.0, 38.4]	2.5	[1.7, 3.6]
2007	107	87.9	[80.0, 92.8]	63.6	[53.7, 71.9]	53.3	[43.4, 62.2]	43.0	[33.5, 52.1]	32.6	[23.9, 41.5]	3.2	[2.4, 4.2]
2008	93	81.7	[72.3, 88.2]	66.3	[55.7, 75.0]	55.3	[44.5, 64.8]	46.4	[35.9, 56.2]	43.1	[32.8, 53.0]	3.6	[2.5, 5.5]
2009	88	80.7	[70.8, 87.5]	69.3	[58.5, 77.8]	50.0	[39.2, 59.9]	39.8	[29.6, 49.8]	34.1	[24.4, 44.0]	3.0	[2.4, 3.8]
2010	70	75.7	[63.9, 84.1]	65.7	[53.4, 75.5]	51.4	[39.2, 62.4]	45.7	[33.8, 56.8]	35.7	[24.7, 46.8]	3.3	[2.1, 4.5]
2011	70	81.4	[70.2, 88.8]	68.6	[56.3, 78.1]	52.9	[40.6, 63.7]	41.4	[29.9, 52.6]	32.9	[22.2, 43.9]	3.6	[2.4, 4.1]
2012	77	85.7	[75.7, 91.8]	71.4	[59.9, 80.2]	49.4	[37.8, 59.9]	39.0	[28.1, 49.6]	32.5	[22.4, 43.0]	3.0	[2.4, 4.0]
2013	85	82.4	[72.4, 89.0]	61.2	[50.0, 70.6]	43.5	[32.9, 53.7]	38.8	[28.5, 49.0]	30.6	[21.2, 40.5]	2.5	[1.9, 3.8]
2014	88	87.5	[78.6, 92.9]	66.8	[55.9, 75.6]	55.3	[44.3, 65.0]	41.5	[31.1, 51.5]	36.9	[26.9, 46.9]	3.3	[2.4, 4.3]
2015	87	79.3	[69.2, 86.4]	70.1	[59.3, 78.6]	62.1	[51.0, 71.3]	54.0	[43.0, 63.8]	44.6	[33.3, 55.3]	4.4	[3.0, .]
2016	60	86.7	[75.1, 93.1]	63.3	[49.8, 74.1]	50.0	[36.8, 61.8]	39.8	[27.0, 52.3]	no FU	—	3.1	[2.0, .]
2017	140	81.4	[73.9, 86.9]	71.3	[63.0, 78.0]	62.8	[53.5, 70.8]	no FU	—	no FU	—	>3	
Combined Stage IIIC													
2004	140	78.6	[70.8, 84.5]	67.1	[58.7, 74.2]	54.3	[45.7, 62.1]	40.7	[32.5, 48.7]	30.0	[22.6, 37.7]	3.2	[2.6, 3.7]
2005	134	77.6	[69.6, 83.8]	61.9	[53.2, 69.6]	50.7	[42.0, 58.8]	40.3	[32.0, 48.5]	31.3	[23.7, 39.3]	3.1	[2.2, 3.8]
2006	129	81.4	[73.5, 87.1]	65.9	[57.0, 73.4]	54.3	[45.3, 62.4]	41.9	[33.3, 50.2]	33.3	[25.4, 41.5]	3.2	[2.3, 4.1]
2007	140	83.6	[76.3, 88.8]	72.1	[63.9, 78.8]	57.9	[49.2, 65.5]	48.6	[40.1, 56.5]	41.4	[33.2, 49.4]	3.6	[2.7, 5.0]



Unadjusted observed survival, %													
		1 year		2 year		3 year		4 year		5 year		Median survival time (year)	
Characteristic	N at risk	%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI	T	95% CI
2008	136	83.1	[75.7, 88.4]	65.4	[56.8, 72.8]	45.6	[37.1, 53.7]	36.0	[28.0, 44.1]	30.1	[22.7, 38.0]	2.7	[2.3, 3.6]
2009	120	80.8	[72.6, 86.8]	64.2	[54.9, 72.0]	55.0	[45.7, 63.4]	40.8	[32.0, 49.4]	34.1	[25.8, 42.6]	3.4	[2.4, 4.0]
2010	157	80.3	[73.1, 85.7]	65.0	[57.0, 71.9]	52.9	[44.8, 60.3]	42.0	[34.3, 49.6]	35.7	[28.3, 43.1]	3.3	[2.3, 4.0]
2011	155	80.0	[72.8, 85.5]	64.5	[56.4, 71.5]	51.6	[43.4, 59.1]	37.2	[29.6, 44.8]	28.7	[21.8, 36.0]	3.0	[2.3, 3.5]
2012	134	83.5	[76.1, 88.8]	68.5	[59.9, 75.6]	53.4	[44.6, 61.5]	37.6	[29.4, 45.8]	30.8	[23.2, 38.7]	3.2	[2.7, 3.7]
2013	166	83.1	[76.5, 88.0]	65.1	[57.3, 71.8]	50.0	[42.2, 57.3]	41.0	[33.4, 48.3]	31.9	[25.0, 39.1]	3.0	[2.4, 3.9]
2014	169	86.3	[80.2, 90.7]	65.5	[57.8, 72.2]	53.6	[45.8, 60.8]	43.5	[35.9, 50.8]	35.7	[28.6, 43.0]	3.4	[2.7, 4.2]
2015	192	82.8	[76.7, 87.5]	65.1	[57.9, 71.4]	54.2	[46.9, 60.9]	46.4	[39.2, 53.2]	39.1	[31.7, 46.5]	3.4	[2.7, 4.2]
2016	148	74.9	[67.1, 81.1]	61.3	[52.9, 68.6]	50.9	[42.6, 58.7]	38.2	[28.2, 48.2]	no FU	—	3.2	[2.3, 3.8]
2017	95	78.9	[69.3, 85.9]	61.1	[50.5, 70.0]	50.2	[39.4, 60.1]	no FU	—	no FU	—	>3	
Combined Stage IV													
2004	138	59.4	[50.7, 67.1]	40.6	[32.4, 48.6]	29.0	[21.7, 36.7]	21.0	[14.7, 28.1]	16.7	[11.0, 23.3]	1.3	[1.1, 1.9]
2005	107	64.5	[54.6, 72.7]	51.4	[41.6, 60.4]	37.4	[28.3, 46.4]	29.9	[21.5, 38.7]	18.7	[12.0, 26.6]	2.0	[1.5, 2.7]
2006	141	61.0	[52.4, 68.5]	39.7	[31.6, 47.7]	29.1	[21.8, 36.7]	19.9	[13.7, 26.8]	14.9	[9.6, 21.3]	1.5	[1.1, 1.9]
2007	176	65.3	[57.8, 71.9]	48.9	[41.3, 56.0]	32.4	[25.6, 39.3]	26.7	[20.4, 33.4]	18.2	[12.9, 24.2]	1.9	[1.5, 2.3]
2008	143	60.1	[51.6, 67.6]	39.9	[31.8, 47.8]	26.6	[19.6, 34.0]	19.6	[13.5, 26.4]	14.7	[9.5, 21.0]	1.6	[1.1, 1.9]
2009	162	62.3	[54.4, 69.3]	50.0	[42.1, 57.4]	37.5	[30.1, 45.0]	29.4	[22.6, 36.6]	23.2	[17.0, 29.9]	2.0	[1.3, 2.5]
2010	198	68.7	[61.7, 74.6]	47.0	[39.9, 53.7]	34.8	[28.3, 41.5]	27.3	[21.3, 33.6]	19.2	[14.0, 25.0]	1.9	[1.6, 2.3]
2011	147	57.7	[49.2, 65.2]	43.9	[35.8, 51.8]	31.6	[24.2, 39.2]	26.8	[19.9, 34.1]	22.0	[15.7, 29.0]	1.4	[1.0, 2.1]
2012	163	71.1	[63.5, 77.4]	56.3	[48.3, 63.5]	39.6	[32.0, 47.0]	30.3	[23.4, 37.5]	26.6	[20.0, 33.6]	2.3	[2.0, 2.9]
2013	186	66.7	[59.4, 72.9]	43.0	[35.8, 50.0]	31.2	[24.7, 37.9]	24.7	[18.8, 31.1]	15.6	[10.8, 21.2]	1.7	[1.5, 2.0]
2014	209	61.2	[54.3, 67.5]	47.8	[40.9, 54.4]	34.0	[27.6, 40.4]	26.8	[21.0, 32.9]	20.6	[15.4, 26.3]	1.9	[1.3, 2.3]
2015	199	63.8	[56.7, 70.1]	51.3	[44.1, 57.9]	42.2	[35.3, 49.0]	33.2	[26.7, 39.7]	28.2	[21.8, 34.9]	2.1	[1.4, 2.9]



Unadjusted observed survival, %													
		1 year		2 year		3 year		4 year		5 year		Median survival time (year)	
Characteristic	N at risk	%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI	T	95% CI
2016	180	67.8	[60.4, 74.1]	46.7	[39.2, 53.7]	32.2	[25.5, 39.1]	21.5	[13.5, 30.7]	no FU	—	1.8	[1.3, 2.4]
2017	191	69.6	[62.6, 75.6]	54.9	[47.6, 61.6]	28.8	[19.1, 39.2]	no FU	—	no FU	—	2.3	[1.8, 2.6]
Combined Stage IV, no debulking													
2004	132	58.3	[49.4, 66.2]	38.6	[30.4, 46.8]	28.0	[20.7, 35.8]	20.5	[14.1, 27.7]	16.7	[10.9, 23.5]	1.3	[0.9, 1.6]
2005	103	64.1	[54.0, 72.5]	51.5	[41.4, 60.6]	36.9	[27.7, 46.1]	30.1	[21.6, 39.1]	18.4	[11.7, 26.5]	2.0	[1.5, 2.7]
2006	134	59.7	[50.9, 67.4]	38.8	[30.6, 46.9]	28.4	[21.0, 36.1]	18.7	[12.6, 25.7]	14.2	[8.9, 20.6]	1.4	[1.1, 1.8]
2007	103	51.5	[41.4, 60.6]	35.0	[25.9, 44.1]	20.4	[13.2, 28.6]	14.6	[8.6, 22.1]	9.7	[5.0, 16.3]	1.1	[0.8, 1.7]
2008	84	46.4	[35.5, 56.6]	25.0	[16.4, 34.6]	13.1	[7.0, 21.2]	11.9	[6.1, 19.8]	9.5	[4.5, 16.9]	0.7	[0.5, 1.3]
2009	81	38.3	[27.8, 48.7]	24.7	[15.9, 34.4]	15.8	[8.8, 24.6]	13.2	[6.9, 21.6]	10.5	[5.0, 18.5]	0.6	[0.5, 0.9]
2010	97	45.4	[35.3, 54.9]	20.6	[13.2, 29.1]	12.4	[6.8, 19.8]	8.2	[3.9, 14.8]	6.2	[2.5, 12.2]	0.8	[0.5, 1.2]
2011	81	30.9	[21.2, 41.0]	18.5	[11.0, 27.6]	9.9	[4.6, 17.5]	7.4	[3.0, 14.4]	6.2	[2.3, 12.8]	0.6	[0.3, 0.9]
2012	73	51.8	[39.8, 62.6]	36.4	[25.5, 47.4]	23.8	[14.7, 34.1]	15.4	[8.2, 24.7]	14.0	[7.2, 23.0]	1.1	[0.4, 2.0]
2013	93	46.2	[35.9, 56.0]	20.4	[12.9, 29.1]	12.9	[7.1, 20.6]	8.6	[4.0, 15.4]	5.4	[2.0, 11.3]	0.9	[0.5, 1.3]
2014	110	40.0	[30.8, 49.0]	28.2	[20.1, 36.8]	17.3	[10.9, 24.9]	10.0	[5.3, 16.4]	8.2	[4.0, 14.2]	0.5	[0.3, 0.8]
2015	108	40.7	[31.4, 49.8]	28.7	[20.5, 37.4]	22.2	[14.9, 30.4]	15.7	[9.6, 23.2]	no FU	—	0.8	[0.5, 1.0]
2016	101	49.5	[39.4, 58.8]	23.8	[16.0, 32.4]	12.9	[7.2, 20.2]	0		0		1.0	[0.5, 1.1]
2017	106	52.8	[42.9, 61.8]	38.7	[29.4, 47.8]	15.2	[7.2, 26.1]	no FU	—	no FU	—	1.2	[0.7, 1.6]
Combined Stage IV, debulking													
2004	6	N<35	—	N<35	—	N<35	—	N<35	—	N<35	—	N<35	—
2005	4	N<35	—	N<35	—	N<35	—	N<35	—	N<35	—	N<35	—
2006	7	N<35	—	N<35	—	N<35	—	N<35	—	N<35	—	N<35	—
2007	73	84.9	[74.4, 91.4]	68.5	[56.5, 77.8]	49.3	[37.4, 60.1]	43.8	[32.3, 54.8]	30.1	[20.1, 40.8]	3.0	[2.3, 4.1]



Characteristic	N at risk	Unadjusted observed survival, %										Median survival time (year)	
		1 year		2 year		3 year		4 year		5 year			
		%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI	T	95% CI
2008	59	79.7	[67.0, 87.9]	61.0	[47.4, 72.1]	45.8	[32.8, 57.8]	30.5	[19.4, 42.4]	22.0	[12.5, 33.2]	2.8	[1.9, 3.4]
2009	81	86.4	[76.8, 92.2]	75.3	[64.4, 83.3]	59.3	[47.8, 69.0]	45.7	[34.6, 56.1]	35.8	[25.6, 46.1]	3.7	[2.6, 4.6]
2010	101	91.1	[83.6, 95.3]	72.3	[62.4, 79.9]	56.4	[46.2, 65.4]	45.5	[35.6, 54.9]	31.7	[22.9, 40.8]	3.8	[2.7, 4.3]
2011	66	90.8	[80.6, 95.8]	75.4	[63.0, 84.1]	58.5	[45.6, 69.3]	50.8	[38.1, 62.1]	41.5	[29.5, 53.1]	4.2	[2.7, 5.2]
2012	90	86.7	[77.7, 92.2]	72.2	[61.7, 80.3]	52.2	[41.5, 61.9]	42.2	[31.9, 52.1]	36.7	[26.8, 46.5]	3.2	[2.5, 4.4]
2013	93	87.1	[78.4, 92.5]	65.6	[55.0, 74.3]	49.5	[39.0, 59.1]	40.9	[30.8, 50.6]	25.8	[17.4, 35.0]	3.0	[2.2, 4.1]
2014	99	84.8	[76.1, 90.6]	69.7	[59.6, 77.7]	52.5	[42.3, 61.8]	45.5	[35.5, 54.9]	34.3	[25.2, 43.7]	3.2	[2.5, 4.4]
2015	91	91.2	[83.2, 95.5]	78.0	[68.0, 85.2]	65.9	[55.2, 74.7]	53.8	[43.1, 63.4]	47.3	[36.0, 57.7]	4.5	[3.5, .]
2016	79	91.1	[82.3, 95.7]	75.9	[64.9, 83.9]	57.0	[45.3, 67.0]	43.1	[30.6, 54.9]	no FU	—	3.3	[2.9, .]
2017	85	90.6	[82.1, 95.2]	75.1	[64.5, 83.0]	48.5	[29.9, 64.8]	no FU	—	no FU	—	2.9	[2.4, .]

Survival results based on small number of persons initially at risk (N<35) can be too variable to be practically meaningful and are therefore not reported.



Table 152 – Epithelial ovarian cancer (2004-2017), time trend relative survival with incidence year

Characteristic	N at risk	Unadjusted relative survival, %									
		1 year		2 year		3 year		4 year		5 year	
		%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI
All											
2004	863	75.9	[72.7, 78.8]	64.8	[61.3, 68.1]	56.6	[53.0, 60.0]	48.1	[44.5, 51.6]	42.8	[39.2, 46.3]
2005	893	76.9	[73.9, 79.7]	64.2	[60.8, 67.5]	55.2	[51.6, 58.6]	48.5	[45.0, 52.1]	42.5	[38.9, 46.0]
2006	888	77.9	[74.9, 80.7]	63.6	[60.1, 66.8]	55.3	[51.8, 58.8]	48.0	[44.4, 51.5]	42.5	[39.0, 46.0]
2007	880	78.4	[75.4, 81.2]	66.9	[63.4, 70.1]	56.3	[52.7, 59.8]	49.6	[46.0, 53.1]	43.7	[40.1, 47.2]
2008	838	77.5	[74.3, 80.3]	65.0	[61.5, 68.4]	54.2	[50.6, 57.8]	48.3	[44.6, 51.9]	43.6	[40.0, 47.3]
2009	751	76.4	[73.0, 79.4]	64.8	[61.0, 68.4]	53.7	[49.8, 57.5]	46.7	[42.8, 50.5]	41.7	[37.9, 45.6]
2010	833	75.7	[72.4, 78.7]	62.7	[59.1, 66.0]	53.3	[49.6, 56.9]	46.9	[43.2, 50.5]	40.7	[37.1, 44.3]
2011	788	75.5	[72.1, 78.5]	63.9	[60.2, 67.3]	54.7	[50.9, 58.3]	46.9	[43.1, 50.7]	41.7	[37.9, 45.5]
2012	743	76.7	[73.3, 79.8]	64.9	[61.1, 68.5]	53.3	[49.4, 57.1]	45.1	[41.2, 48.9]	41.5	[37.6, 45.3]
2013	731	78.4	[75.1, 81.5]	63.5	[59.7, 67.1]	53.0	[49.1, 56.8]	48.2	[44.3, 52.1]	41.1	[37.2, 44.9]
2014	807	75.9	[72.6, 78.9]	63.8	[60.2, 67.2]	54.5	[50.8, 58.1]	46.5	[42.7, 50.1]	41.7	[38.0, 45.4]
2015	771	77.7	[74.4, 80.7]	68.0	[64.3, 71.4]	61.0	[57.1, 64.6]	55.1	[51.2, 58.9]	49.2	[45.0, 53.4]
2016	683	76.7	[73.1, 79.9]	64.2	[60.3, 67.9]	54.9	[50.8, 58.8]	47.7	[43.3, 52.1]	no FU	—
2017	728	80.0	[76.7, 82.9]	69.6	[65.9, 73.1]	56.9	[52.4, 61.2]	no FU	—	no FU	—
Combined Stage I											
2004	129	97.0	[91.4, 99.6]	95.5	[89.1, 99.1]	95.6	[88.8, 99.7]	95.9	[88.6, 100.5]	93.8	[85.7, 99.4]
2005	113	96.1	[89.9, 99.0]	93.0	[85.6, 97.3]	89.9	[81.6, 95.4]	87.7	[78.8, 94.0]	83.6	[73.9, 90.9]
2006	138	98.8	[94.1, 100.6]	93.1	[86.4, 97.3]	91.8	[84.5, 96.7]	90.5	[82.7, 96.1]	89.4	[81.0, 95.6]
2007	147	95.5	[89.9, 98.6]	94.8	[88.5, 98.7]	94.2	[87.3, 98.9]	93.0	[85.4, 98.5]	91.6	[83.3, 97.8]
2008	156	99.1	[94.9, 100.7]	93.5	[87.5, 97.4]	89.9	[82.9, 94.9]	89.5	[82.1, 94.9]	86.4	[78.4, 92.5]
2009	94	94.5	[86.7, 98.4]	89.8	[80.6, 95.7]	90.8	[81.2, 97.1]	90.9	[80.7, 97.8]	92.3	[81.6, 99.6]



Characteristic	N at risk	Unadjusted relative survival, %									
		1 year		2 year		3 year		4 year		5 year	
		%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI
2010	129	94.1	[87.8, 97.8]	92.8	[85.7, 97.3]	89.8	[81.9, 95.4]	89.4	[80.9, 95.5]	86.5	[77.3, 93.5]
2011	120	98.7	[93.2, 100.8]	95.6	[88.6, 99.5]	95.0	[87.4, 99.8]	93.7	[85.3, 99.4]	91.5	[82.2, 98.1]
2012	133	96.8	[91.4, 99.4]	94.3	[87.9, 98.1]	90.3	[82.9, 95.4]	87.0	[78.7, 93.0]	83.7	[74.8, 90.6]
2013	154	96.9	[92.0, 99.3]	92.4	[86.2, 96.4]	85.6	[78.2, 91.1]	83.5	[75.7, 89.6]	82.9	[74.8, 89.3]
2014	128	96.9	[91.3, 99.5]	94.4	[87.8, 98.2]	94.3	[87.3, 98.7]	89.3	[81.1, 95.1]	89.3	[80.7, 95.5]
2015	153	95.7	[90.5, 98.5]	93.7	[87.7, 97.5]	94.4	[88.2, 98.4]	93.9	[87.3, 98.4]	90.0	[81.6, 96.1]
2016	124	98.2	[93.0, 100.3]	97.1	[91.1, 100.2]	94.3	[87.2, 98.6]	94.3	[86.2, 99.2]	no FU	—
2017	138	100.2	[95.9, 101.3]	96.7	[90.8, 100.0]	95.9	[88.4, 100.2]	no FU	—	no FU	—
Combined Stage II											
2004	39	91.2	[76.3, 97.6]	84.7	[68.2, 93.8]	78.0	[60.5, 89.4]	68.4	[50.2, 82.0]	58.4	[40.2, 73.8]
2005	35	96.8	[81.3, 101.2]	87.4	[69.5, 96.9]	80.2	[60.7, 92.6]	75.6	[55.5, 89.7]	67.7	[47.1, 83.7]
2006	51	83.8	[70.3, 91.8]	78.6	[64.2, 88.2]	73.2	[58.2, 84.0]	61.4	[46.0, 74.0]	59.9	[44.5, 72.9]
2007	51	80.4	[66.3, 89.5]	76.1	[61.1, 86.6]	62.9	[47.3, 75.7]	55.0	[39.5, 68.7]	53.7	[38.1, 67.7]
2008	62	81.0	[68.3, 89.4]	65.7	[51.9, 76.9]	56.5	[42.5, 68.8]	52.6	[38.5, 65.4]	52.2	[37.9, 65.5]
2009	31	N<35	—	N<35	—	N<35	—	N<35	—	N<35	—
2010	38	88.6	[72.6, 96.3]	76.8	[59.2, 88.4]	72.7	[54.5, 85.6]	71.2	[52.6, 84.8]	64.0	[45.2, 79.1]
2011	48	90.1	[76.6, 96.8]	83.7	[68.6, 93.1]	78.8	[62.9, 89.8]	66.7	[50.0, 80.0]	67.8	[50.8, 81.4]
2012	46	86.4	[71.8, 94.4]	79.4	[63.3, 90.0]	77.1	[60.2, 89.0]	69.7	[52.1, 83.4]	64.4	[46.4, 79.5]
2013	54	86.4	[73.1, 93.8]	85.8	[72.1, 93.9]	81.4	[66.7, 91.0]	78.8	[63.6, 89.5]	66.2	[50.4, 79.1]
2014	34	N<35	—	N<35	—	N<35	—	N<35	—	N<35	—
2015	38	94.2	[79.2, 99.6]	84.9	[67.7, 94.6]	75.0	[56.7, 87.5]	67.6	[48.7, 81.9]	69.0	[49.7, 83.6]
2016	37	82.7	[65.7, 92.3]	81.8	[64.0, 92.4]	78.1	[59.4, 90.4]	80.4	[61.1, 93.1]	no FU	—
2017	37	93.8	[78.5, 99.3]	87.0	[70.1, 95.8]	82.8	[61.3, 94.7]	no FU	—	no FU	—



Characteristic	N at risk	Unadjusted relative survival, %									
		1 year		2 year		3 year		4 year		5 year	
		%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI
Combined Stage IIIA/B											
2004	60	77.6	[64.2, 86.8]	58.4	[44.4, 70.4]	49.8	[36.0, 62.4]	35.6	[23.1, 48.7]	32.8	[20.6, 46.0]
2005	68	79.2	[67.0, 87.7]	60.2	[47.2, 71.3]	53.4	[40.2, 65.4]	39.4	[27.1, 51.9]	33.5	[21.9, 45.9]
2006	72	79.5	[67.6, 87.9]	59.4	[46.5, 70.5]	47.4	[34.8, 59.3]	38.3	[26.5, 50.3]	31.4	[20.4, 43.4]
2007	107	89.2	[81.0, 94.3]	65.7	[55.4, 74.3]	56.1	[45.7, 65.6]	46.0	[35.8, 55.7]	35.4	[26.0, 45.1]
2008	93	83.4	[73.6, 90.2]	69.1	[57.9, 78.1]	58.6	[47.2, 68.7]	50.4	[39.1, 61.0]	47.9	[36.5, 58.8]
2009	88	83.0	[73.0, 89.9]	72.2	[61.0, 81.0]	52.9	[41.5, 63.3]	42.4	[31.4, 53.1]	36.9	[26.4, 47.7]
2010	70	77.2	[64.9, 85.9]	68.0	[55.1, 78.3]	53.7	[40.7, 65.4]	48.7	[35.8, 60.8]	38.6	[26.6, 50.8]
2011	70	82.2	[70.6, 89.8]	70.5	[57.8, 80.3]	55.1	[42.3, 66.4]	44.3	[32.1, 56.0]	35.4	[24.0, 47.3]
2012	77	86.9	[76.6, 93.2]	73.5	[61.4, 82.7]	52.1	[40.0, 63.2]	42.1	[30.5, 53.6]	36.1	[25.0, 47.6]
2013	85	84.1	[74.1, 90.9]	63.5	[51.8, 73.3]	45.6	[34.4, 56.3]	41.2	[30.2, 52.1]	33.2	[23.1, 43.9]
2014	88	89.2	[80.1, 94.6]	69.5	[58.2, 78.5]	58.2	[46.6, 68.5]	44.7	[33.5, 55.4]	40.4	[29.5, 51.3]
2015	87	80.4	[69.8, 87.9]	72.4	[61.0, 81.3]	65.3	[53.6, 75.2]	58.1	[46.2, 68.7]	47.2	[34.4, 59.4]
2016	60	88.3	[76.4, 94.9]	64.8	[50.7, 76.2]	51.9	[38.1, 64.4]	40.3	[26.5, 54.0]	no FU	—
2017	140	83.4	[75.6, 89.2]	74.6	[65.8, 81.7]	64.3	[53.9, 73.3]	no FU	—	no FU	—
Combined Stage IIIC											
2004	140	79.5	[71.4, 85.7]	69.0	[60.2, 76.4]	56.6	[47.6, 64.9]	42.7	[34.0, 51.2]	32.0	[24.1, 40.3]
2005	134	78.5	[70.0, 85.0]	63.5	[54.2, 71.5]	52.5	[43.2, 61.1]	42.4	[33.6, 51.1]	33.4	[25.2, 41.9]
2006	129	82.9	[74.8, 88.8]	68.1	[58.8, 76.0]	57.1	[47.5, 65.8]	44.7	[35.3, 53.8]	36.5	[27.7, 45.6]
2007	140	85.1	[77.7, 90.4]	74.5	[66.0, 81.4]	60.4	[51.4, 68.5]	51.1	[42.0, 59.6]	44.1	[35.3, 52.8]
2008	136	84.6	[77.1, 90.0]	67.5	[58.7, 75.1]	47.9	[39.0, 56.3]	38.5	[30.1, 47.0]	32.7	[24.7, 41.1]
2009	120	82.4	[74.1, 88.5]	66.6	[57.1, 74.7]	57.8	[48.1, 66.6]	43.7	[34.4, 52.8]	36.9	[27.9, 46.0]
2010	157	81.5	[74.2, 87.1]	66.9	[58.6, 74.0]	54.7	[46.2, 62.6]	44.1	[35.9, 52.1]	38.0	[30.1, 46.0]



Characteristic	N at risk	Unadjusted relative survival, %									
		1 year		2 year		3 year		4 year		5 year	
		%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI
2004	132	57.0	[47.6, 65.5]	38.1	[29.6, 46.8]	28.3	[20.7, 36.5]	21.0	[14.3, 28.6]	17.5	[11.4, 24.8]
2005	103	65.0	[54.4, 73.9]	54.1	[43.5, 63.8]	39.5	[29.5, 49.5]	33.2	[23.8, 43.2]	20.7	[13.0, 29.8]
2006	134	60.6	[51.5, 68.7]	40.3	[31.7, 48.8]	29.9	[22.1, 38.1]	20.0	[13.5, 27.6]	15.4	[9.6, 22.4]
2007	103	52.5	[42.2, 62.0]	36.9	[27.4, 46.6]	21.8	[14.1, 30.7]	16.2	[9.5, 24.5]	11.2	[5.8, 18.7]
2008	84	43.6	[32.5, 54.3]	23.9	[15.4, 33.6]	13.3	[7.2, 21.5]	12.4	[6.4, 20.6]	10.3	[4.9, 18.2]
2009	81	37.7	[27.2, 48.2]	25.2	[16.2, 35.5]	16.7	[9.2, 26.3]	14.6	[7.5, 24.2]	12.3	[5.8, 21.8]
2010	97	42.8	[32.4, 52.8]	21.2	[13.8, 29.9]	13.5	[7.6, 21.2]	9.0	[4.3, 16.2]	7.0	[2.9, 13.6]
2011	81	29.4	[20.2, 39.4]	17.9	[10.5, 26.9]	9.0	[4.0, 16.5]	6.9	[2.7, 13.8]	5.7	[2.0, 12.3]
2012	73	48.9	[36.1, 60.7]	35.4	[24.2, 47.0]	23.5	[14.3, 34.3]	15.2	[7.9, 24.9]	14.0	[7.1, 23.6]
2013	93	44.2	[33.7, 54.3]	21.3	[13.7, 30.0]	13.9	[7.8, 21.8]	9.5	[4.5, 16.7]	6.2	[2.4, 12.7]
2014	110	36.1	[26.9, 45.4]	26.2	[18.3, 34.9]	16.5	[10.3, 24.2]	10.2	[5.4, 16.8]	8.6	[4.2, 15.0]
2015	108	38.6	[29.4, 47.9]	27.8	[19.6, 36.7]	22.0	[14.5, 30.5]	16.3	[9.9, 24.2]	no FU	—
2016	101	47.1	[36.7, 57.0]	22.3	[14.7, 31.0]	12.9	[7.3, 20.2]	no FU	—	no FU	—
2017	106	52.1	[41.7, 61.7]	39.0	[29.3, 48.7]	19.7	[12.0, 29.0]	no FU	—	no FU	—
Combined Stage IV, debulking											
2004	6	N<35	—	N<35	—	N<35	—	N<35	—	N<35	—
2005	4	N<35	—	N<35	—	N<35	—	N<35	—	N<35	—
2006	7	N<35	—	N<35	—	N<35	—	N<35	—	N<35	—
2007	73	86.1	[75.6, 92.5]	70.3	[58.1, 79.7]	51.4	[39.1, 62.5]	46.0	[33.9, 57.5]	31.7	[21.0, 43.0]
2008	59	80.8	[67.8, 89.2]	63.4	[49.5, 74.8]	48.9	[35.4, 61.4]	32.7	[20.8, 45.4]	23.9	[13.6, 36.2]
2009	81	88.1	[78.7, 93.8]	77.7	[66.6, 85.9]	62.1	[50.2, 72.3]	48.8	[37.1, 59.8]	39.0	[27.9, 50.3]
2010	101	92.4	[84.9, 96.6]	74.6	[64.6, 82.4]	59.2	[48.6, 68.5]	48.7	[38.3, 58.6]	34.3	[24.8, 44.1]
2011	66	92.4	[82.2, 97.3]	77.8	[65.0, 86.9]	61.4	[47.9, 72.8]	53.8	[40.3, 66.0]	44.8	[31.8, 57.3]



Characteristic	N at risk	Unadjusted relative survival, %									
		1 year		2 year		3 year		4 year		5 year	
		%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI
2012	90	87.8	[78.8, 93.4]	74.3	[63.6, 82.5]	54.5	[43.4, 64.5]	44.4	[33.6, 54.9]	39.2	[28.7, 49.6]
2013	93	88.4	[79.7, 93.8]	68.0	[57.2, 76.7]	52.0	[41.1, 62.1]	43.9	[33.3, 54.3]	28.1	[19.1, 38.1]
2014	99	86.0	[77.1, 91.8]	71.7	[61.3, 79.9]	54.8	[44.1, 64.5]	48.2	[37.5, 58.2]	37.1	[27.2, 47.2]
2015	91	92.6	[84.6, 96.9]	80.4	[70.1, 87.8]	69.2	[57.9, 78.4]	57.8	[46.2, 68.0]	51.3	[38.9, 62.8]
2016	79	92.6	[83.9, 97.1]	78.2	[67.0, 86.4]	60.0	[47.9, 70.3]	43.3	[30.1, 56.0]	no FU	—
2017	85	91.9	[83.4, 96.5]	77.9	[67.2, 85.7]	52.5	[38.7, 64.8]	no FU	—	no FU	—

Survival results based on small number of persons initially at risk (N<35) can be too variable to be practically meaningful and are therefore not reported.



Appendix 10.1.2. Uptake of selected drugs

Table 153 – Epithelial ovarian cancer stage IIIA/B: uptake of selected drugs

Drug/incidence year (n)	2004 (60)	2005 (68)	2006 (72)	2007 (107)	2008 (93)	2009 (88)	2010 (70)	2011 (70)	2012 (77)	2013 (85)	2014 (89)	2015 (87)	2016 (60)	2017 (140)
Bevacizumab					1.1%	1.1%	8.6%	7.1%	14.3%	37.6%	44.9%*	37.9%	33.3%	17.1%

* The number in yellow indicates the first calendar year of reimbursement. Bevacizumab was first reimbursed in 2014. The columns in this table indicate the incidence year. For example, for incidence year 2009, 1.1% of patients received reimbursed bevacizumab during the 5 years after diagnosis. Source: BCR-IMA.

Remark: IMA data were only available up to the second trimester of 2019. Five-year follow-up data are thus not complete for the last years in this table.

Table 154 – Epithelial ovarian cancer stage IIIC: uptake of selected drugs

Drug/incidence year (n)	2004 (140)	2005 (134)	2006 (129)	2007 (141)	2008 (136)	2009 (120)	2010 (157)	2011 (155)	2012 (134)	2013 (166)	2014 (169)	2015 (192)	2016 (148)	2017 (95)
Bevacizumab			0.8%	0.7%		2.5%	5.7%	5.2%	17.9%	30.1%	38.5%*	34.9%	25.0%	18.9%

Remark: IMA data were only available up to the second trimester of 2019. Five-year follow-up data are thus not complete for the last years in this table. Source: BCR-IMA

Table 155 – Epithelial ovarian cancer stage IV: uptake of selected drugs

Drug/incidence year (n)	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
Bevacizumab	0.7%					1.9%	2.5%	6.7%	16.0%	23.1%	42.6%*	47.7%	45.1%	50.3%

Remark: IMA data were only available up to the second trimester of 2019. Five-year follow-up data are thus not complete for the last years in this table. Source: BCR-IMA



Appendix 10.2. Reimbursement criteria for selected drugs

Table 156 – targeted therapy in ovarian cancer

Drug	Trade name	Date start reimbursement	Indication NI	Indication Fr
Bevacizumab	Avastin	1/3/2014	<ul style="list-style-type: none"> De volgende specialiteit wordt vergoed indien zij wordt toegediend in het kader van een eerstelijnsbehandeling van een FIGO stadium IV epitheliaal ovarium-, tuba- of primair peritoneaal carcinoom, in combinatie met carboplatine en paclitaxel gedurende maximum 6 cycli en dan verder in monotherapie tot een maximum van 15 maanden in totaal, rekening houdend met het feit dat het aantal terugbetaalde cycli tot een maximum van 22 beperkt is, of tot progressie van de ziekte of totdat onacceptabele toxiciteit zich voordoet, afhankelijk van wat als eerste optreedt. Deze behandeling is slechts terugbetaald als die, voorafgaand aan de opstart ervan, goedgekeurd werd door het multidisciplinair oncologisch consult (MOC) en voor zover deze behandeling in strikte overeenkomst met elke bepaling vermeld in de Samenvatting van de Productkenmerken (SKP) van AVASTIN wordt voorgeschreven.. 	<ul style="list-style-type: none"> La spécialité suivante fait l'objet d'un remboursement si elle est administrée dans le cadre du traitement de première ligne du stade FIGO IV d'un cancer épithélial de l'ovaire, des trompes de Fallope ou péritonéal primitif en association au carboplatine et au paclitaxel pendant 6 cycles de traitement maximum, et ensuite en monothérapie, jusqu'à un maximum de 15 mois au total, en tenant compte du fait que le nombre de cycles remboursés est limité à un maximum de 22, ou jusqu'à progression de la maladie ou jusqu'à la survenue d'une toxicité inacceptable, selon ce qui survient en premier. Ce traitement n'est remboursé que s'il a été approuvé, préalablement à son initiation, lors d'une consultation oncologique multidisciplinaire (COM) et pour autant que ce traitement soit prescrit en stricte conformité avec chacune des dispositions mentionnées dans le Résumé des Caractéristiques du Produit (RCP) d'AVASTIN.
		1/3/2014	<ul style="list-style-type: none"> De volgende specialiteit wordt vergoed indien zij wordt toegediend in het kader van een eerste terugkerend platineumsensitief epitheliaal ovarium-, tuba- of primair peritoneaal carcinoom bij volwassen patiënten die niet eerder zijn behandeld met bevacizumab of andere VEGF-inhibitoren of middelen die aan de VEGF-receptor binden, in combinatie met carboplatine en gemcitabine gedurende 6 cycli tot maximum 10 cycli, en dan verder in monotherapie tot progressie van de ziekte optreedt. Deze behandeling is slechts terugbetaald als die, voorafgaand aan de opstart ervan, goedgekeurd werd door het multidisciplinair oncologisch consult (MOC) en voor zover deze behandeling in strikte overeenkomst met elke bepaling vermeld in de Samenvatting van de 	<ul style="list-style-type: none"> La spécialité suivante fait l'objet d'un remboursement si elle est administrée dans le cadre du traitement d'une première récurrence d'un cancer épithélial de l'ovaire, des trompes de Fallope ou péritonéal primitif, sensible aux sels de platine chez les patientes adultes qui n'ont pas été préalablement traitées par du bevacizumab ou d'autres inhibiteurs du VEGF ou d'autres agents ciblant le récepteur du VEGF, en association au carboplatine et à la gemcitabine pendant 6 cycles à 10 cycles maximum, et ensuite en monothérapie jusqu'à progression de la maladie. Ce traitement n'est remboursé que s'il a été approuvé, préalablement à son initiation, lors d'une consultation oncologique multidisciplinaire (COM) et pour autant que ce traitement soit prescrit en stricte conformité avec chacune des dispositions mentionnées dans le



	Productkenmerken (SKP) van AVASTIN wordt voorgeschreven.	Résumé des Caractéristiques du Produit (RCP) d'AVASTIN.
1/7/2015	<ul style="list-style-type: none">De volgende specialiteit wordt vergoed indien zij wordt toegediend voor de behandeling van volwassen patiënten met een terugkerend platinum-resistent epitheliaal ovarium-, tuba- of primair peritoneaal carcinoom die niet meer dan twee voorafgaande behandelingslijnen van chemotherapie kregen en niet eerder zijn behandeld met bevacizumab of andere VEGF-inhibitoren of middelen die aan de VEGF-receptor binden. De specialiteit wordt toegediend in combinatie met paclitaxel, topotecan, of gepegyleerde liposomale doxorubicine tot progressie van de ziekte of onacceptabele toxiciteit optreedt. Deze behandeling is slechts terugbetaald als die, voorafgaand aan de opstart ervan, goedgekeurd werd door het multidisciplinair oncologisch consult (MOC) en voor zover deze behandeling in strikte overeenkomst met elke bepaling vermeld in de Samenvatting van de Productkenmerken (SKP) van AVASTIN wordt voorgeschreven	<ul style="list-style-type: none">La spécialité suivante fait l'objet d'un remboursement si elle est administrée chez les patientes adultes atteintes d'un cancer épithélial de l'ovaire, des trompes de Fallope ou péritonéal primitif récidivant résistant au platine, n'ayant pas reçu plus de deux lignes de chimiothérapie antérieurement et n'ayant pas été préalablement traitées par bevacizumab ou d'autres inhibiteurs du VEGF ou d'autres agents ciblant le récepteur du VEGF. La spécialité est administrée en association au paclitaxel, au topotécan ou à la doxorubicine liposomale pégylée jusqu'à progression de la maladie ou toxicité inacceptable. Ce traitement n'est remboursé que s'il a été approuvé, préalablement à son initiation, lors d'une consultation oncologique multidisciplinaire (COM) et pour autant que ce traitement soit prescrit en stricte conformité avec chacune des dispositions mentionnées dans le Résumé des Caractéristiques du Produit (RCP) de l'AVASTIN.



Appendix 10.3. medical literature: Search for evidence

Appendix 10.3.1. Search medical literature (systematic reviews)

The search for systematic reviews in MEDLINE, PreMedline and the Cochrane library of systematic reviews (inception to search date) specifically developed for this research question, yielded 88 records (Figure 450). After de-duplication, 69 (2020-2013) of the 84 remaining reviews were screened based on title and abstract, of which 52 were excluded. In total 17 full text articles were assessed for eligibility. Based on full text evaluation, 15 reviews were excluded (Figure 451).

The KCE report 'Bevacizumab in the treatment of ovarian cancer' was added as an additional reference.²⁶⁰

Figure 294– Ovarian cancer – Selection of SRs - Study flow

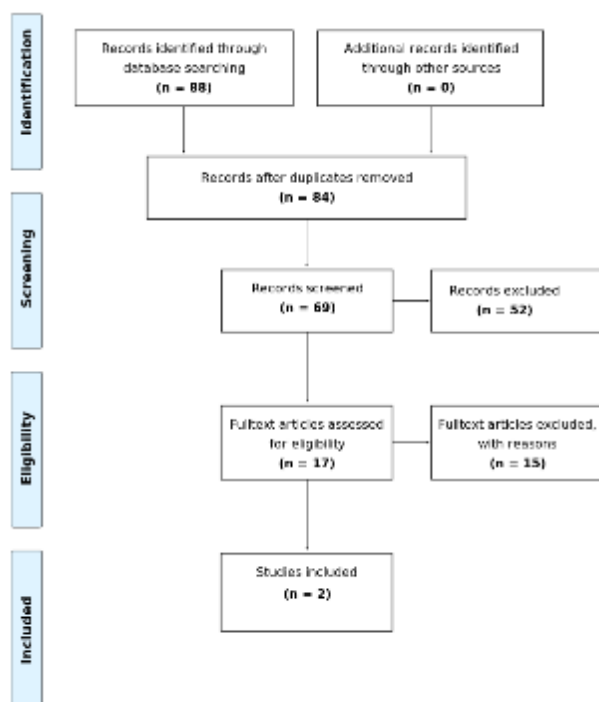


**Table 157 – ovarian cancer: excluded reviews and reason for exclusion**

	Year	Publication	Reason for exclusion
1	2019	Xu, X. Yin, S. Guo, H. et al. Comparative efficacy of targeted maintenance therapy for newly diagnosed epithelial ovarian cancer: a network meta-analysis. <i>Cancer Manag Res</i> 2019;11:4119-4128	Included
2	2019	Raouf, S. Bertelli, G. Ograbek, A. et al. Real-world use of bevacizumab in metastatic colorectal, metastatic breast, advanced ovarian and cervical cancer: a systematic literature review. <i>Fut Oncol</i> 2019;15(5):543-561	Wrong research question
3	2018	Wang, H. Xu, T. Zheng, L. Li, G. Angiogenesis Inhibitors for the Treatment of Ovarian Cancer: An Updated Systematic Review and Meta-analysis of Randomized Controlled Trials. <i>Int J Gynecol Cancer</i> 2018;28(5):903-914	No separate results for bevacizumab
4	2018	Ruan, G. Ye, L. Liu, G. et al. The role of bevacizumab in targeted vascular endothelial growth factor therapy for epithelial ovarian cancer: an updated systematic review and meta-analysis. <i>Onco Targets Ther</i> 2018;11:521-528	No separate results for 1 st –line and recurrence
5	2018	Chellappan, D. K. Leng, K. H. Jia, L. J. et al. The role of bevacizumab on tumour angiogenesis and in the management of gynaecological cancers: A review. 2018;102:1127-1144	Not a systematic review
6	2017	Yi, S. Zeng, L. Kuang, Y. et al. Antiangiogenic drugs used with chemotherapy for patients with recurrent ovarian cancer: a meta-analysis. 2017;10:973-984	No separate results for 1 st –line and recurrence
7	2017	Wu, Y. S. Shui, L. Shen, D. Chen, X. Bevacizumab combined with chemotherapy for ovarian cancer: an updated systematic review and meta-analysis of randomized controlled trials. <i>Oncotarget</i> 2017;8(6):10703-107013	No separate results for 1 st –line and recurrence
8	2017	Roviello, G. Bachelot, T. Hudis, C. A. et al. The role of bevacizumab in solid tumours: A literature based meta-analysis of randomised trials. <i>Eur J Cancer</i> 2017;75:245-258	No separate results for 1 st –line and recurrence
9	2017	Diab, Y. Muallem, M. Z. Targeted Therapy in Ovarian Cancer. A Comprehensive Systematic Review of Literature. <i>Anticancer Res</i> 2017;37(6):2809-2815	No critical appraisal
10	2016	Marchetti, C. De Felice, F. Palaia, I. et al. Efficacy and toxicity of bevacizumab in recurrent ovarian disease: an update meta-analysis on phase III trials. <i>Oncotarget</i> 2016;7(11):13221-7	Not a systematic review
11	2016	Li, X. Zhu, S. Hong, C. Cai, H. Angiogenesis inhibitors for patients with ovarian cancer: a meta-analysis of 12 randomized controlled trials. <i>Curr Med Res Opin</i> 2016;32(3):555-562	No additional information
12	2015	Poonawalla, I. B. Parikh, R. C. Du, X. L. et al. Cost Effectiveness of Chemotherapeutic Agents and Targeted Biologics in Ovarian Cancer: A Systematic Review. <i>Pharmacoeconomics</i> 2015;33(11):1155-1185	No additional information
13	2015	Li, J. Zhou, L. Chen, X. Ba, Y. Addition of bevacizumab to chemotherapy in patients with ovarian cancer: a systematic review and meta-analysis of randomized trials. <i>Clin Transl Oncol</i> 2015;17(9):673-83	Included (no separate results for platinum-sensitive and platinum-resistant)
14	2014	Wang, T. S. Lei, W. Cui, W. et al. A meta-analysis of bevacizumab combined with chemotherapy in the treatment of ovarian cancer. <i>Indian J Cancer</i> 2014;51:e95-8	No additional information
15	2014	Aravantinos, G. Pectasides, D. Bevacizumab in combination with chemotherapy for the treatment of advanced ovarian cancer: a systematic review. <i>J Ovarian Res</i> 2014;7:57	No critical appraisal



	Year	Publication	Reason for exclusion
16	2013	Zhou, M. Yu, P. Qu, X. et al. Phase III trials of standard chemotherapy with or without bevacizumab for ovarian cancer: a meta-analysis. PLoS ONE 2013;8(12): e81858	No critical appraisal
17	2013	Ye, Q. Chen, H. L. Bevacizumab in the treatment of ovarian cancer: a meta-analysis from four phase III randomized controlled trials. Arch Gynecol Obstet 2013;288(3):655-66	No additional information

Appendix 10.3.2. Critical appraisal systematic reviews

	Xu 2019 ²⁶¹		Wang 2018 ²⁶²	
	Score	Rationale/comment	score	Rationale/comment
1. PICO	Y		Y	
2. A priori study design	N		N	
3. Inclusion study designs	Y		Y	
4. Comprehensive literature search	Partial Y	No search of trial registers	Partial Y	No search of reference lists and trial registers
5. Duplicate study selection	Y		Y	
6. Duplicate data extraction	Y		Y	
7. List of excluded studies and rationale	N		N	
8. Characteristics of included studies provided	Y		Y	
9. Assessment of risk of bias	Y		Y	
10. Sources of funding reported	N	Source of funding of included studies not reported	N	
11. Appropriate methods to combine findings	Y		Y	
12. Assessment of impact RoB in included studies on results MA	Y		N	
13. RoB assessment used in interpretation of results and in conclusions	Y		N	
14. Explanation for and discussion of any observed heterogeneity	N		N	



Xu 2019 ²⁶¹		Wang 2018 ²⁶²	
	Score		Rationale/comment
15. Adequate investigation of publication bias and its impact on the results	Y	Y	
16. Potential sources of conflict of interest reported	Y	Y	

Li 2015 ²⁶³	
	Score
1. PICO	Y
2. A priori study design	N
3. Inclusion study designs	Y
4. Comprehensive literature search	Y
5. Duplicate study selection	Y
6. Duplicate data extraction	Y
7. List of excluded studies and rationale	N
8. Characteristics of included studies provided	Y
9. Assessment of risk of bias	Partial Y
10. Sources of funding reported	N
11. Appropriate methods to combine findings	Y
12. Assessment of impact RoB in included studies on results MA	Y
13. RoB assessment used in interpretation of results and in conclusions	Y
14. Explanation for and discussion of any observed heterogeneity	N
15. Adequate investigation of publication bias and its impact on the results	N
16. Potential sources of conflict of interest reported	Y



Appendix 10.3.3. Search strategy

Appendix 10.3.3.1. Cochrane library of systematic reviews

Date	24/06/2020 20:39:59	
Database	Cochrane@Wiley.com	
Search strategy		
#1	[mh "Ovarian Neoplasms"]	1928
#2	(ovar* NEAR/5 (cancer* or neoplas* or malignan* or tumor* or tumour* or carcin* or adenocarcin* or metasta*)):ab,ti	6277
#3	#1 or #2	6542
#4	[mh ^"Bevacizumab"]	1857
#5	bevacizumab:ab,ti	5628
#6	avastin:ab,ti	839
#7	mvasi:ab,ti	0
#8	zirabev:ab,ti	0
#9	ainex:ab,ti	0
#10	altuzan:ab,ti	1
#11	bevax:ab,ti	0
#12	bryxta:ab,ti	0
#13	krabeva:ab,ti	0
#14	kyomarc:ab,ti	0
#15	2S9ZZM9Q9V:ab,ti	0
#16	"1438851-35-4":ab,ti	1
#17	"216974-75-3":ab,ti	185
#18	RHUMAB:ab,ti	152
#19	"rhuMAb-VEGF":ab,ti	58
#20	"12-IGG1":ab,ti	0
#21	"ABP-215":ab,ti	17
#22	ABP215:ab,ti	0
#23	AVA1:ab,ti	0
#24	"AVA-1":ab,ti	14
#25	"ask b1202":ab,ti	0
#26	askb1202:ab,ti	1
#27	"BI 695502":ab,ti	5
#28	BI695502:ab,ti	0
#29	BS503:ab,ti	0
#30	"BS-503":ab,ti	0



Date	24/06/2020 20:39:59	
#31	"BS-503A":ab,ti	1
#32	BS503A:ab,ti	0
#33	"bat 1706":ab,ti	0
#34	bat1706:ab,ti	8
#35	"bcd 021":ab,ti	5
#36	bcd021:ab,ti	0
#37	"bevz 92":ab,ti	0
#38	bevz92:ab,ti	6
#39	"CHS-5217":ab,ti	0
#40	CHS5217:ab,ti	0
#41	"CT-16":ab,ti	22
#42	CT16:ab,ti	0
#43	"CT-P16":ab,ti	7
#44	CTP16:ab,ti	7
#45	"FKB-238":ab,ti	0
#46	FKB238:ab,ti	3
#47	"hd 204":ab,ti	0
#48	hd204:ab,ti	5
#49	"HLX-04":ab,ti	0
#50	HLX04:ab,ti	5
#51	"mb 02":ab,ti	0
#52	mb02:ab,ti	11
#53	"mil 60":ab,ti	0
#54	mil60:ab,ti	3
#55	"myl 14020":ab,ti	0
#56	myl14020:ab,ti	0
#57	"myl 1402o":ab,ti	5
#58	myl1402o:ab,ti	0
#59	"nsc 704865":ab,ti	6
#60	nsc704865:ab,ti	0
#61	"ons 1045":ab,ti	0
#62	ons1045:ab,ti	0
#63	"ons 5010":ab,ti	1
#64	ons5010:ab,ti	0
#65	PF06439535:ab,ti	0
#66	"PF-06439535":ab,ti	12



Date	24/06/2020 20:39:59	
#67	PF6439535:ab,ti	0
#68	"PF-6439535":ab,ti	0
#69	"ql 1101":ab,ti	0
#70	ql1101:ab,ti	5
#71	"RG-435":ab,ti	0
#72	RG435:ab,ti	0
#73	"R-435":ab,ti	1
#74	R435:ab,ti	4
#75	"ro 4876646":ab,ti	9
#76	ro4876646:ab,ti	74
#77	"sb 8":ab,ti	5
#78	sb8:ab,ti	4
#79	"stc 103":ab,ti	0
#80	stc103:ab,ti	0
#81	#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77 OR #78 OR #79 OR #80	5855
#82	#4 or #81	6003
#83	#3 and #82	432
#84	[mh "Vascular Endothelial Growth Factors"/AI]	539
#85	[mh "Receptors, Vascular Endothelial Growth Factor"/AI]	86
#86	#84 or #85	620
#87	(vegfr NEAR/5 (inhibit* or antagonist? or target* or block* or against or anti or "multi-target" or "multi-targets" or "multi-targeting" or reduc*)):ab,ti	2077
#88	(vegfr* NEAR/5 (inhibit* or antagonist? or target* or block* or against or anti or "multi-target" or "multi-targets" or "multi-targeting" or reduc*)):ab,ti	590
#89	#87 or #88	2528
#90	#86 or #89	2985
#91	#3 and #90	83
#92	[mh "Antibodies, Monoclonal"]	12727
#93	(monoclonal NEAR/3 antibod*):ab,ti	8824
#94	#92 or #93	19138
#95	#3 and #94	255



Date	24/06/2020 20:39:59	
#96	((("new class" or "new classes" or innovative or target*) NEAR/3 (drug? or therapy or therapies or therapeutic* or treatment? or chemotherap*)):ab,ti	11940
#97	#3 and #96	127
#98	#83 or #91 or #95 or #97	712
#99	#98 in Cochrane Reviews	4
Comments		

Appendix 10.3.3.2. Medline + PreMedline

Date	June 23, 2020	
Database	Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946 to June 23, 2020>	
Search strategy		
1	exp Ovarian Neoplasms/	83601
2	(ovar* adj5 (cancer* or neoplas* or malignan* or tumor* or tumour* or carcin* or adenocarcin* or metasta*)):ab,ti,kf.	96855
3	1 or 2	116348
4	Bevacizumab/	11513
5	bevacizumab.ab,ti,kf,rn.	18098
6	avastin.ab,ti,kf,rn.	1534
7	mvasi.ab,ti,kf,rn.	5
8	zirabev.ab,ti,kf,rn.	2
9	ainex.ab,ti,kf,rn.	1
10	altuzan.ab,ti,kf,rn.	2
11	bevax.ab,ti,kf,rn.	0
12	bryxta.ab,ti,kf,rn.	0
13	krabeva.ab,ti,kf,rn.	0
14	kyomarc.ab,ti,kf,rn.	0
15	2S9ZZM9Q9V.ab,ti,kf,rn.	11514
16	1438851-35-4.ab,ti,kf,rn.	0
17	216974-75-3.ab,ti,kf,rn.	1
18	RHUMAB.ab,ti,kf,rn.	137
19	rhuMAb-VEGF.ab,ti,kf,rn.	18
20	12-IGG1.ab,ti,kf,rn.	3
21	ABP-215.ab,ti,kf,rn.	9
22	ABP215.ab,ti,kf,rn.	1
23	AVA1.ab,ti,kf,rn.	8
24	AVA-1.ab,ti,kf,rn.	42



Date	June 23, 2020	
25	ask b1202.ab,ti,kf,rn.	0
26	askb1202.ab,ti,kf,rn.	0
27	BI 695502.ab,ti,kf,rn.	1
28	BI695502.ab,ti,kf,rn.	0
29	BS503.ab,ti,kf,rn.	0
30	BS-503.ab,ti,kf,rn.	0
31	BS-503A.ab,ti,kf,rn.	1
32	BS503A.ab,ti,kf,rn.	0
33	bat 1706.ab,ti,kf,rn.	0
34	bat1706.ab,ti,kf,rn.	2
35	"bcd 021".ab,ti,kf,rn.	0
36	bcd021.ab,ti,kf,rn.	1
37	bevz 92.ab,ti,kf,rn.	0
38	bevz92.ab,ti,kf,rn.	1
39	CHS-5217.ab,ti,kf,rn.	0
40	CHS5217.ab,ti,kf,rn.	0
41	CT-16.ab,ti,kf,rn.	120
42	CT16.ab,ti,kf,rn.	37
43	CT-P16.ab,ti,kf,rn.	1
44	CTP16.ab,ti,kf,rn.	0
45	FKB-238.ab,ti,kf,rn.	0
46	FKB238.ab,ti,kf,rn.	0
47	hd 204.ab,ti,kf,rn.	2
48	hd204.ab,ti,kf,rn.	0
49	HLX-04.ab,ti,kf,rn.	0
50	HLX04.ab,ti,kf,rn.	0
51	"mb 02".ab,ti,kf,rn.	18
52	mb02.ab,ti,kf,rn.	4
53	mil 60.ab,ti,kf,rn.	2
54	mil60.ab,ti,kf,rn.	2
55	myl 14020.ab,ti,kf,rn.	0
56	myl14020.ab,ti,kf,rn.	0
57	myl 1402o.ab,ti,kf,rn.	0
58	myl1402o.ab,ti,kf,rn.	0
59	nsc 704865.ab,ti,kf,rn.	2
60	nsc704865.ab,ti,kf,rn.	0



Date	June 23, 2020	
61	ons 1045.ab,ti,kf,rn.	0
62	ons1045.ab,ti,kf,rn.	0
63	ons 5010.ab,ti,kf,rn.	0
64	ons5010.ab,ti,kf,rn.	0
65	PF06439535.ab,ti,kf,rn.	0
66	PF-06439535.ab,ti,kf,rn.	5
67	PF6439535.ab,ti,kf,rn.	0
68	PF-6439535.ab,ti,kf,rn.	0
69	ql 1101.ab,ti,kf,rn.	0
70	ql1101.ab,ti,kf,rn.	1
71	RG-435.ab,ti,kf,rn.	1
72	RG435.ab,ti,kf,rn.	0
73	R-435.ab,ti,kf,rn.	53
74	R435.ab,ti,kf,rn.	15
75	ro 4876646.ab,ti,kf,rn.	0
76	ro4876646.ab,ti,kf,rn.	0
77	sb 8.ab,ti,kf,rn.	30
78	sb8.ab,ti,kf,rn.	19
79	stc 103.ab,ti,kf,rn.	0
80	stc103.ab,ti,kf,rn.	0
81	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80	18733
82	4 or 81	18733
83	3 and 82	913
84	exp Vascular Endothelial Growth Factors/ai	8313
85	exp Receptors, Vascular Endothelial Growth Factor/ai	2960
86	84 or 85	10865
87	(vegfr adj5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)).ab,ti,kf.	20933
88	(vegfr* adj5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)).ab,ti,kf.	4593
89	87 or 88	23748
90	86 or 89	28968
91	3 and 90	595
92	exp Antibodies, Monoclonal/	235325
93	(monoclonal adj3 antibod*).ab,ti,kf.	196475



Date	June 23, 2020	
94	92 or 93	320037
95	3 and 94	4289
96	((new class* or innovative or target*) adj3 (drug? or therapy or therapies or therapeutic* or treatment? or chemotherap*)).ab,ti,kf.	330433
97	3 and 96	5773
98	83 or 91 or 95 or 97	10100
99	((systematic review or systematic literature review or systematic scoping review or systematic narrative review or systematic qualitative review or systematic evidence review or systematic quantitative review or systematic meta-review or systematic critical review or systematic mixed studies review or systematic mapping review or systematic cochrane review or "systematic search and review" or systematic integrative review).ti. not comment.pt. not (protocol or protocols).ti. not medline.st.) or (Cochrane Database Syst Rev.ja. and review.pt.) or systematic review.pt.	159535
100	meta-analys*.ti.	109097
101	meta-analysis.pt.	116362
102	exp Technology Assessment, Biomedical/	11075
103	health technology assessment.ti,kf.	1925
104	HtA.ti,kf.	596
105	99 or 100 or 101 or 102 or 103 or 104	253258
106	98 and 105	84
Comments		



Appendix 10.4. Economic literature

Appendix 10.4.1. Search economic literature (HTA reports)

The search strategy in CRD's HTA database identified 88 references (Table 158). In a first round, 5 references were selected based on a review of title, keywords and abstract. The 83 remaining references were excluded for the following reasons: intervention (82) and design (1). In a second round, the full text of the 5 selected references was reviewed. Four references were excluded (design (2), price (1), full text could not be retrieved (1)). One reference was retained. This reference is indicated in Table 27 with an asterix (*).

Furthermore, in May 2020, the website of the National Institute for Health Research (NIHR) was searched for relevant reports. The following search term was used: bevacizumab (43 hits, 2 with a focus on ovarian cancer, 2 not previously identified).

Finally, also in May 2020, the website of the National Institute for Health and Care Excellence (NICE) was searched. The following search term was used: bevacizumab (47 hits, 4 relevant Technology Assessments (TAs), 4 not previously identified).

An overview of the identified references is provided in Table 159.

Table 158 – Search strategy and results for CRD: HTA

Date			
Date covered	All		
Search Strategy	1	MeSH DESCRIPTOR Ovarian Neoplasms EXPLODE ALL TREES	325
	2	* IN HTA	17351
	3	#1 AND #2	88 references
Note	/		

**Table 159 – Epithelial Ovarian Cancer – Identified HTA reports for the selected drugs****Selected reports****Bevacizumab**

- Neyt M, Devriese S, Camberlin C, Vlayen J. Bevacizumab in the treatment of ovarian cancer. Health Technology Assessment (HTA) Brussels: Belgian Health Care Knowledge Centre (KCE). 2017. KCE Reports 285.²⁶⁰ *
- NICE, TA284. May 2013. Bevacizumab in combination with paclitaxel and carboplatin for first-line treatment of advanced ovarian cancer.²⁶⁴ β
 - Cooper K, Pickett K, Frampton GK, Copley V, Bryant J. Bevacizumab in combination with carboplatin and paclitaxel for the first-line treatment of ovarian cancer. A Single Technology Appraisal. SHTAC. 2012.²⁶⁵ α
- NICE, TA285. May 2013. Bevacizumab in combination with gemcitabine and carboplatin for treating the first recurrence of platinum-sensitive advanced ovarian cancer.²⁶⁶ β
 - Edwards SJ, Barton S, Thurgar E, Nherera L, Hamilton V, Karner C, Trevor N. Bevacizumab for the treatment of recurrent advanced ovarian cancer: A Single Technology Appraisal. BMJ-TAG, London, 2012.²⁶⁷ α
- NICE, TA353. August 2015. Bevacizumab for treating relapsed, platinum-resistant epithelial ovarian, fallopian tube or primary peritoneal cancer (terminated appraisal).²⁶⁸ β
- NICE, TA560. February 2019. Bevacizumab with carboplatin, gemcitabine and paclitaxel for treating the first recurrence of platinum-sensitive advanced ovarian cancer (terminated appraisal).²⁶⁹ β

* These references were identified in CRD's HTA database. α References identified on NIHR's website. β References identified on NICE's website.



Appendix 10.4.2. Results economic literature (HTA reports)

Appendix 10.4.2.1. KCE (2017): bevacizumab

- QoL:
 - “The effect of first-line bevacizumab on QoL was reported in the GOG-0218 trial (measured with the FACT-O TOI instrument) and ICON7 trial (measured with the EORTC QLQ-C30 and QLQ-OV28 instruments). Lower QoL scores were reported in the bevacizumab arms The pooled results showed a significant better QoL for the standard chemotherapy group at 18 weeks and no further significant difference at 54-60 weeks. Unfortunately, no utility values were reported. Good QoL estimates measured with a generic utility instrument are unfortunately lacking.”²⁶⁰
 - “In the NICE TA284 manufacturer submission, QoL data from the ICON7 trial, measured with the generic EQ-5D questionnaire were presented. We remark that no such information was presented in the original publication of the ICON7 trial. The publication of Oza et al. just mentions that “quality of life was assessed with the European Organisation for Research and Treatment of Cancer QLQ-C30 and QLQ-OV28 questionnaires.”²⁷⁰ The manufacturer’s submission does not model the QoL results per treatment arm. In contrast, they transfer these results to utility values for the PFS and PD health states As such, an improvement in QoL is modelled indirectly. In contrast with the available evidence, no decrease in QoL during the first cycles with bevacizumab was modelled. Further, we remark that the QoL values from the TA284 manufacturer submission come from the ICON7 study. As previously mentioned by the ERG, this trial “employed a lower dose of bevacizumab than in the NICE scope. Any AEs caused by the higher dose of bevacizumab as specified in the NICE scope would not be captured using the utility data from the ICON7 trial.”²⁶⁵²⁶⁰
 - “Unfortunately, in the NICE submission, the EQ-5D scores were not published per treatment arm, but immediately pooled per non-progressed or progressed health state.”²⁶⁰
 - “In the AURELIA trial, no generic utility instrument was used to enable the generation of utility values.”²⁶⁰
- Results:
 - “First-line bevacizumab
 - ... GOG-0218: Average ICER: €158 000/QALY.
 - ... GOG-0218 stage IV subgroup: Average ICER: €52 000/QALY.
 - ... ICON7: Average ICER: €443 000/QALY.
 - ... ICON7 high-risk subgroup: Average ICER: €82 000/QALY
 - Second-line bevacizumab
 - ... OCEANS: Average ICER: €587 000/QALY.
 - ... AURELIA: Average ICER: €172 000/QALY.”²⁶⁰
- Uncertainty/sensitivity:



- “In general, we notice the high uncertainty around the treatment effect, as seen by the wide confidence interval around the incremental effects and part of the simulations situated in the fourth quadrant of the cost-effectiveness plane. The results are most sensitive to both the price of bevacizumab and the time horizon. The alternative QoL scenarios do not have a major impact on results.”²⁶⁰
- Conclusions:
 - “In general, from a health economic point of view, the results for second-line bevacizumab treatment are not favourable. The average ICER based on the OCEANS and AURELIA trials amount to €587 000/QALY and €172 000/QALY, respectively.
 - In the first-line setting, results are not favourable when results for the whole population of the GOG-0218 or ICON7 trials are modelled, with ICERs of on average 158 000/QALY and 443 000/QALY, respectively. The most optimistic results are based on the stage IV subgroup of the GOG-0218 trial. However, even in this subgroup analysis, average ICERs amount to €52 000/QALY in a rather optimistic scenario (e.g. no decrease of QoL with bevacizumab treatment, extrapolation of results to lifetime time horizon with constant mortality, not taking into account costs for all AEs).”²⁶⁰
- (Confidential) prices:
 - “The reimbursement of bevacizumab for the treatment of ovarian cancer is based on a confidential contract”²⁶⁰
 - “Concerning the confidential price agreements, sensitivity analyses were performed with price discounts between 0% and 100%. As such, policy makers can link e.g. the necessary price discounts to reach a specific willingness/ability-to-pay value.”²⁶⁰

Reference Costs (list prices & remarks)	Population, Intervention & comparator IC, IE and ICERs	Remarks on use of generic utility instrument (e.g. EQ- 5D) to measure impact on QoL in economic evaluations	Most uncertain variables or important variables in sensitivity analysis												
Bevacizumab															
KCE, 2017 ²⁶⁰	The description of the eligible population reflects the population included in the trials. These trials include previously untreated ‘incompletely resectable stage III or any stage IV’ (GOG-0218) or ‘stage IIb–IV or high-risk (grade 3 or clear cell histology) stage I–IIa disease’ (ICON7) or ‘progression > 6 months after completion of front-line platinum-based chemotherapy’ (OCEANS) or ‘progressed within 6 months of completing > four cycles of platinum-based therapy’ (AURELIA) GOG-0218 and ICON7: Bevacizumab + carboplatin + paclitaxel compared with the standard chemotherapy arm (carboplatin + paclitaxel) OCEANS: bevacizumab + gemcitabine + carboplatin compared with gemcitabine + carboplatin AURELIA: bevacizumab + chemotherapy compared with single-agent chemotherapy														
List prices, negotiated discounts are unknown. Scenarios with 0-100% discount are presented.	Results of the incremental analysis (with list prices): A) GOG-0218 <table><tr><th>Control</th><th>Costs</th><th>IC</th><th>QALYs</th><th>IE</th><th>ICER</th></tr><tr><td></td><td>/</td><td></td><td>2.93</td><td></td><td></td></tr></table>	Control	Costs	IC	QALYs	IE	ICER		/		2.93			From the four trials, QoL was only measured with a generic utility instrument in the ICON7 trial.	Treatment effect Price of bevacizumab Time horizon.
Control	Costs	IC	QALYs	IE	ICER										
	/		2.93												



In the Belgian sample of ovarian cancer patients receiving bevacizumab, the average cost per cycle was €3169.

Bevacizumab	/	€47 268	3.22	0.30	€157 816
B) GOG-0218 st.IV					
	Costs	IC	QALYs	IE	ICER
Control	/		2.36		
Bevacizumab	/	€39 984	3.13	0.77	€51 931
C) ICON7					
	Costs	IC	QALYs	IE	ICER
Control	/		4.49		
Bevacizumab	/	€27 188	4.56	0.06	€443 027
D) ICON7 HR					
	Costs	IC	QALYs	IE	ICER
Control	/		2.63		
Bevacizumab	/	€27 189	2.97	0.33	€82 277
E) OCEANS					
	Costs	IC	QALYs	IE	ICER
Control	/		2.64		
Bevacizumab	/	€56 897	2.74	0.10	€587 182
F) AURELIA					
	Costs	IC	QALYs	IE	ICER
Control	/		1.05		
Bevacizumab	/	€30 259	1.23	0.18	€172 370



Appendix 10.4.2.2. NICE, TA284 (2013): bevacizumab

- QoL:
 - “The key evidence for the clinical effectiveness of bevacizumab plus paclitaxel and carboplatin came from 1 randomised controlled trial (GOG-0218). The trial assessed the efficacy and safety of bevacizumab (at its licensed dose of 15 mg/kg body weight) plus paclitaxel and carboplatin in people with previously untreated stage III (incompletely resected) or stage IV epithelial ovarian, fallopian tube or primary peritoneal cancer who had undergone debulking surgery. This evidence was supported by results from a randomised open-label trial (ICON7) that assessed the efficacy and safety of bevacizumab at an unlicensed dose (7.5 mg/kg body weight) plus paclitaxel and carboplatin in people with high-risk early stage or advanced epithelial ovarian, fallopian tube or primary peritoneal cancer.”²⁶⁴
 - GOG-0218: “health-related quality of life measured using the Functional Assessment of Cancer Therapy-Ovarian (FACT-O) questionnaire, the Ovarian Cancer Subscale measure and abdominal discomfort score.”²⁶⁴
 - ICON7: “Health-related quality of life was measured using the European Organization for the Research and Treatment of Cancer (EORTC) QLQ-C30 and QLQ-OV28 questionnaires.”²⁶⁴
 - “The manufacturer applied EQ-5D utility values from an expanded high-risk subgroup in the ICON7 study, which included all patients with stage III disease with suboptimal debulking or stage IV disease or patients with unresectable disease (n=495).”²⁶⁴
 - “The Committee noted that the EQ-5D utilities from the expanded high-risk subgroup of ICON7 were used in the model.”²⁶⁴
- Results:
 - “The Committee noted that the manufacturer's base-case ICER was approximately £144,000 per QALY gained. The Committee considered the ERG's exploratory analyses, which examined the changes in the ICER with a treatment duration of 15 months or a time horizon of 25 years or both, and gave a range of ICERs from £128,000 to £161,000 per QALY gained.”²⁶⁴
- Uncertainty/sensitivity:
 - “The Committee concluded that the overall survival benefit of bevacizumab plus carboplatin and paclitaxel is uncertain from the results of GOG-0218 because of the uncertainty related to the extent to which patients received bevacizumab after progression and the impact of this.”²⁶⁴
 - “The manufacturer's deterministic sensitivity analysis for GOG-0218 suggested that the cost-effectiveness results are influenced by the parametric functions used for the PFS extrapolation and the time horizon used in the model. The manufacturer's scenario analyses identified the key drivers of the cost-effectiveness results as the dose and duration of bevacizumab treatment.”²⁶⁴
- Conclusions:
 - “The model results suggest that bevacizumab is not cost effective at the licensed dose for a willingness-to-pay threshold of £20,000-£30,000 per QALY.”²⁶⁵
 - “The Committee agreed that the range of ICERs obtained from the cost-effectiveness model of bevacizumab plus paclitaxel and carboplatin were outside the range normally considered as a cost-effective use of NHS resources. It therefore concluded that bevacizumab within its marketing



authorisation (that is, at a dose of 15 mg/kg), plus paclitaxel and carboplatin, would not be a cost-effective use of NHS resources for first-line treatment of advanced ovarian cancer compared with paclitaxel and carboplatin alone.”²⁶⁴

- “Bevacizumab in combination with paclitaxel and carboplatin is not recommended for first-line treatment of advanced ovarian cancer (International Federation of Gynaecology and Obstetrics [FIGO] stages IIIB, IIIC and IV epithelial ovarian, fallopian tube or primary peritoneal cancer).”²⁶⁴
- (Confidential) prices:
 - “The manufacturer estimated the cost of bevacizumab (excluding VAT and assuming wastage) to be £36,078 for a patient weighing 65 kg at a dosage of 15 mg/kg every 3 weeks, amounting to an average monthly cost of £2577. Costs may vary in different settings because of negotiated procurement discounts.”²⁶⁴

Reference Costs (list prices & remarks)	Population, Intervention & comparator IC, IE and ICERs					Remarks on use of generic utility instrument (e.g. EQ- 5D) to measure impact on QoL in economic evaluations	Most uncertain variables or important variables in sensitivity analysis	
Bevacizumab								
NICE, TA284 (2013) ²⁶⁴ Cooper, 2012 ²⁶⁵	Patients with advanced ovarian cancer (Stage III and Stage IV patients) Bevacizumab in combination with carboplatin and paclitaxel versus combination chemotherapy using carboplatin with paclitaxel (1 st -line treatment).							
List prices: bevacizumab is available in 100 mg and 400 mg vials at prices of £242.66 and £924.40. Drug costs per cycle: Bebacizumab: £2229 Paclitaxel: £21.80 Carboplatin: £18.51	Results of the incremental analysis (with list prices): base case					Key RCT (GOG-0218 - dose 15mg/kg): no use of a generic utility instrument. Supporting trial (ICON7 - dose 7.5mg/kg): EQ-5D utilities from the expanded high-risk subgroup of ICON7 were used in the model	PFS extrapolation Time horizon Dose and duration of bevacizumab.	
		Costs (£)	IC	QALYs	IE			ICER
	CP	17,166		2.97				
	CPB	44,254	27,089	3.16	0.19			144,066
Remark: NICE reiterated its position that the Committee was only permitted to make a recommendation on the licensed dose of bevacizumab (15 mg/kg). The Committee therefore concluded that it was reasonable not to consider further the cost effectiveness of bevacizumab at its unlicensed dose.								

CP: carboplatin and paclitaxel; CPB: Bevacizumab in combination with carboplatin and paclitaxel.



Appendix 10.4.2.3. NICE, TA285 (2013): bevacizumab

- QoL:
 - “The key evidence for the clinical effectiveness of bevacizumab plus gemcitabine and carboplatin came from 1 randomised controlled trial (OCEANS). ... The Committee noted that health-related quality-of-life data were not collected in the OCEANS trial. It agreed that health-related quality-of-life data collected in the trial would have been preferable for deriving the utilities for the economic model.”²⁶⁶
 - Both an over- and underestimation of impact on QoL is possible: “The Committee agreed that it may be plausible for a larger decrement in utility to occur when a person moves from the progression-free health state to a progressed-disease health state and that the difference in utility between the PFS state and progressed state used by the manufacturer could be an underestimate. It also noted that a disutility associated with adverse events was not applied and that there were more serious adverse events in the bevacizumab arm than in the placebo arm.”²⁶⁶
 - “As health-related quality of life data (HRQoL) data were not collected as part of the OCEANS trial, the manufacturer carried out a systematic review to identify health state utility value (HSUV) studies relevant to the health states considered in the model. The review identified 35 publications, of which five were deemed relevant to the submission by the manufacturer (Brundage et al.,²⁷¹ Krasner et al.,²⁷² Pokrzywinski et al.,²⁷³ Havrilesky et al.,²⁷⁴ Vergote et al.²⁷⁵). The manufacturer notes that Brundage et al.,²⁷¹ Pokrzywinski et al.,²⁷³ Havrilesky et al.,²⁷⁴ and Vergote et al.²⁷⁵ do not present EuroQol 5 dimensions questionnaire (EQ-5D) data and commented that mapping to EQ-5D would not be possible from the HRQoL measures collected in these papers. The manufacturer also noted that Krasner et al.²⁷² collected and reported EQ-5D. ... a utility for each treatment group at baseline and a utility change from baseline to end of treatment by therapy is reported However, the paper does not report utilities associated with PFS or PD health states.”²⁶⁷
 - “Health-related quality of life and utilities applied in the model were obtained from Trabectedin for the treatment of relapsed ovarian cancer (NICE technology appraisal guidance 222). The data used in this guidance were taken from the OVA-301 trial using EQ-5D.”²⁶⁶
- Results:
 - “The base-case results estimated that adding bevacizumab to carboplatin and gemcitabine provides an additional 0.42 life years and 0.298 quality-adjusted life years (QALYs). These benefits are achieved with an incremental cost of £44,428, resulting in an incremental cost-effectiveness ratio (ICER) of £149,050 per QALY gained for bevacizumab plus carboplatin and gemcitabine compared with carboplatin and gemcitabine alone.”²⁶⁶
 - “The Committee agreed that the manufacturer's base-case ICER, using the September 2010 overall survival data of £149,000 per QALY gained, was likely to be an optimistic cost-effectiveness estimate and that the most plausible ICER could be much higher than this.”²⁶⁶
- Uncertainty/sensitivity:
 - “The Committee concluded that overall survival was the biggest driver of the cost-effectiveness estimate and that, in principle, it would have liked to have seen a sensitivity analysis from the manufacturer that used the March 2012 data [more mature data], which would have resulted in a higher ICER than the base case.”²⁶⁶
 - “The ERG acknowledges that OS data from OCEANS are immature and that analysis once the defined number of events has occurred will provide more robust evidence on this issue.”²⁶⁷



- “The manufacturer's deterministic sensitivity analysis suggested that the cost-effectiveness results were most sensitive to assumptions around the extrapolation of overall survival, the duration of treatment and the utility of patients in PFS. The manufacturer's probabilistic sensitivity analyses concluded that the probability of bevacizumab plus carboplatin and gemcitabine being cost effective compared with carboplatin and gemcitabine alone at a threshold of £30,000 per QALY gained was 0%. The manufacturer identified the key drivers of the cost-effectiveness results to be the cost and duration of treatment with bevacizumab and the time horizon of the analysis.”²⁶⁶
- Conclusions:
 - “The Committee agreed that the OCEANS trial had shown the clinical effectiveness of bevacizumab plus gemcitabine and carboplatin in terms of progression-free survival (PFS) but noted that there was insufficient evidence of clinical benefit in terms of overall survival.”²⁶⁶
 - “The Committee noted that the cost-effectiveness estimates for bevacizumab plus gemcitabine and carboplatin were outside the range normally considered to be a cost-effective use of NHS resources. It therefore concluded that bevacizumab plus gemcitabine and carboplatin would not be a cost-effective use of NHS resources for treating the first recurrence of platinum-sensitive advanced ovarian cancer compared with gemcitabine and carboplatin alone.”²⁶⁶
 - “Bevacizumab in combination with gemcitabine and carboplatin is not recommended within its marketing authorisation, that is, for treating people with the first recurrence of platinum-sensitive advanced ovarian cancer (including fallopian tube and primary peritoneal cancer) who have not received prior therapy with bevacizumab or other vascular endothelial growth factor (VEGF) inhibitors or VEGF receptor-targeted agents.”²⁶⁶
- (Confidential) prices:
 - “The manufacturer estimated the cost of a course of treatment with bevacizumab (excluding VAT and assuming vials are not shared between patients) to be £25,208 for a patient weighing 60.5 kg at a dosage of 15 mg/kg every 3 weeks for a mean treatment duration of 10.8 cycles (7.5 months). Costs may vary in different settings because of negotiated procurement discounts.”²⁶⁶



Reference Costs (list prices & remarks)	Population, Intervention & comparator IC, IE and ICERs	Remarks on use of generic utility instrument (e.g. EQ- 5D) to measure impact on QoL in economic evaluations	Most uncertain variables or important variables in sensitivity analysis
Bevacizumab			
NICE, TA285 (2013) ²⁶⁶	Patients with advanced, recurrent, platinum-sensitive ovarian cancer.		
Edwards (2012) ²⁶⁷	Bevacizumab plus carboplatin and gemcitabine compared with placebo plus carboplatin and gemcitabine.		
List prices: bevacizumab is available in 100 mg and 400 mg vials at prices of £242.66 and £924.40.	Results of the incremental analysis (with list prices): deterministic	Key trial: OCEANS. Health-related quality-of-life data were not collected in the OCEANS trial.	Extrapolation of overall survival (time horizon), cost and duration of treatment, utility of patients in PFS.
Average total cost per administration:	Costs (£) IC QALYs IE ICER		
CG	£14,912 1.98		
CGB	£59,340 £44,428 2.28 0.298 £149,050	Utilities were obtained from trabectedin for the treatment of relapsed ovarian cancer (NICE TA222).	
Bebacizumab: £2,556	Remark: The manufacturer estimated the incremental cost-effectiveness ratio (ICER) for the bevacizumab group compared with the placebo group to be £149,050 per quality adjusted life year (QALY; deterministic) and £221,750 per QALY (probabilistic).		
Carboplatin: £155			
Gemcitabine: £21			

CG: carboplatin and gemcitabine; CGB: bevacizumab plus carboplatin and gemcitabine.



Appendix 10.4.2.4. NICE, TA353 (2015): bevacizumab

- “Roche Products was invited to submit evidence for this single technology appraisal for bevacizumab in March 2015.
- Roche conceded that it would not be possible to demonstrate the cost effectiveness of bevacizumab for relapsed, platinum-resistant epithelial ovarian, fallopian tube or primary peritoneal cancer. Bevacizumab cannot be given special consideration as a treatment used at the end of life because the total population eligible for treatment across all its licensed indications is too large.
- NICE has therefore terminated this single technology appraisal.”²⁶⁸
- “NICE is unable to make a recommendation about the use in the NHS of bevacizumab for treating relapsed, platinum-resistant epithelial ovarian, fallopian tube or primary peritoneal cancer because no evidence submission was received from Roche Products for the technology.”²⁶⁸

Appendix 10.4.2.5. NICE, TA560 (2019): bevacizumab

- “NICE is unable to make a recommendation about the use in the NHS of bevacizumab with carboplatin, gemcitabine and paclitaxel for treating the first recurrence of platinum-sensitive advanced ovarian cancer because no evidence submission was received from Roche. The company has confirmed that it does not intend to make a submission because the technology is unlikely to be used at this point in the treatment pathway and is unlikely to be a cost-effective use of NHS resources.”²⁶⁹



APPENDIX 11. PROSTATE CANCER

Appendix 11.1. BCR DATA

Appendix 11.1.1. Descriptive statistics

Appendix 11.1.1.1. Prostate cancer, exploration

Table 160 – Prostate cancer (2004-2017): Frequency table of patient and tumour characteristics

Characteristic	Total	Incidence period		
		2004-2008	2009-2013	2014-2017
Overall	123,495	46,148	42,543	34,804
Gender				
Male	123495 (100.0)	46,148 (100.0)	42,543 (100.0)	34,804 (100.0)
Age at diagnosis (year)				
<50 years	1,456 (1.2)	599 (1.3)	478 (1.1)	379 (1.1)
50-59 years	17,503 (14.2)	6,899 (14.9)	6,155 (14.5)	4,449 (12.8)
60-69 years	42,704 (34.6)	15,292 (33.1)	14,963 (35.2)	12,449 (35.8)
70-79 years	43,615 (35.3)	17,014 (36.9)	14,683 (34.5)	11,918 (34.2)
80+ years	18,217 (14.8)	6,344 (13.7)	6,264 (14.7)	5,609 (16.1)
WHO - Performance Status				
0 – Asymptomatic	41,385 (33.5)	11,950 (25.9)	15,453 (36.3)	13,982 (40.2)
1 – Symptomatic but completely ambulatory	37,787 (30.6)	8,978 (19.5)	14,958 (35.2)	13,851 (39.8)
2 – Symptomatic, <50% in bed during the day	2,395 (1.9)	949 (2.1)	553 (1.3)	893 (2.6)
3 – Symptomatic, >50% in bed, but not bedbound	336 (0.3)	117 (0.3)	111 (0.3)	108 (0.3)
4 – Bedbound	104 (0.1)	33 (0.1)	37 (0.1)	34 (0.1)
Not reported	41,488 (33.6)	24,121 (52.3)	11,431 (26.9)	5,936 (17.1)
Combined stage				



0	1 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
I	24,150 (19.6)	1,021 (2.2)	11,403 (26.8)	11,726 (33.7)
II	41,552 (33.6)	20,617 (44.7)	12,490 (29.4)	8,445 (24.3)
III	17,312 (14.0)	5,807 (12.6)	6,052 (14.2)	5,453 (15.7)
IV	10,982 (8.9)	2,883 (6.2)	3,687 (8.7)	4,412 (12.7)
X/NA	29,498 (23.9)	15,820 (34.3)	8,911 (20.9)	4,767 (13.7)

Note: the values between parentheses are column percentages.



Table 161 – Prostate cancer (2004-2017): Frequency table of patient and tumour characteristics (cut-off point: 2011)

Characteristic	Total	Incidence period	
		2004-2010	2012-2017
Overall	114 449	63 519	50 930
Gender			
Male	114 449 (100.0)	63 519 (100.0)	50 930 (100.0)
Age at diagnosis (year)			
<50 years	1 357 (1.2)	796 (1.3)	561 (1.1)
50-59 years	16 177 (14.1)	9 400 (14.8)	6 777 (13.3)
60-69 years	39 531 (34.5)	21 207 (33.4)	18 324 (36.0)
70-79 years	40 469 (35.4)	23 223 (36.6)	17 246 (33.9)
80+ years	16 915 (14.8)	8 893 (14.0)	8 022 (15.8)
WHO - Performance Status			
0 – Asymptomatic	38 124 (33.3)	17 810 (28.0)	20 314 (39.9)
1 – Symptomatic but completely ambulatory	34 617 (30.2)	14 790 (23.3)	19 827 (38.9)
2 – Symptomatic, <50% in bed during the day	2 280 (2.0)	1 140 (1.8)	1 140 (2.2)
3 – Symptomatic, >50% in bed, but not bedbound	315 (0.3)	168 (0.3)	147 (0.3)
4 – Bedbound	93 (0.1)	53 (0.1)	40 (0.1)
Not reported	39 020 (34.1)	29 558 (46.5)	9 462 (18.6)
Combined stage			
0	1 (0.0)	0 (0.0)	1 (0.0)
I	21 432 (18.7)	3 981 (6.3)	17 451 (34.3)
II	39 364 (34.4)	27 014 (42.5)	12 350 (24.2)
III	16 002 (14.0)	8 132 (12.8)	7 870 (15.5)
IV	10 222 (8.9)	4 165 (6.6)	6 057 (11.9)
X/NA	27 428 (24.0)	20 227 (31.8)	7 201 (14.1)

Note: the values between parentheses are column percentages.


Table 162 – Prostate cancer (2004-2017), Combined stage I, Frequency table of patient and tumour characteristics

Characteristic	Total	Incidence period		
		2004-2008	2009-2013	2014-2017
Overall	24,150	1,021	11,403	11,726
Gender				
Male	24,150 (100.0)	1,021 (100.0)	11,403 (100.0)	11,726 (100.0)
Age at diagnosis (year)				
<50 years	201 (0.8)	14 (1.4)	89 (0.8)	98 (0.8)
50-59 years	2,602 (10.8)	94 (9.2)	1,303 (11.4)	1,205 (10.3)
60-69 years	7,651 (31.7)	289 (28.3)	3,540 (31.0)	3,822 (32.6)
70-79 years	9,709 (40.2)	450 (44.1)	4,661 (40.9)	4,598 (39.2)
80+ years	3,987 (16.5)	174 (17.0)	1,810 (15.9)	2,003 (17.1)
WHO - Performance Status				
0 – Asymptomatic	10,414 (43.1)	314 (30.8)	4,996 (43.8)	5,104 (43.5)
1 – Symptomatic but completely ambulatory	10,376 (43.0)	373 (36.5)	4,893 (42.9)	5,110 (43.6)
2 – Symptomatic, <50% in bed during the day	530 (2.2)	54 (5.3)	161 (1.4)	315 (2.7)
3 – Symptomatic, >50% in bed, but not bedbound	31 (0.1)	6 (0.6)	11 (0.1)	14 (0.1)
4 – Bedbound	10 (0.0)	1 (0.1)	7 (0.1)	2 (0.0)
Not reported	2,789 (11.5)	273 (26.7)	1,335 (11.7)	1,181 (10.1)

Note: the values between parentheses are column percentages.



Table 163 – Prostate cancer (2004-2017), Combined stage I, Frequency table of patient and tumour characteristics (cut-off point: 2011)

Characteristic	Total	Incidence period	
		2004-2010	2012-2017
Overall	21 432	3 981	17 451
Gender			
Male	21 432 (100.0)	3 981 (100.0)	17 451 (100.0)
Age at diagnosis (year)			
<50 years	181 (0.8)	32 (0.8)	149 (0.9)
50-59 years	2 277 (10.6)	433 (10.9)	1 844 (10.6)
60-69 years	6 821 (31.8)	1 211 (30.4)	5 610 (32.1)
70-79 years	8 576 (40.0)	1 715 (43.1)	6 861 (39.3)
80+ years	3 577 (16.7)	590 (14.8)	2 987 (17.1)
WHO - Performance Status			
0 – Asymptomatic	9 154 (42.7)	1 602 (40.2)	7 552 (43.3)
1 – Symptomatic but completely ambulatory	9 253 (43.2)	1 679 (42.2)	7 574 (43.4)
2 – Symptomatic, <50% in bed during the day	501 (2.3)	87 (2.2)	414 (2.4)
3 – Symptomatic, >50% in bed, but not bedbound	28 (0.1)	10 (0.3)	18 (0.1)
4 – Bedbound	8 (0.0)	5 (0.1)	3 (0.0)
Not reported	2 488 (11.6)	598 (15.0)	1 890 (10.8)

Note: the values between parentheses are column percentages.


Table 164 – Prostate cancer (2004-2017), Combined stage II, Frequency table of patient and tumour characteristics

Characteristic	Total	Incidence period		
		2004-2008	2009-2013	2014-2017
Overall	41,552	20,617	12,490	8,445
Gender				
Male	41,552 (100.0)	20,617 (100.0)	12,490 (100.0)	8,445 (100.0)
Age at diagnosis (year)				
<50 years	742 (1.8)	354 (1.7)	236 (1.9)	152 (1.8)
50-59 years	8,342 (20.1)	3,927 (19.0)	2,730 (21.9)	1,685 (20.0)
60-69 years	16,955 (40.8)	7,850 (38.1)	5,372 (43.0)	3,733 (44.2)
70-79 years	12,464 (30.0)	6,833 (33.1)	3,338 (26.7)	2,293 (27.2)
80+ years	3,049 (7.3)	1,653 (8.0)	814 (6.5)	582 (6.9)
WHO - Performance Status				
0 – Asymptomatic	18,194 (43.8)	8,274 (40.1)	5,658 (45.3)	4,262 (50.5)
1 – Symptomatic but completely ambulatory	12,910 (31.1)	5,264 (25.5)	4,486 (35.9)	3,160 (37.4)
2 – Symptomatic, <50% in bed during the day	589 (1.4)	437 (2.1)	67 (0.5)	85 (1.0)
3 – Symptomatic, >50% in bed, but not bedbound	54 (0.1)	37 (0.2)	13 (0.1)	4 (0.0)
4 – Bedbound	7 (0.0)	4 (0.0)	1 (0.0)	2 (0.0)
Not reported	9,798 (23.6)	6,601 (32.0)	2,265 (18.1)	932 (11.0)

Note: the values between parentheses are column percentages.



Table 165 – Prostate cancer (2004-2017), Combined stage II, Frequency table of patient and tumour characteristics (cut-off point: 2011)

Characteristic	Total	Incidence period	
		2004-2010	2012-2017
Overall	39 364	27 014	12 350
Gender			
Male	39 364 (100.0)	27 014 (100.0)	12 350 (100.0)
Age at diagnosis (year)			
<50 years	697 (1.8)	463 (1.7)	234 (1.9)
50-59 years	7 804 (19.8)	5 208 (19.3)	2 596 (21.0)
60-69 years	15 945 (40.5)	10 398 (38.5)	5 547 (44.9)
70-79 years	11 973 (30.4)	8 792 (32.5)	3 181 (25.8)
80+ years	2 945 (7.5)	2 153 (8.0)	792 (6.4)
WHO - Performance Status			
0 – Asymptomatic	17 251 (43.8)	11 127 (41.2)	6 124 (49.6)
1 – Symptomatic but completely ambulatory	12 152 (30.9)	7 621 (28.2)	4 531 (36.7)
2 – Symptomatic, <50% in bed during the day	580 (1.5)	480 (1.8)	100 (0.8)
3 – Symptomatic, >50% in bed, but not bedbound	51 (0.1)	44 (0.2)	7 (0.1)
4 – Bedbound	7 (0.0)	4 (0.0)	3 (0.0)
Not reported	9 323 (23.7)	7 738 (28.6)	1 585 (12.8)

Note: the values between parentheses are column percentages.



Table 166 – Prostate cancer (2004-2017), Combined stage III, Frequency table of patient and tumour characteristics

Characteristic	Total	Incidence period		
		2004-2008	2009-2013	2014-2017
Overall	17,312	5,807	6,052	5,453
Gender				
Male	17,312 (100.0)	5,807 (100.0)	6,052 (100.0)	5,453 (100.0)
Age at diagnosis (year)				
<50 years	168 (1.0)	78 (1.3)	50 (0.8)	40 (0.7)
50-59 years	2,706 (15.6)	1,074 (18.5)	910 (15.0)	722 (13.2)
60-69 years	7,349 (42.5)	2,439 (42.0)	2,629 (43.4)	2,281 (41.8)
70-79 years	5,370 (31.0)	1,772 (30.5)	1,822 (30.1)	1,776 (32.6)
80+ years	1,719 (9.9)	444 (7.6)	641 (10.6)	634 (11.6)
WHO - Performance Status				
0 – Asymptomatic	7,201 (41.6)	2,153 (37.1)	2,554 (42.2)	2,494 (45.7)
1 – Symptomatic but completely ambulatory	5,952 (34.4)	1,458 (25.1)	2,304 (38.1)	2,190 (40.2)
2 – Symptomatic, <50% in bed during the day	278 (1.6)	143 (2.5)	54 (0.9)	81 (1.5)
3 – Symptomatic, >50% in bed, but not bedbound	32 (0.2)	11 (0.2)	10 (0.2)	11 (0.2)
4 – Bedbound	10 (0.1)	5 (0.1)	4 (0.1)	1 (0.0)
Not reported	3,839 (22.2)	2,037 (35.1)	1,126 (18.6)	676 (12.4)

Note: the values between parentheses are column percentages.



Table 167 – Prostate cancer (2004-2017), Combined stage III, Frequency table of patient and tumour characteristics (cut-off point: 2011)

Characteristic	Total	Incidence period	
		2004-2010	2012-2017
Overall	16 002	8 132	7 870
Gender			
Male	16 002 (100.0)	8 132 (100.0)	7 870 (100.0)
Age at diagnosis (year)			
<50 years	155 (1.0)	99 (1.2)	56 (0.7)
50-59 years	2 498 (15.6)	1 426 (17.5)	1 072 (13.6)
60-69 years	6 782 (42.4)	3 384 (41.6)	3 398 (43.2)
70-79 years	4 979 (31.1)	2 521 (31.0)	2 458 (31.2)
80+ years	1 588 (9.9)	702 (8.6)	886 (11.3)
WHO - Performance Status			
0 – Asymptomatic	6 641 (41.5)	3 083 (37.9)	3 558 (45.2)
1 – Symptomatic but completely ambulatory	5 465 (34.2)	2 355 (29.0)	3 110 (39.5)
2 – Symptomatic, <50% in bed during the day	264 (1.6)	162 (2.0)	102 (1.3)
3 – Symptomatic, >50% in bed, but not bedbound	31 (0.2)	19 (0.2)	12 (0.2)
4 – Bedbound	8 (0.0)	6 (0.1)	2 (0.0)
Not reported	3 593 (22.5)	2 507 (30.8)	1 086 (13.8)

Note: the values between parentheses are column percentages.



Table 168 – Prostate cancer (2004-2017), Combined stage IV, Frequency table of patient and tumour characteristics

Characteristic	Total	Incidence period		
		2004-2008	2009-2013	2014-2017
Overall	10,982	2,883	3,687	4,412
Gender				
Male	10,982 (100.0)	2,883 (100.0)	3,687 (100.0)	4,412 (100.0)
Age at diagnosis (year)				
<50 years	135 (1.2)	44 (1.5)	36 (1.0)	55 (1.2)
50-59 years	1,236 (11.3)	345 (12.0)	439 (11.9)	452 (10.2)
60-69 years	3,179 (28.9)	790 (27.4)	1,083 (29.4)	1,306 (29.6)
70-79 years	3,825 (34.8)	1,119 (38.8)	1,235 (33.5)	1,471 (33.3)
80+ years	2,607 (23.7)	585 (20.3)	894 (24.2)	1,128 (25.6)
WHO - Performance Status				
0 – Asymptomatic	3,086 (28.1)	724 (25.1)	1,117 (30.3)	1,245 (28.2)
1 – Symptomatic but completely ambulatory	5,433 (49.5)	1,229 (42.6)	1,906 (51.7)	2,298 (52.1)
2 – Symptomatic, <50% in bed during the day	775 (7.1)	244 (8.5)	197 (5.3)	334 (7.6)
3 – Symptomatic, >50% in bed, but not bedbound	177 (1.6)	49 (1.7)	60 (1.6)	68 (1.5)
4 – Bedbound	58 (0.5)	19 (0.7)	19 (0.5)	20 (0.5)
Not reported	1,453 (13.2)	618 (21.4)	388 (10.5)	447 (10.1)

Note: the values between parentheses are column percentages.



Table 169 – Prostate cancer (2004-2017), Combined stage IV, Frequency table of patient and tumour characteristics (cut-off point: 2011)

Characteristic	Total	Incidence period	
		2004-2010	2012-2017
Overall	10 222	4 165	6 056
Gender			
Male	10 222 (100.0)	4 165 (100.0)	6 056 (100.0)
Age at diagnosis (year)			
<50 years	128 (1.3)	60 (1.4)	68 (1.1)
50-59 years	1 131 (11.1)	489 (11.7)	642 (10.6)
60-69 years	2 966 (29.0)	1 161 (27.9)	1 805 (29.8)
70-79 years	3 565 (34.9)	1 548 (37.2)	2 017 (33.3)
80+ years	2 432 (23.8)	907 (21.8)	1 525 (25.2)
WHO - Performance Status			
0 – Asymptomatic	2 869 (28.1)	1 082 (26.0)	1 787 (29.5)
1 – Symptomatic but completely ambulatory	5 032 (49.2)	1 911 (45.9)	3 121 (51.5)
2 – Symptomatic, <50% in bed during the day	731 (7.2)	312 (7.5)	419 (6.9)
3 – Symptomatic, >50% in bed, but not bedbound	170 (1.7)	76 (1.8)	94 (1.6)
4 – Bedbound	53 (0.5)	30 (0.7)	23 (0.4)
Not reported	1 367 (13.4)	754 (18.1)	613 (10.1)

Note: the values between parentheses are column percentages.

Appendix 11.1.1.2. Prostate cancer (2004-2017), Observed and Relative Survival graphs

Prostate cancer (2004-2017)

Figure 295 – Prostate cancer (2004-2017), Kaplan-Meier graphs observed survival by incidence period

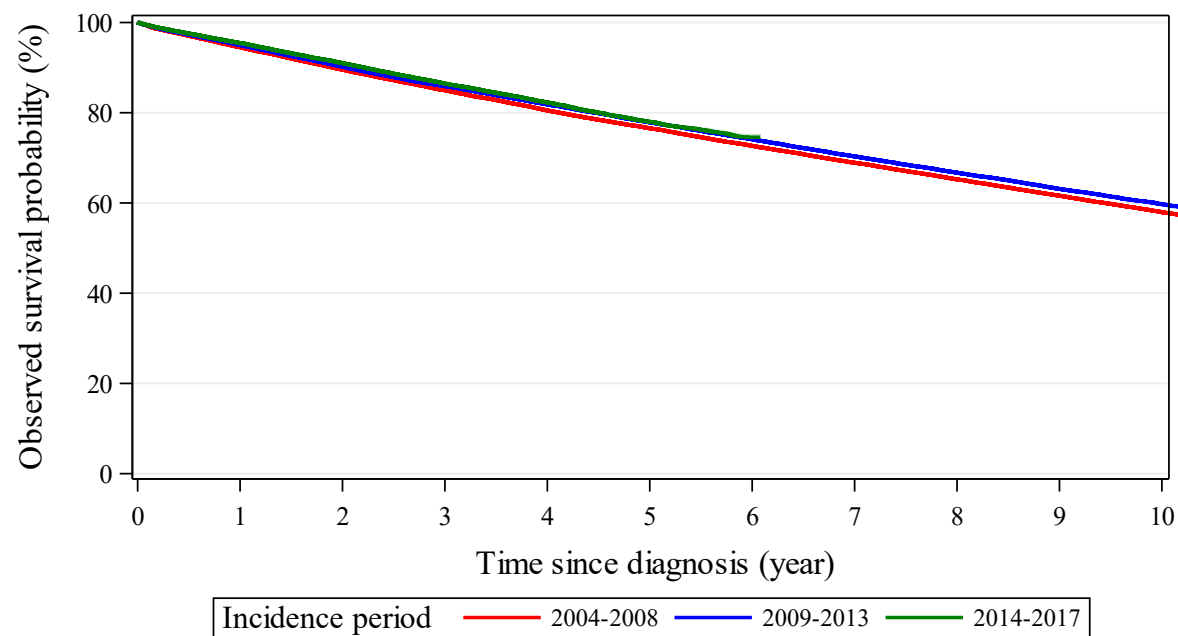




Figure 296 – Prostate cancer (2004-2017), Kaplan-Meier graphs observed survival by incidence period (cut-off point: 2011)

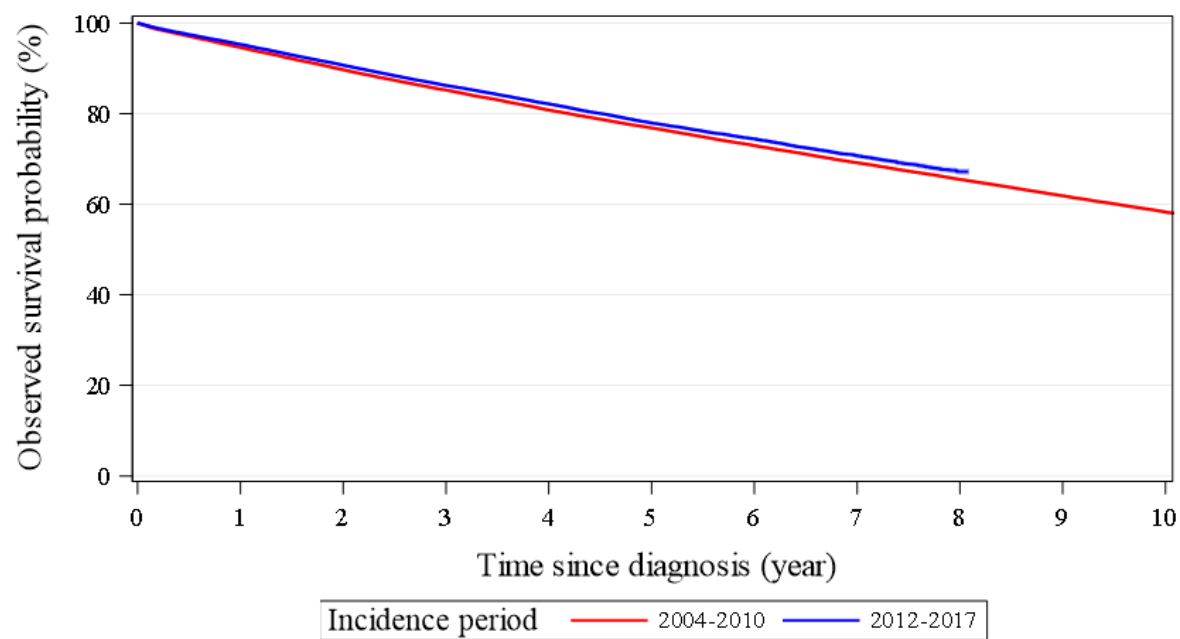




Figure 297 – Prostate cancer (2004-2017), relative survival graphs by incidence period

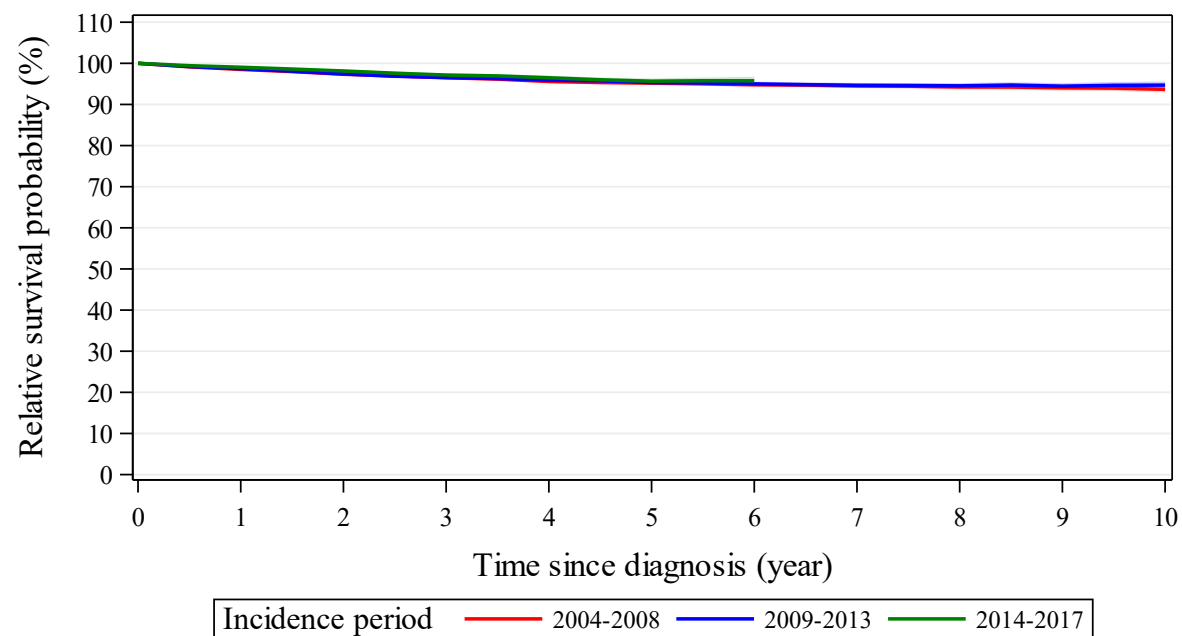
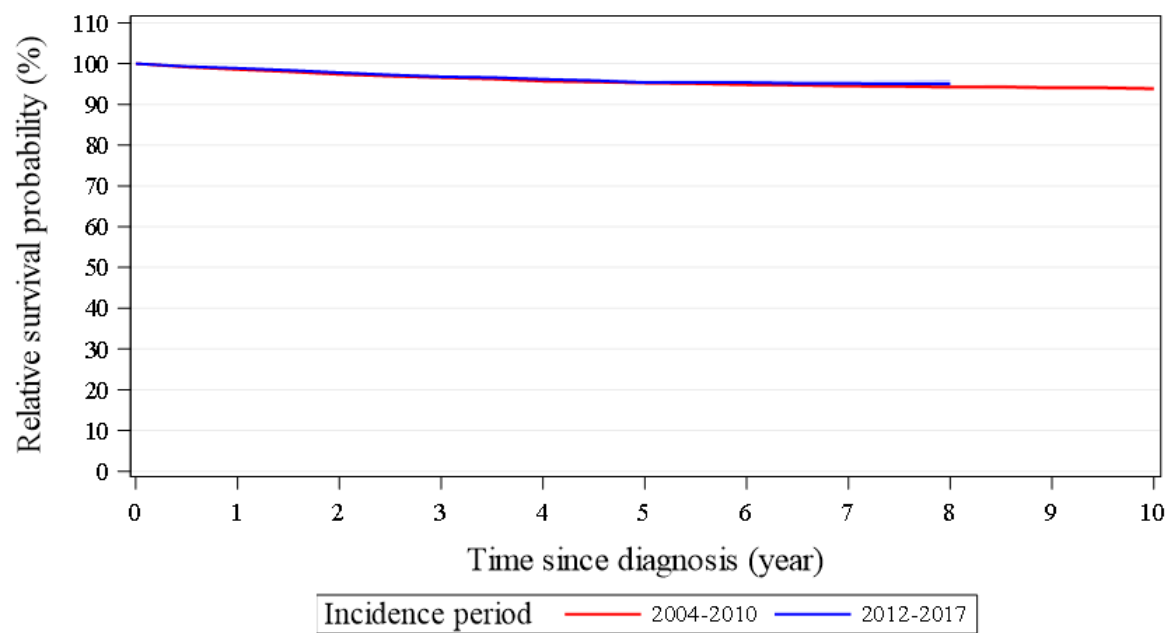




Figure 298 – Prostate cancer (2004-2017), relative survival graphs by incidence period (cut-off point: 2011)



Prostate cancer, combined stage I (2004-2017)

Figure 299 – Prostate cancer (2004-2017), combined stage I, Kaplan-Meier graphs observed survival by incidence period

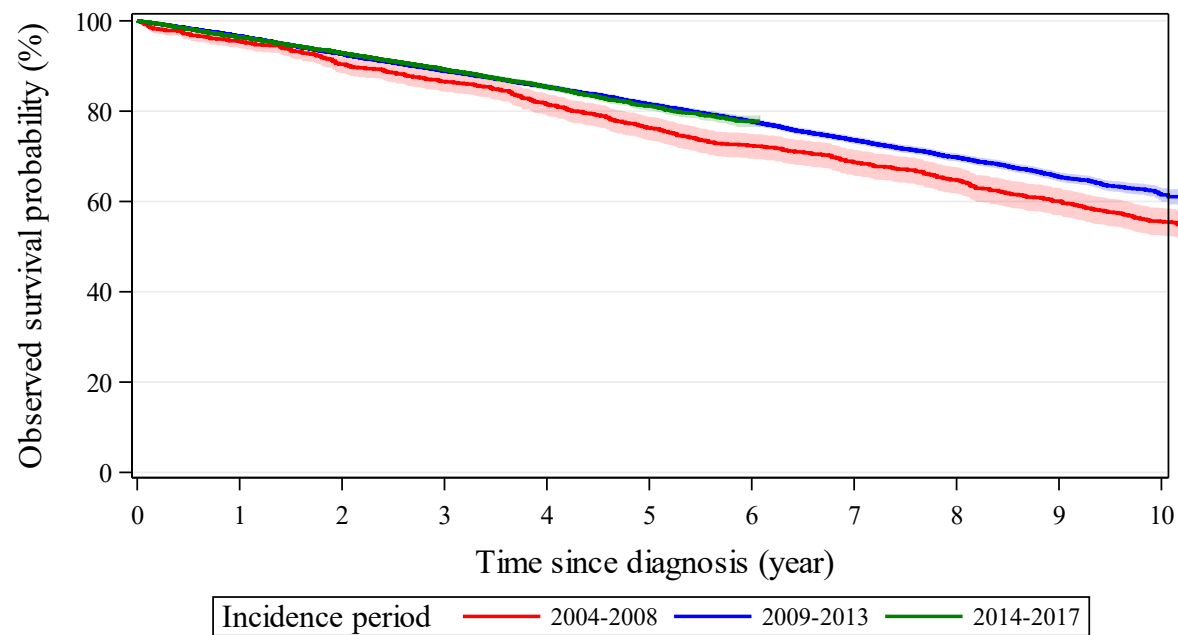




Figure 300 – Prostate cancer (2004-2017), combined stage I, Kaplan-Meier graphs observed survival by incidence period (cut-off point: 2011)

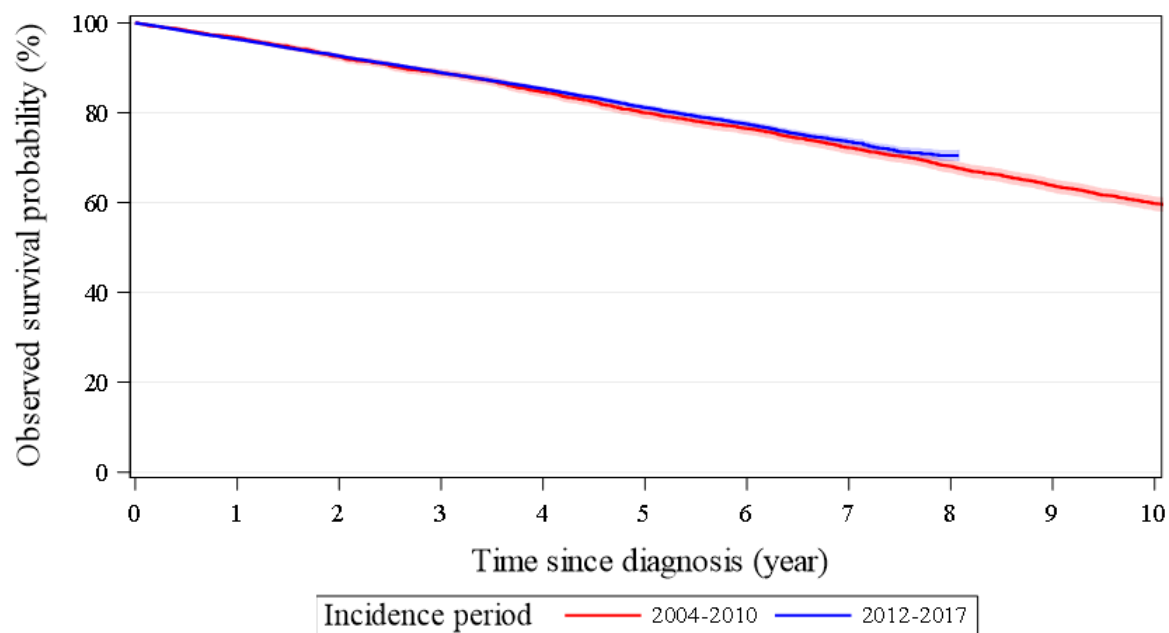


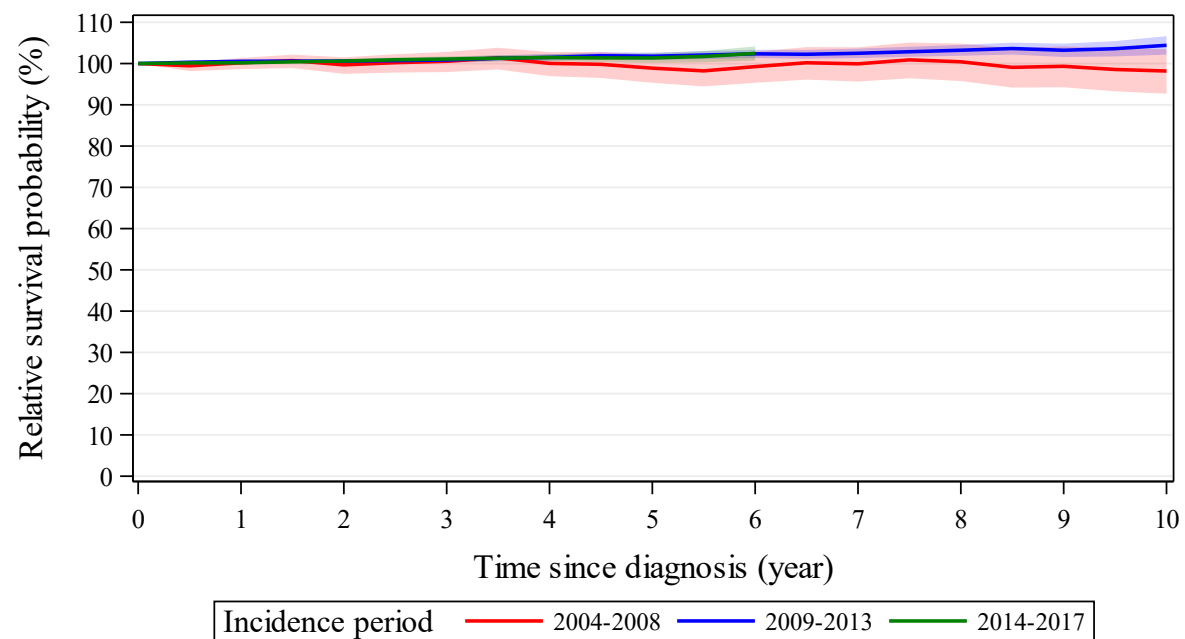
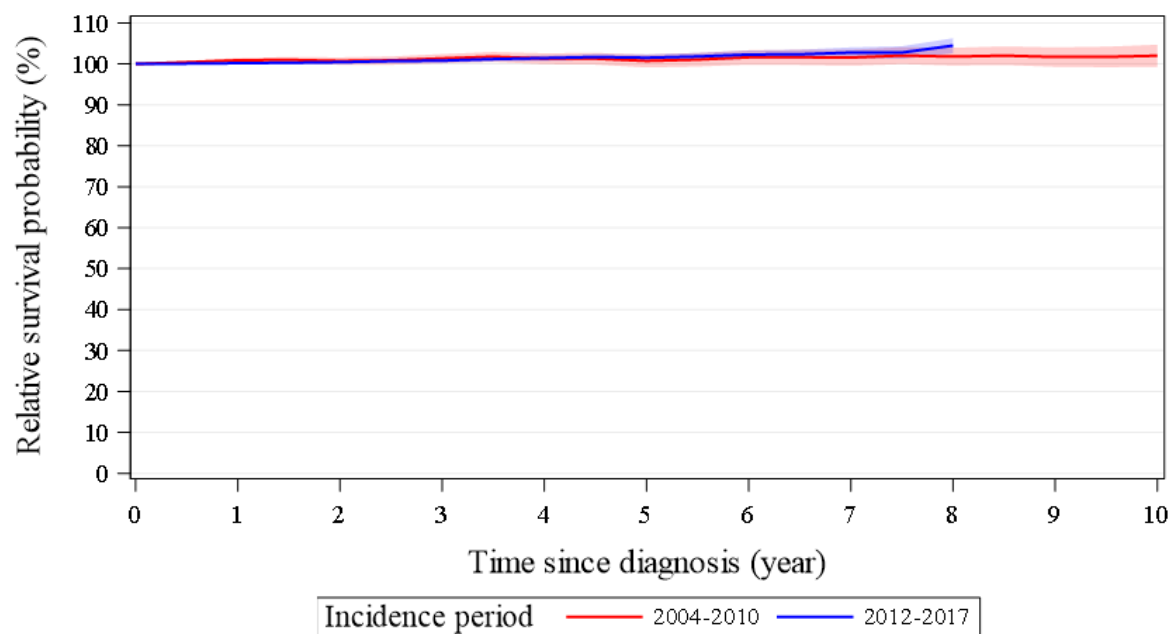
**Figure 301 – Prostate cancer (2004-2017), combined stage I, relative survival graphs by incidence period**



Figure 302 – Prostate cancer (2004-2017), combined stage I, relative survival graphs by incidence period (cut-off point: 2011)



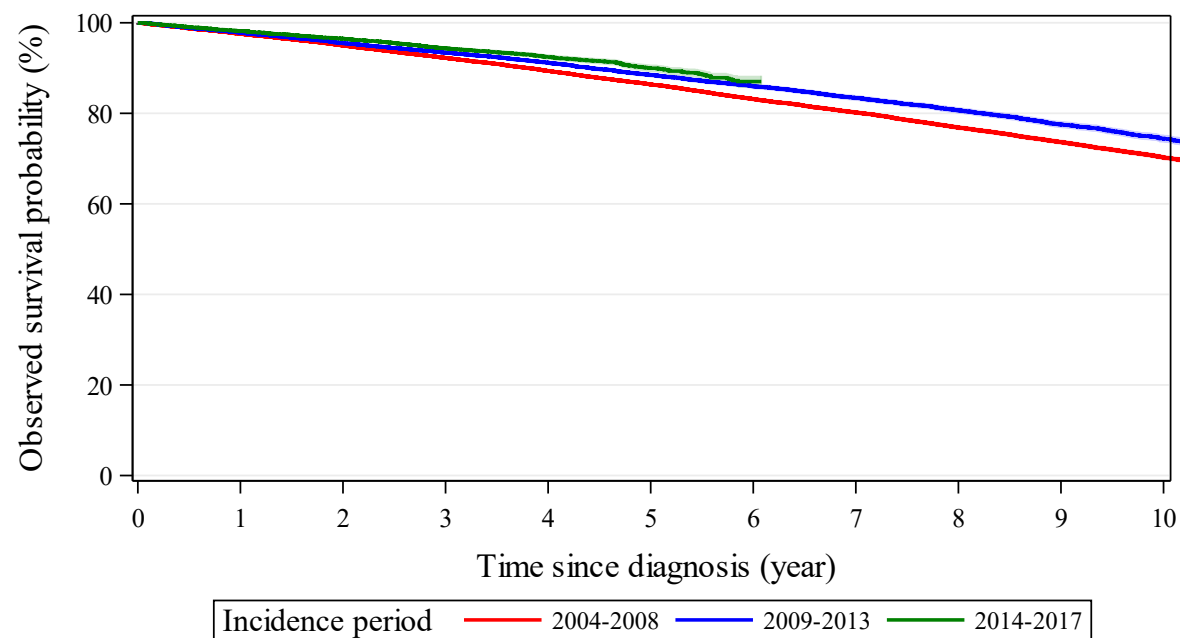
**Prostate cancer, combined stage II (2004-2017)****Figure 303 – Prostate cancer (2004-2017), combined stage II, Kaplan-Meier graphs observed survival by incidence period**



Figure 304 – Prostate cancer (2004-2017), combined stage II, Kaplan-Meier graphs observed survival by incidence period (cut-off point: 2011)

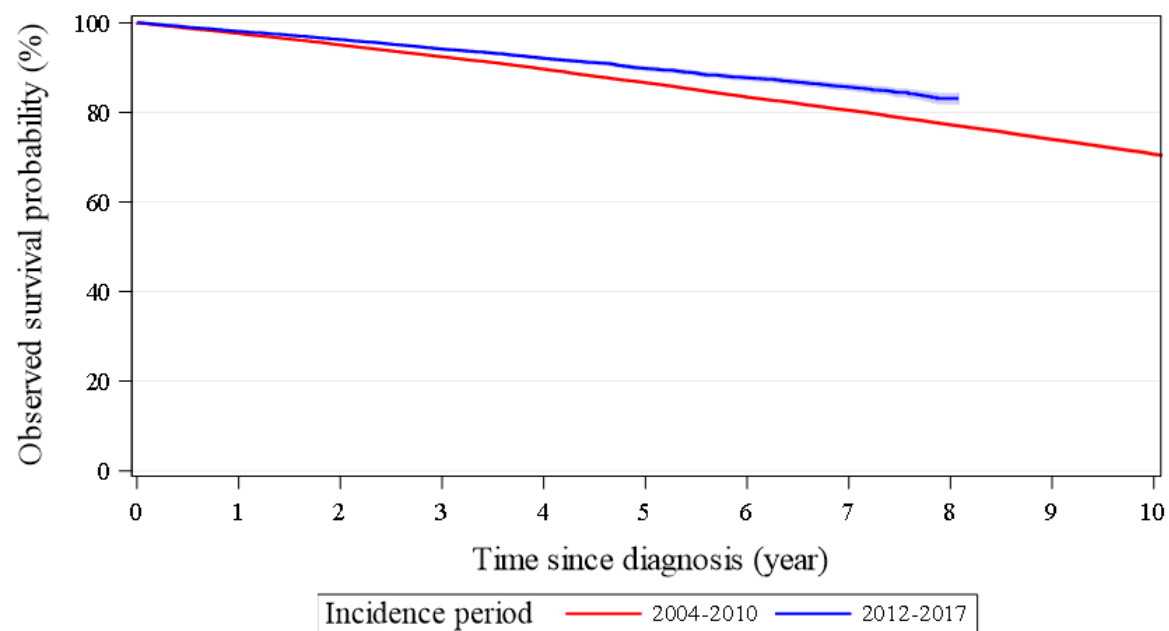




Figure 305 – Prostate cancer (2004-2017), combined stage II, relative survival graphs by incidence period

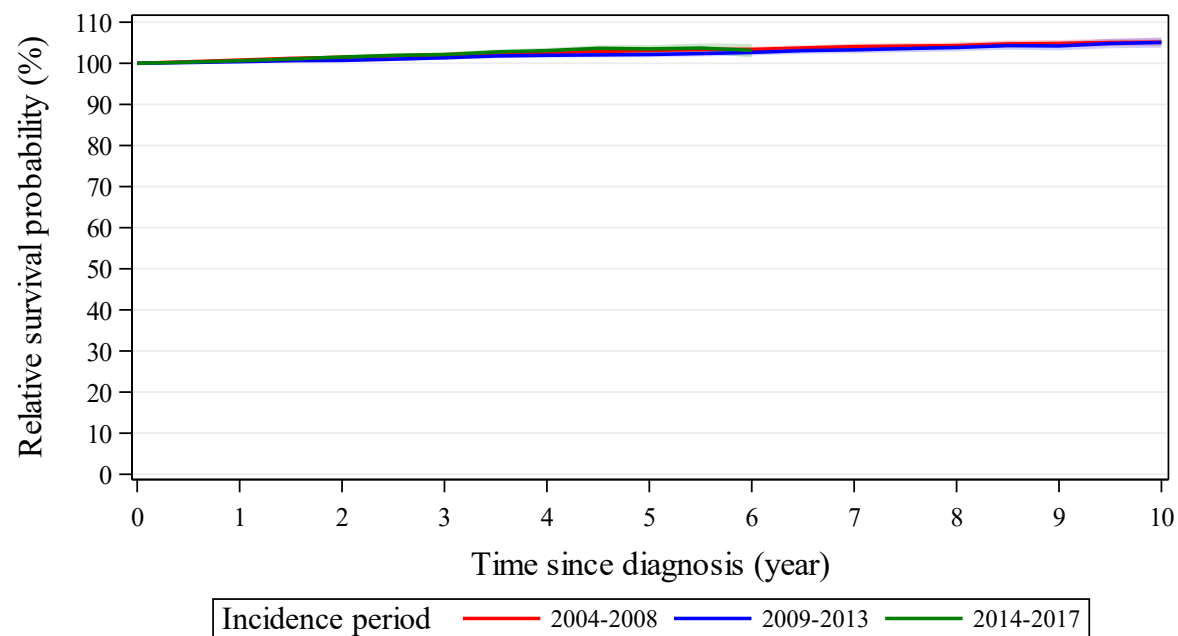
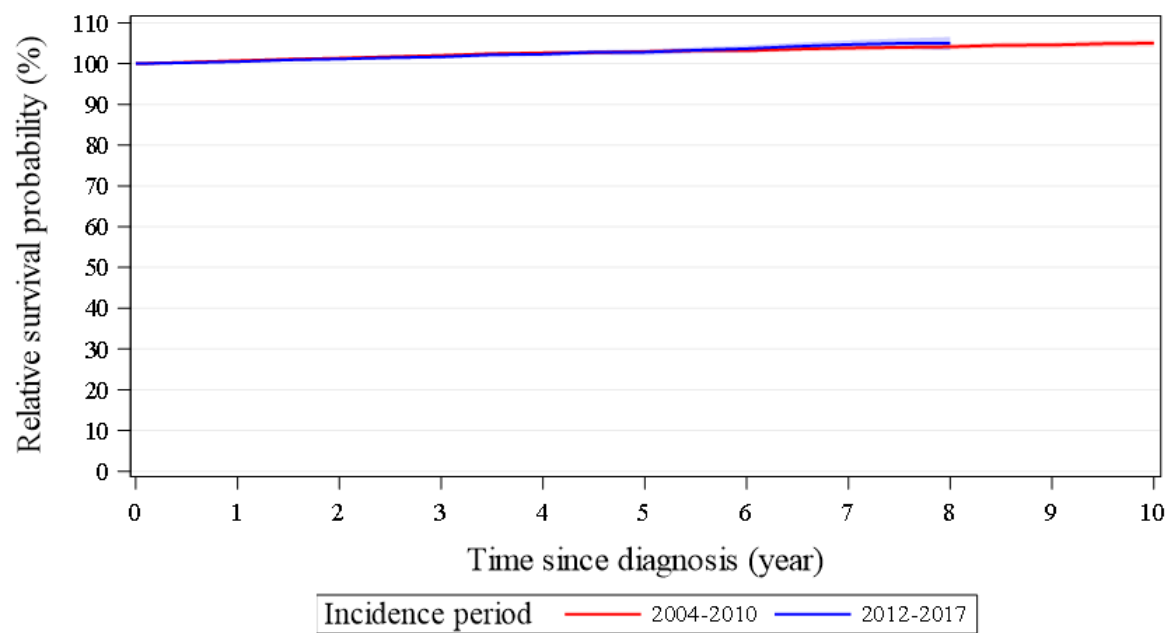




Figure 306 – Prostate cancer (2004-2017), combined stage II, relative survival graphs by incidence period (cut-off point: 2011)



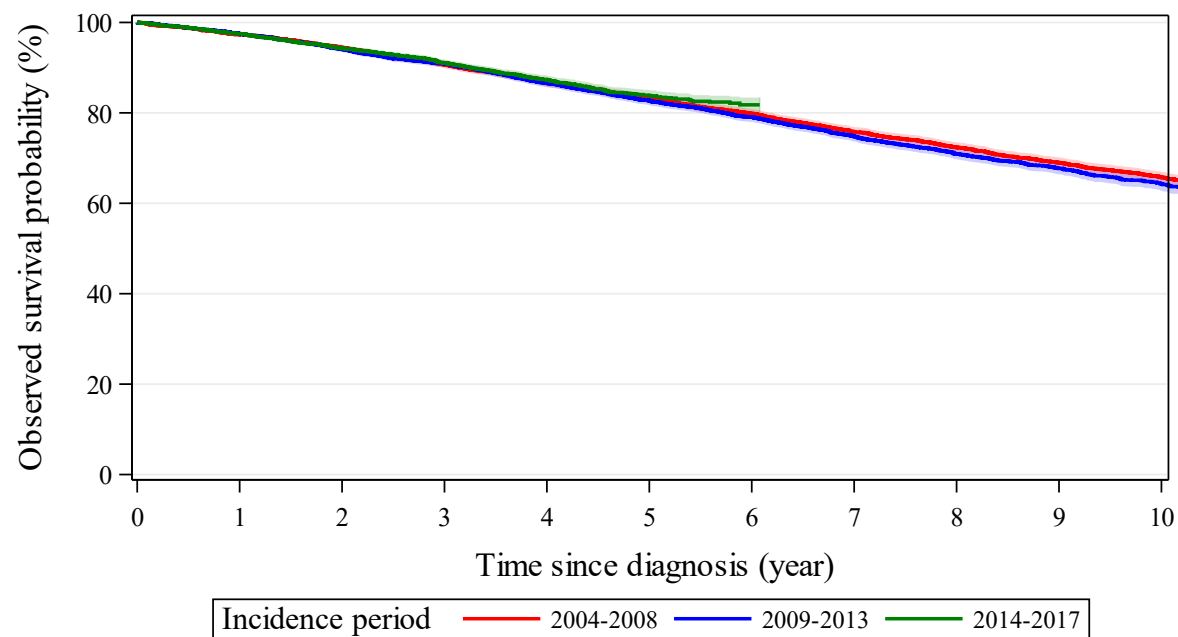
**Prostate cancer, combined stage III (2004-2017)****Figure 307 – Prostate cancer (2004-2017), combined stage III, Kaplan-Meier graphs observed survival by incidence period**



Figure 308 – Prostate cancer (2004-2017), combined stage III, Kaplan-Meier graphs observed survival by incidence period (cut-off point: 2011)

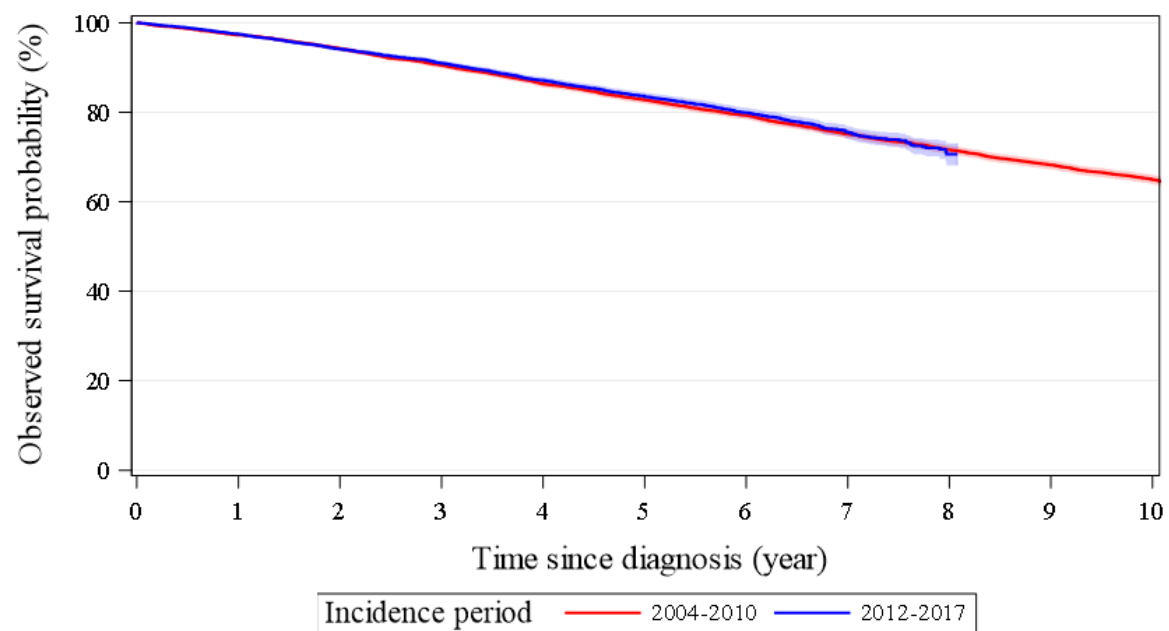




Figure 309 – Prostate cancer (2004-2017), combined stage III, relative survival graphs by incidence period

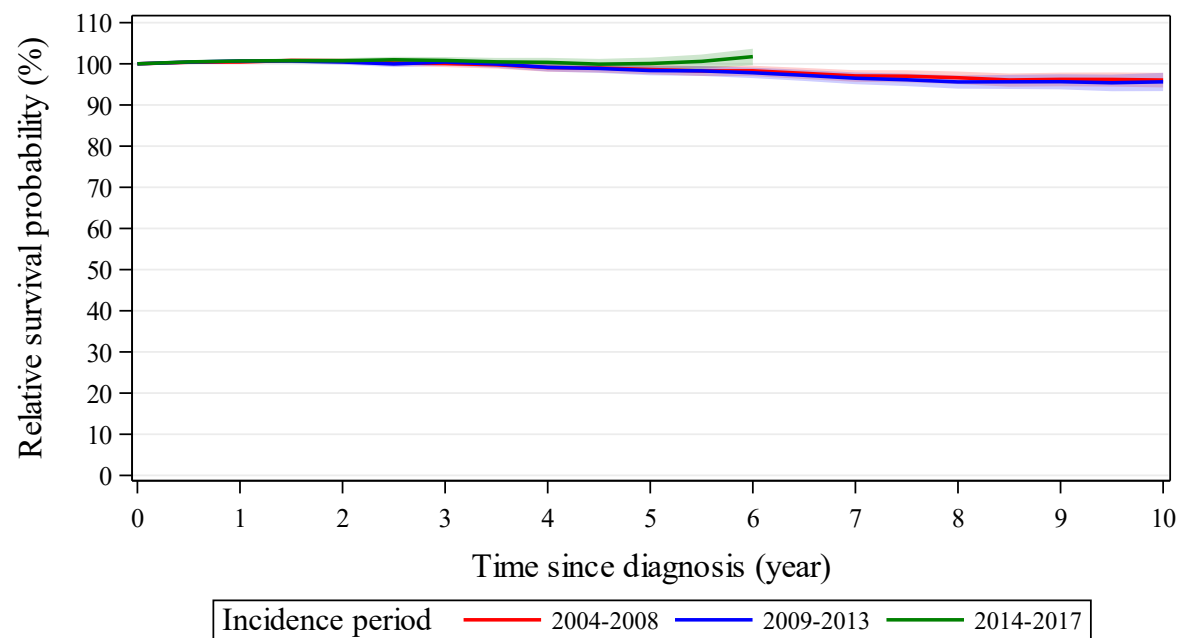
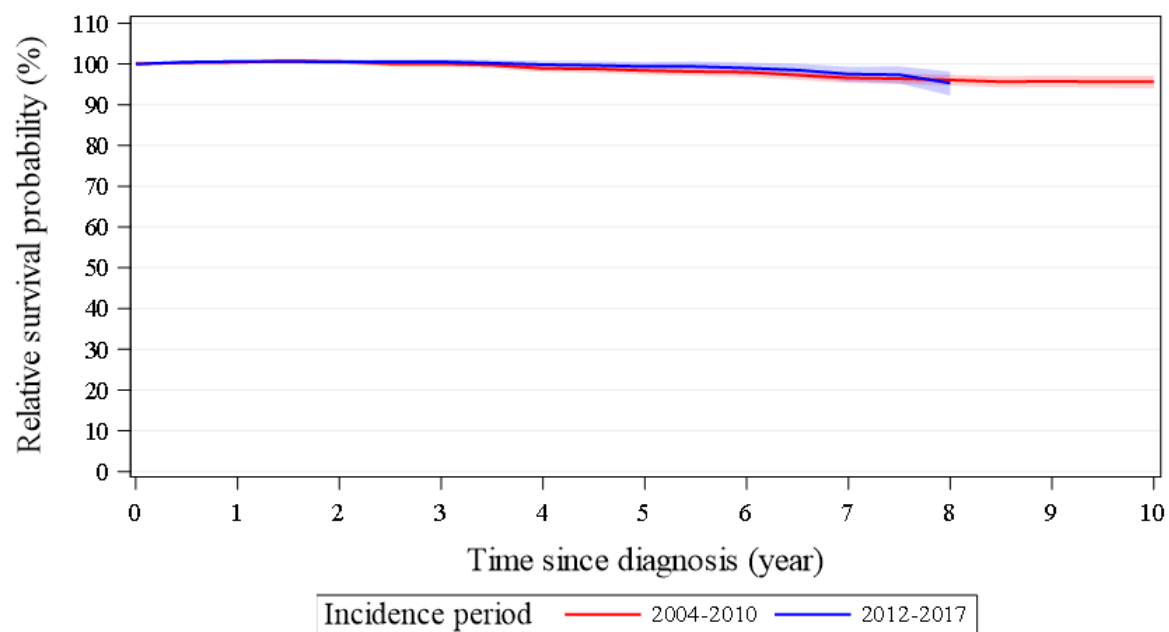




Figure 310 – Prostate cancer (2004-2017), combined stage III, relative survival graphs by incidence period (cut-off point: 2011)



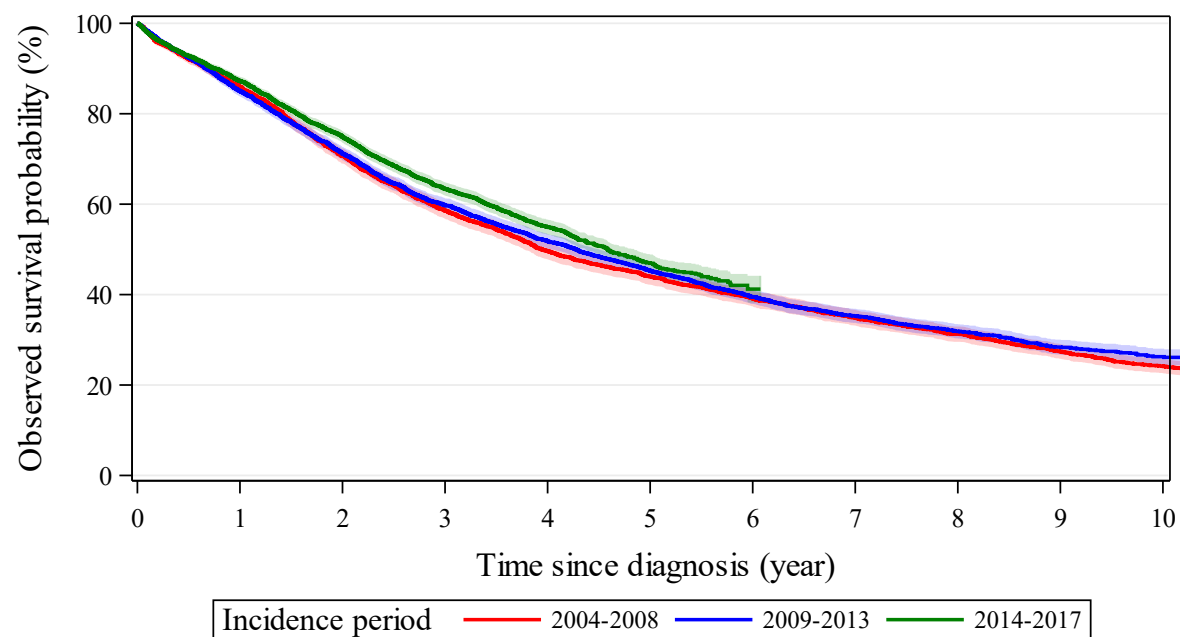
**Prostate cancer, combined stage IV (2004-2017)****Figure 311 – Prostate cancer (2004-2017), combined stage IV, Kaplan-Meier graphs observed survival by incidence period**



Figure 312 – Prostate cancer (2004-2017), combined stage IV, Kaplan-Meier graphs observed survival by incidence period (cut-off point: 2011)

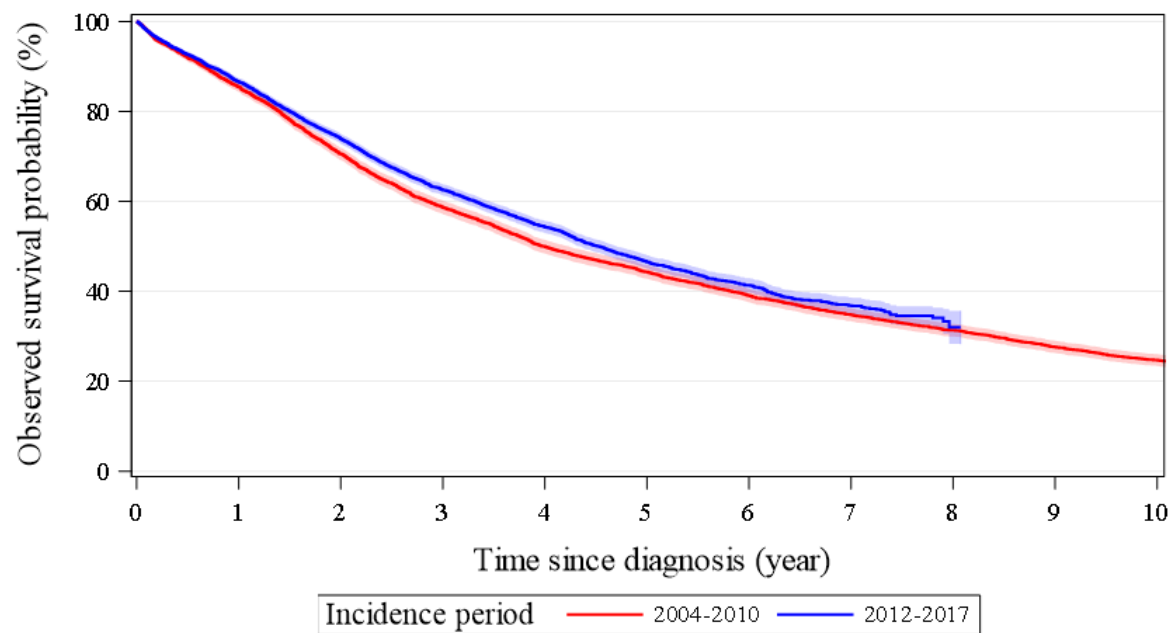




Figure 313 – Prostate cancer (2004-2017), combined stage IV, relative survival graphs by incidence period

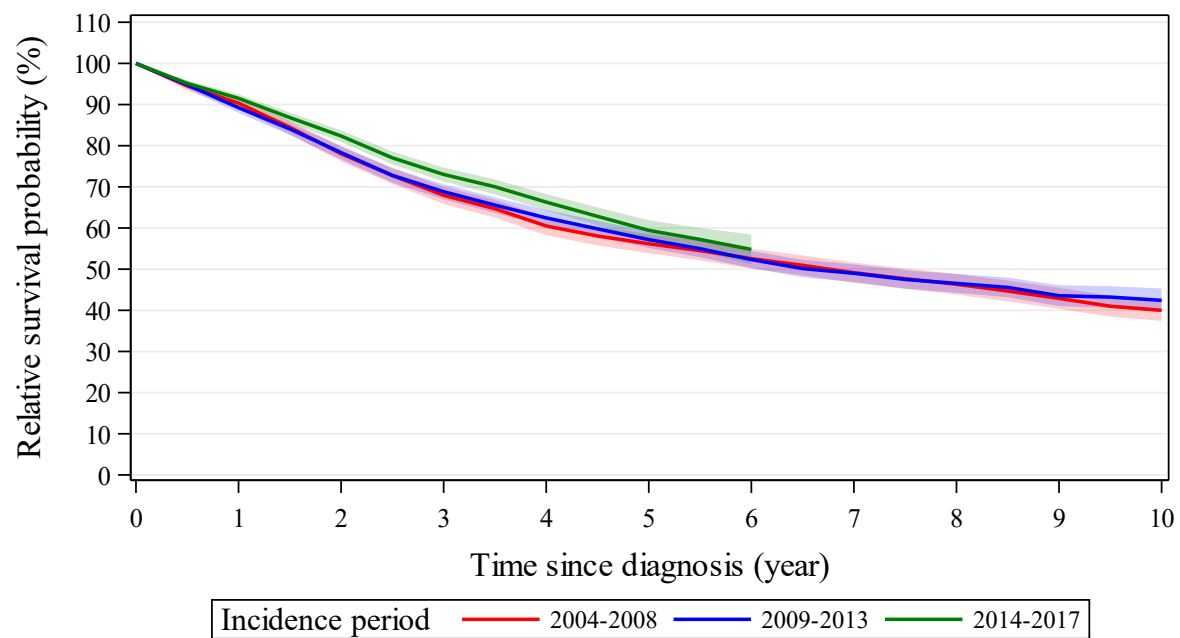
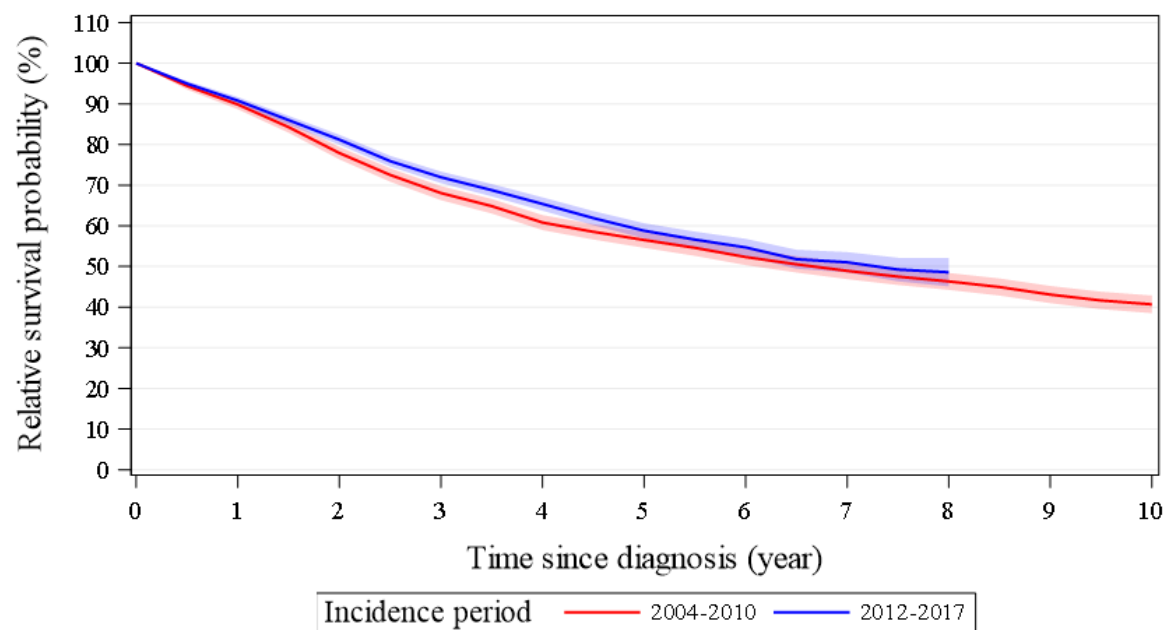




Figure 314 – Prostate cancer (2004-2017), combined stage IV, relative survival graphs by incidence period (cut-off point: 2011)

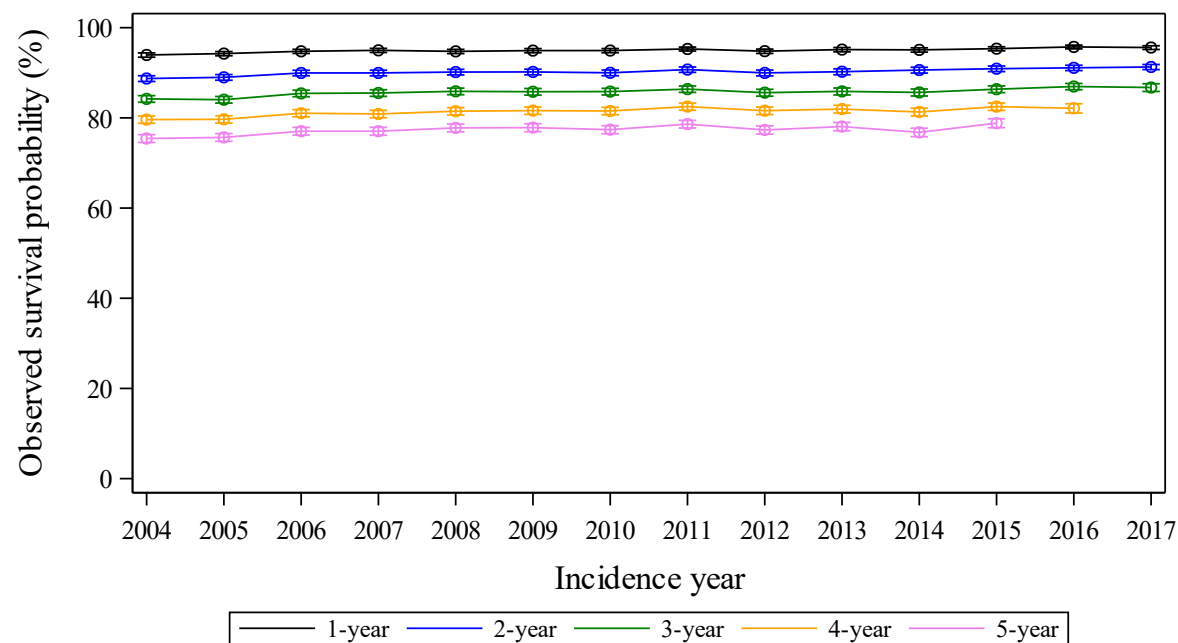




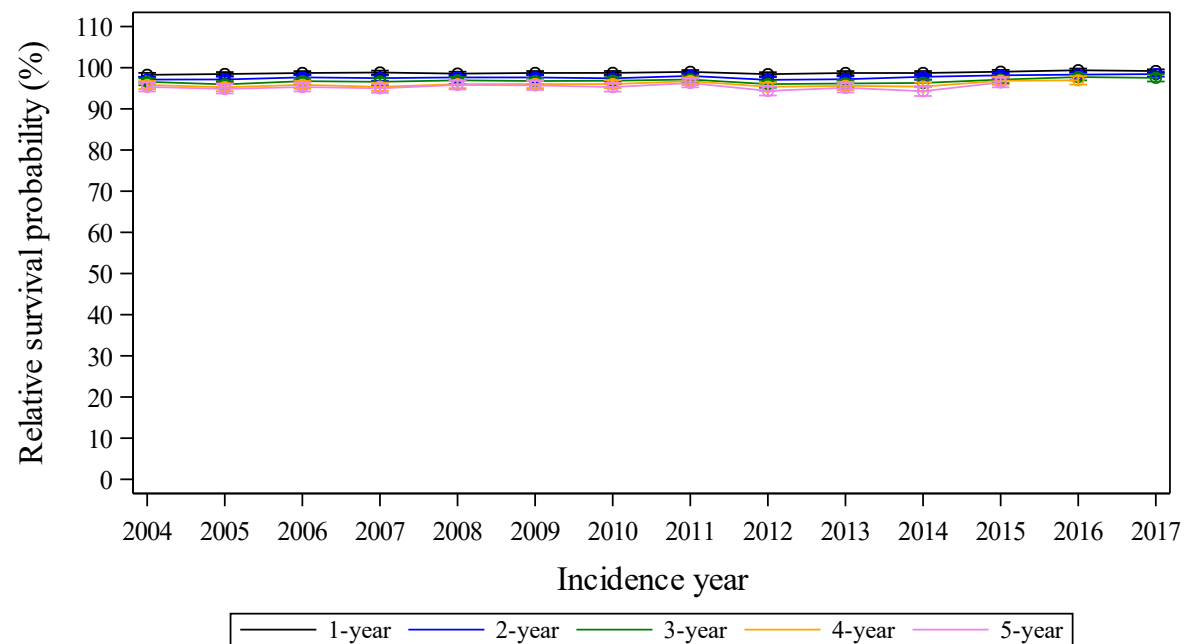
Appendix 11.1.1.3. Prostate cancer, time trend Observed and Relative Survival

Prostate cancer (2004-2017)

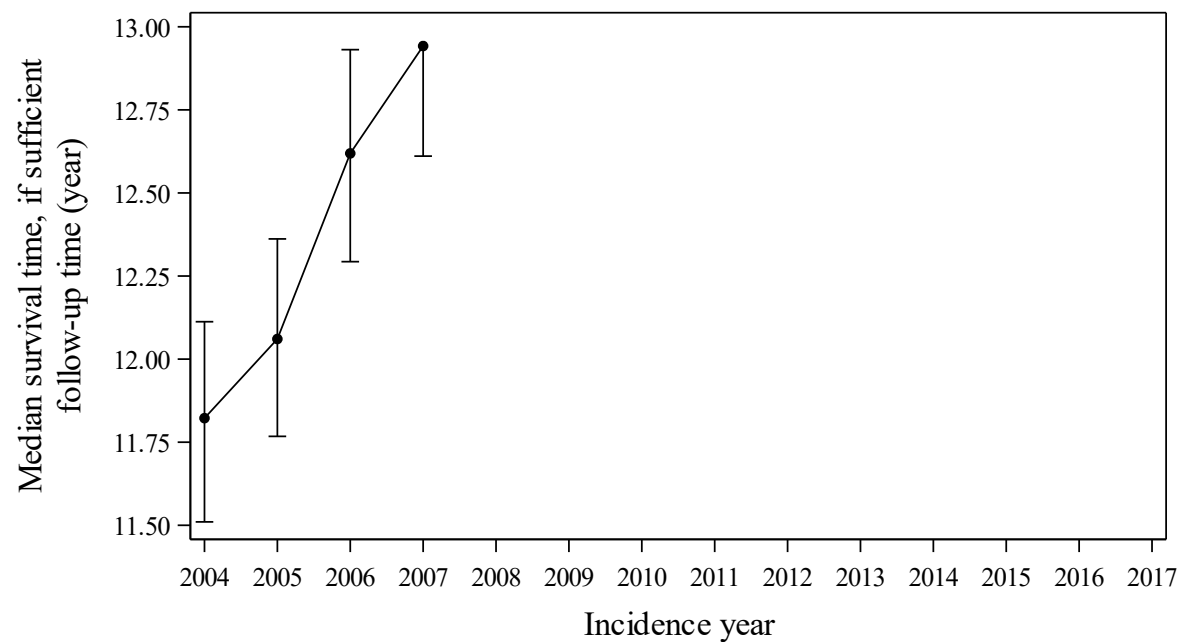
Figure 315 – Prostate cancer (2004-2017), time trend observed survival with incidence year



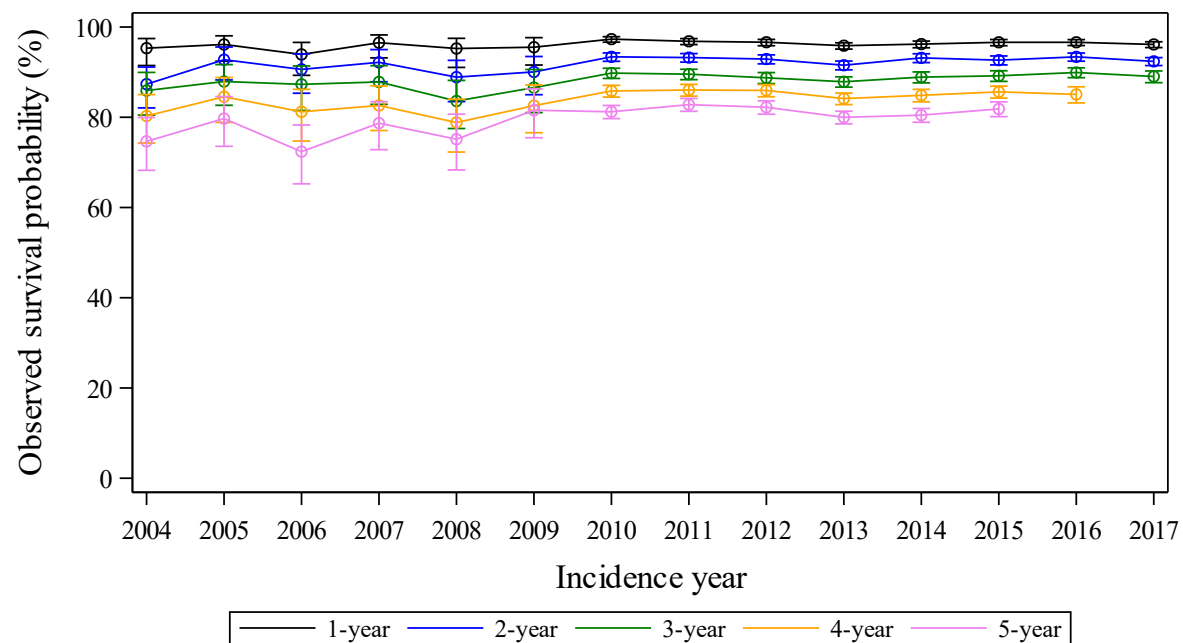
Note: the error bars represent the 95% CI.

**Figure 316 – Prostate cancer (2004-2017), time trend relative survival with incidence year**

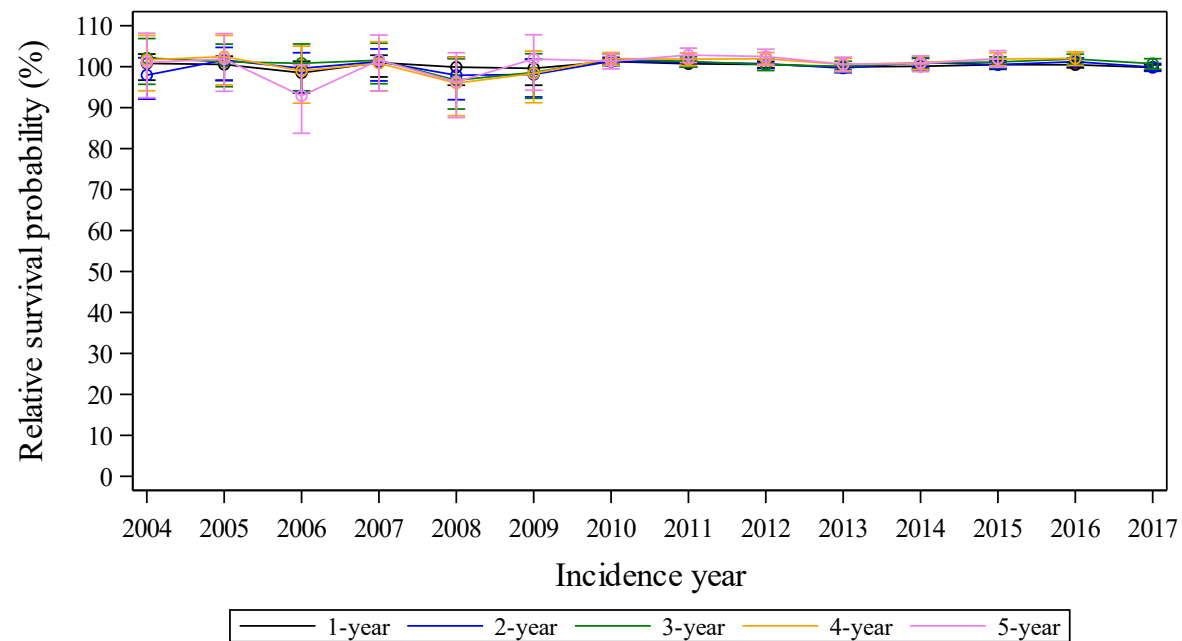
Note: the error bars represent the 95% CI.

**Figure 317 – Prostate cancer (2004-2017), Median time observed survival**

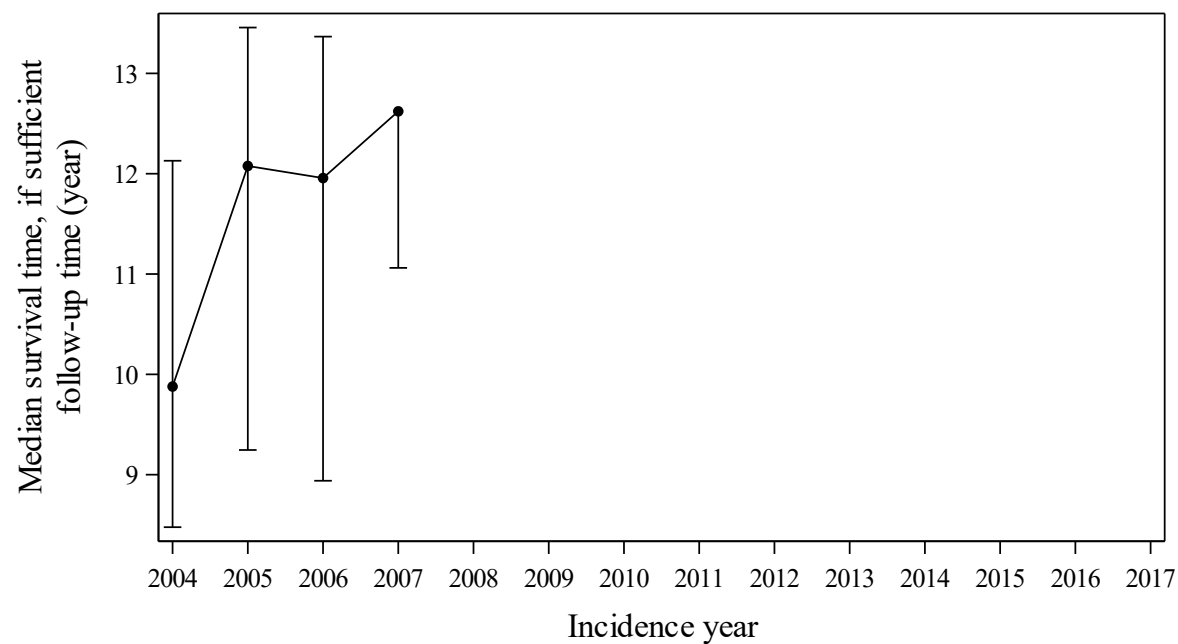
Note: the error bars represent the 95% CI. When the upper error is not plotted, the upper limit could not be determined with the follow-up available.

**Prostate cancer, combined stage I (2004-2017)****Figure 318 – Prostate cancer (2004-2017), combined stage I, time trend observed survival with incidence year**

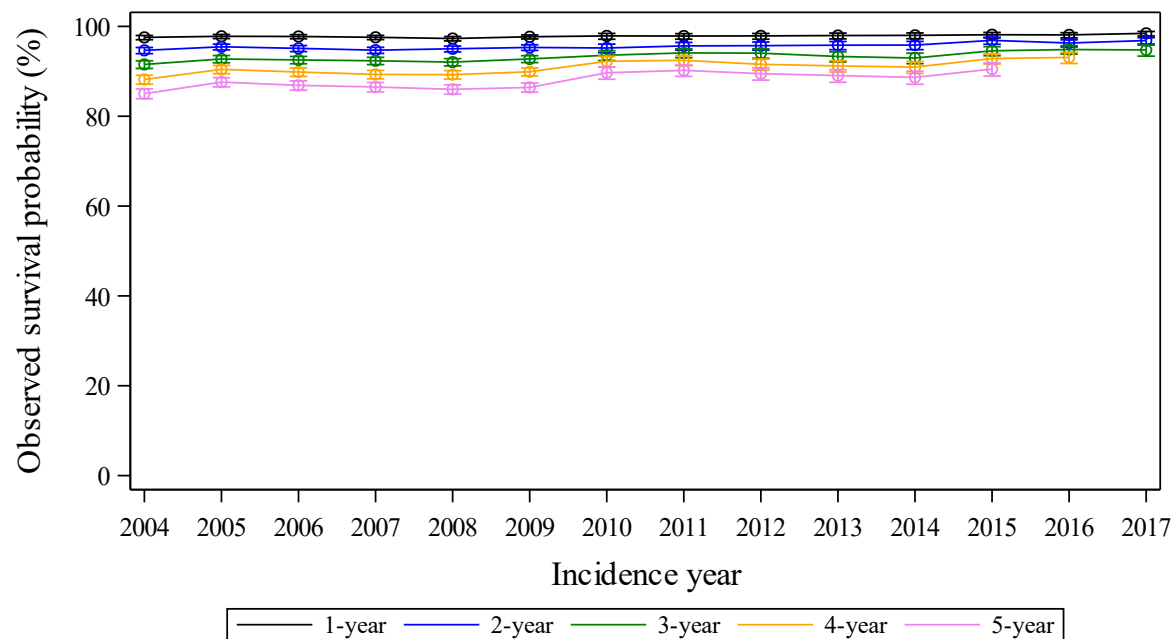
Note: the error bars represent the 95% CI.

**Figure 319 – Prostate cancer (2004-2017), combined stage I, time trend relative survival with incidence year**

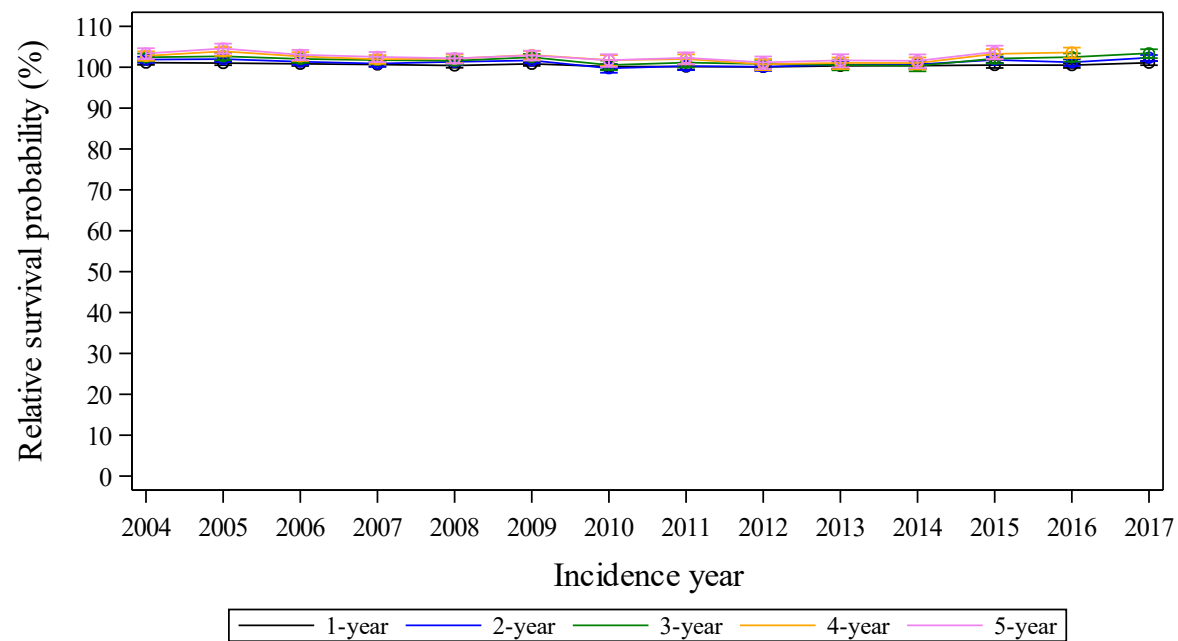
Note: the error bars represent the 95% CI.

**Figure 320 – Prostate cancer (2004-2017), combined stage I, median time observed survival**

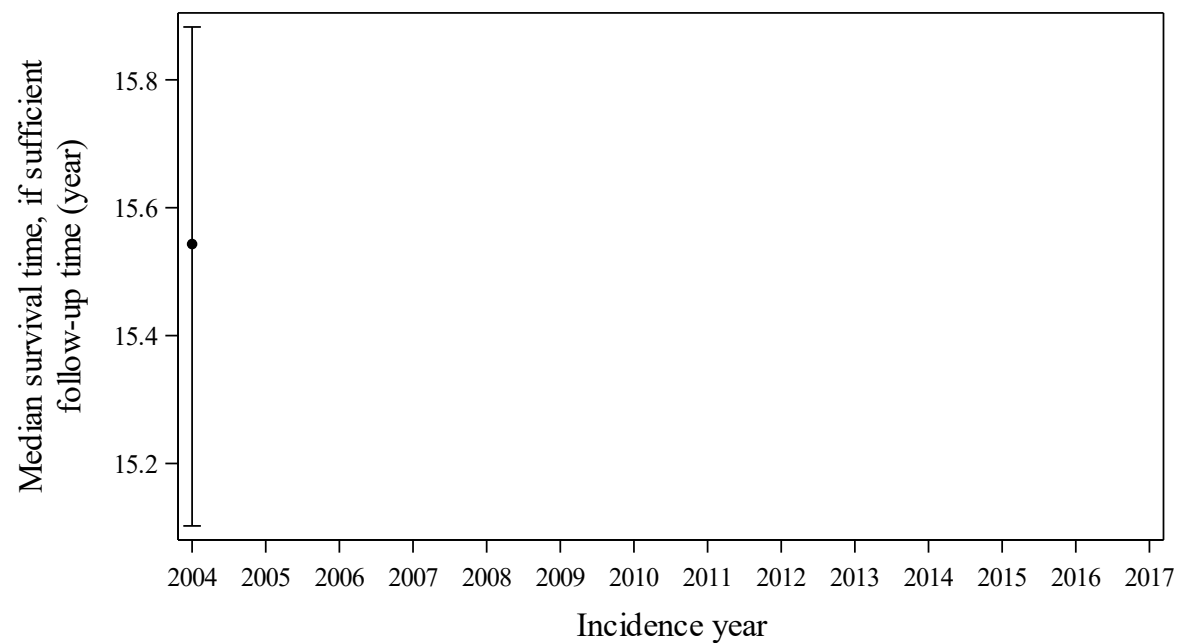
Note: the error bars represent the 95% CI. When the upper error is not plotted, the upper limit could not be determined with the follow-up available.

**Prostate cancer, combined stage II (2004-2017)****Figure 321 – Prostate cancer (2004-2017), combined stage II, time trend observed survival with incidence year**

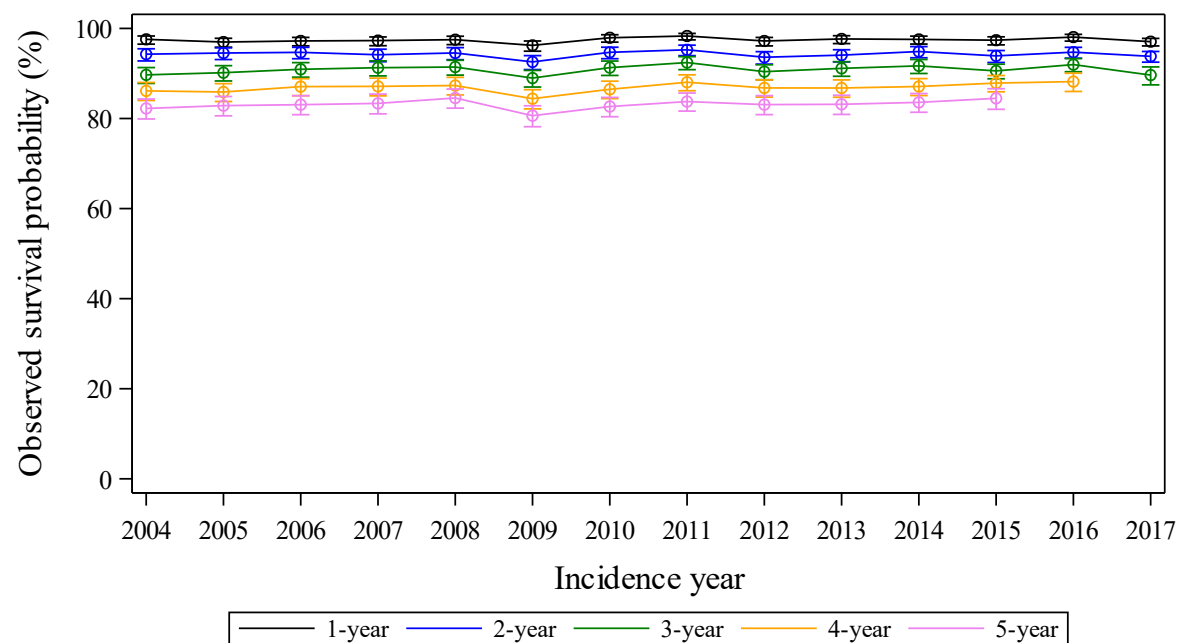
Note: the error bars represent the 95% CI.

**Figure 322 – Prostate cancer (2004-2017), combined stage II, time trend relative survival with incidence year**

Note: the error bars represent the 95% CI.

**Figure 323 – Prostate cancer (2004-2017), combined stage II, median time observed survival**

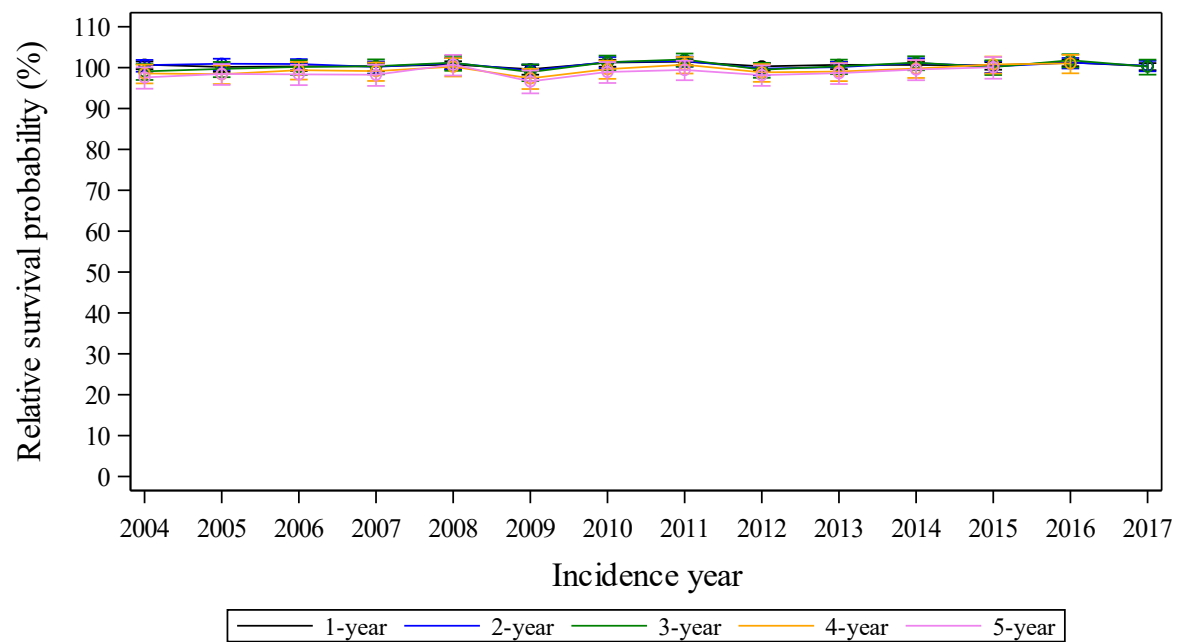
Note: the error bars represent the 95% CI. When the upper error is not plotted, the upper limit could not be determined with the follow-up available.

**Prostate cancer, combined stage III (2004-2017)****Figure 324 – Prostate cancer (2004-2017), combined stage III, time trend observed survival with incidence year**

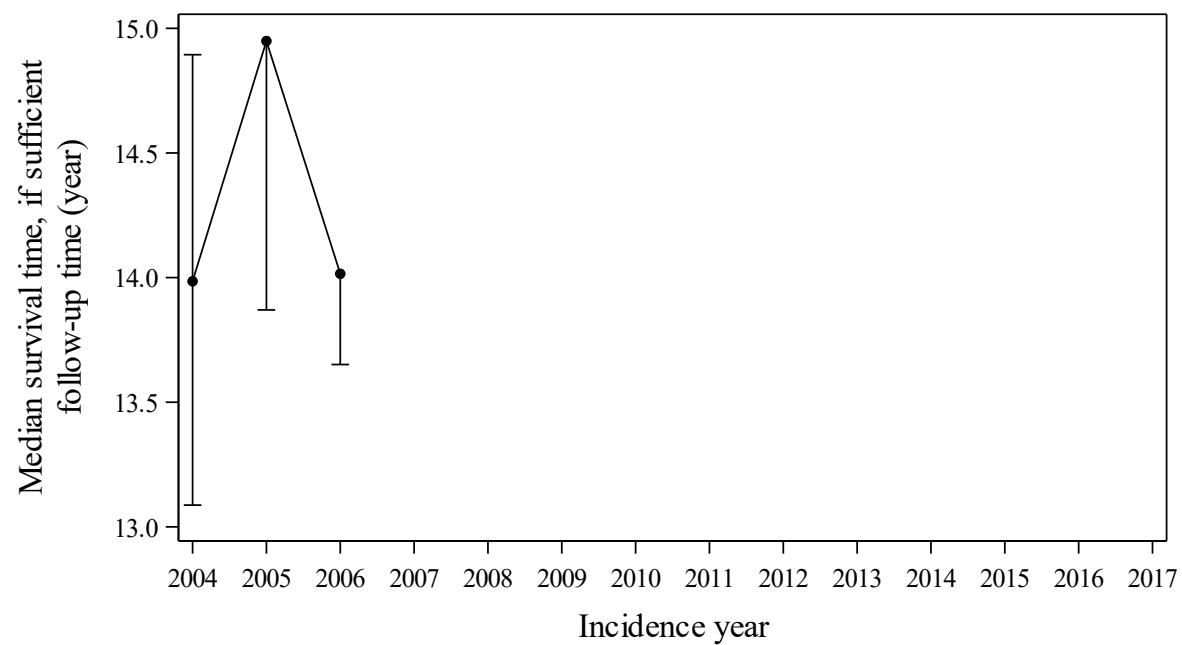
Note: the error bars represent the 95% CI.



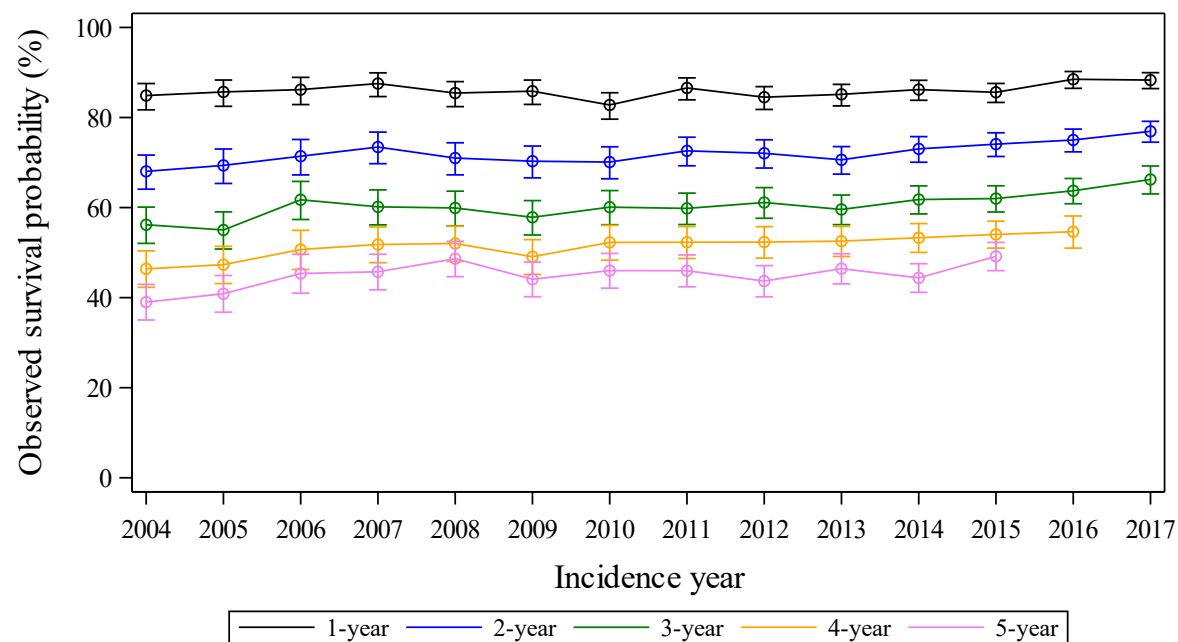
Figure 325 – Prostate cancer (2004-2017), combined stage III, time trend relative survival with incidence year



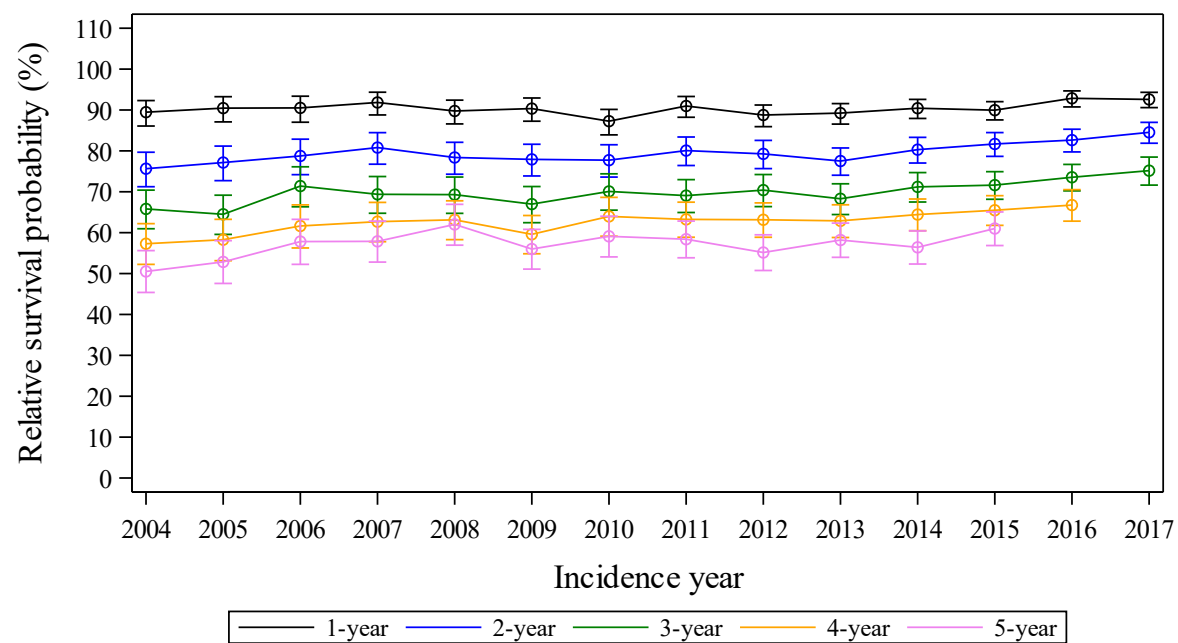
Note: the error bars represent the 95% CI.

**Figure 326 – Prostate cancer (2004-2017), combined stage III, median time observed survival**

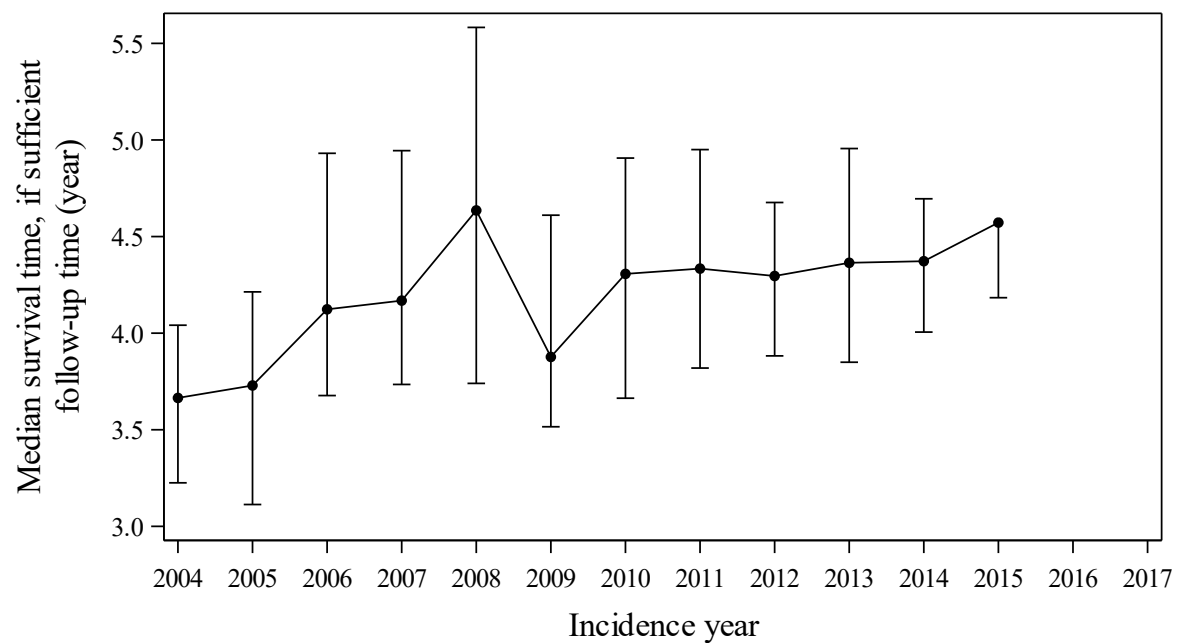
Note: the error bars represent the 95% CI. When the upper error is not plotted, the upper limit could not be determined with the follow-up available.

**Prostate cancer, combined stage IV (2004-2017)****Figure 327 – Prostate cancer (2004-2017), combined stage IV, time trend observed survival with incidence year**

Note: the error bars represent the 95% CI.

**Figure 328 – Prostate cancer (2004-2017), combined stage IV, time trend relative survival with incidence year**

Note: the error bars represent the 95% CI.

**Figure 329 – Prostate cancer (2004-2017), combined stage IV, median time observed survival**

Note: the error bars represent the 95% CI. When the upper error is not plotted, the upper limit could not be determined with the follow-up available.



Appendix 11.1.1.4. Prostate cancer, time trend tables Observed and Relative Survival

Table 170 – Prostate cancer (2004-2017), time trend observed survival with incidence year

Unadjusted observed survival, %													
		1 year		2 year		3 year		4 year		5 year		Median survival time (year)	
Characteristic	N at risk	%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI	T	95% CI
All													
2004	9,582	93.9	[93.4, 94.4]	88.7	[88.1, 89.3]	84.2	[83.5, 84.9]	79.6	[78.8, 80.4]	75.4	[74.5, 76.3]	11.8	[11.5, 12.1]
2005	9,620	94.2	[93.8, 94.7]	89.0	[88.3, 89.6]	84.0	[83.3, 84.7]	79.7	[78.9, 80.5]	75.7	[74.8, 76.5]	12.1	[11.8, 12.4]
2006	9,239	94.8	[94.3, 95.2]	90.0	[89.3, 90.6]	85.4	[84.7, 86.1]	81.0	[80.2, 81.8]	77.0	[76.2, 77.9]	12.6	[12.3, 12.9]
2007	8,895	95.0	[94.5, 95.4]	90.0	[89.3, 90.6]	85.5	[84.8, 86.2]	80.9	[80.0, 81.7]	77.0	[76.2, 77.9]	12.9	[12.6, .]
2008	8,809	94.7	[94.3, 95.2]	90.2	[89.5, 90.8]	85.9	[85.1, 86.6]	81.5	[80.6, 82.3]	77.8	[76.9, 78.6]	>12	
2009	8,675	94.9	[94.4, 95.4]	90.2	[89.5, 90.8]	85.8	[85.0, 86.5]	81.6	[80.8, 82.4]	77.8	[76.9, 78.7]	>11	
2010	8,696	94.9	[94.4, 95.4]	90.0	[89.3, 90.6]	85.8	[85.1, 86.5]	81.5	[80.7, 82.3]	77.4	[76.5, 78.3]	>10	
2011	9,044	95.3	[94.8, 95.7]	90.7	[90.1, 91.3]	86.4	[85.6, 87.1]	82.5	[81.7, 83.3]	78.6	[77.8, 79.4]	>9	
2012	8,255	94.8	[94.3, 95.2]	90.0	[89.3, 90.6]	85.6	[84.8, 86.3]	81.6	[80.7, 82.4]	77.3	[76.4, 78.2]	>8	
2013	7,869	95.1	[94.6, 95.6]	90.2	[89.6, 90.9]	85.9	[85.1, 86.6]	81.9	[81.1, 82.8]	78.1	[77.1, 79.0]	>7	
2014	7,903	95.1	[94.6, 95.5]	90.6	[89.9, 91.2]	85.6	[84.8, 86.4]	81.3	[80.4, 82.1]	76.8	[75.8, 77.7]	>6	
2015	8,353	95.3	[94.9, 95.8]	90.9	[90.3, 91.5]	86.4	[85.6, 87.1]	82.5	[81.7, 83.3]	78.8	[77.8, 79.8]	>5	
2016	9,026	95.7	[95.3, 96.1]	91.1	[90.5, 91.7]	87.0	[86.2, 87.6]	82.1	[81.1, 83.1]	no FU	—	>4	
2017	9,516	95.6	[95.2, 96.0]	91.3	[90.7, 91.8]	86.7	[85.9, 87.6]	no FU	—	no FU	—	>3	
Combined Stage I													
2004	214	95.3	[91.5, 97.5]	87.3	[82.1, 91.1]	85.9	[80.5, 89.9]	80.3	[74.3, 85.0]	74.7	[68.2, 80.0]	9.9	[8.5, 12.1]
2005	207	96.1	[92.4, 98.0]	92.8	[88.3, 95.6]	87.9	[82.7, 91.7]	84.5	[78.9, 88.8]	79.7	[73.6, 84.6]	12.1	[9.2, 13.5]
2006	181	93.9	[89.3, 96.6]	90.6	[85.3, 94.1]	87.3	[81.5, 91.4]	81.2	[74.7, 86.2]	72.4	[65.2, 78.3]	12.0	[8.9, 13.4]
2007	230	96.5	[93.2, 98.2]	92.2	[87.9, 95.0]	87.8	[82.9, 91.4]	82.6	[77.1, 86.9]	78.7	[72.8, 83.4]	12.6	[11.1, .]
2008	189	95.2	[91.0, 97.5]	88.9	[83.5, 92.6]	83.6	[77.5, 88.2]	78.8	[72.3, 84.0]	75.1	[68.3, 80.7]	>12	



Unadjusted observed survival, %													
		1 year		2 year		3 year		4 year		5 year		Median survival time (year)	
Characteristic	N at risk	%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI	T	95% CI
2009	201	95.5	[91.6, 97.6]	90.0	[85.0, 93.5]	86.6	[81.0, 90.6]	82.6	[76.6, 87.2]	81.6	[75.5, 86.3]	>11	
2010	2,759	97.3	[96.6, 97.9]	93.4	[92.4, 94.3]	89.8	[88.6, 90.9]	85.8	[84.5, 87.1]	81.2	[79.7, 82.6]	>10	
2011	2,718	96.8	[96.1, 97.4]	93.2	[92.2, 94.1]	89.5	[88.3, 90.6]	86.0	[84.7, 87.3]	82.8	[81.3, 84.2]	>9	
2012	2,579	96.6	[95.9, 97.3]	92.9	[91.8, 93.8]	88.7	[87.5, 89.9]	85.9	[84.5, 87.2]	82.2	[80.7, 83.6]	>8	
2013	3,146	95.9	[95.1, 96.5]	91.5	[90.5, 92.5]	87.9	[86.7, 89.0]	84.1	[82.8, 85.4]	80.0	[78.5, 81.3]	>7	
2014	2,590	96.2	[95.4, 96.9]	93.2	[92.1, 94.1]	88.9	[87.6, 90.0]	84.9	[83.4, 86.2]	80.5	[78.9, 81.9]	>6	
2015	2,685	96.6	[95.9, 97.2]	92.7	[91.6, 93.6]	89.2	[87.9, 90.3]	85.6	[84.3, 86.9]	81.8	[80.1, 83.4]	>5	
2016	2,954	96.6	[95.9, 97.2]	93.4	[92.4, 94.2]	89.9	[88.8, 91.0]	85.1	[83.2, 86.8]	no FU	—	>4	
2017	3,496	96.1	[95.4, 96.7]	92.4	[91.5, 93.2]	89.0	[87.7, 90.3]	no FU	—	no FU	—	>3	
Combined Stage II													
2004	4,125	97.5	[97.0, 98.0]	94.7	[93.9, 95.3]	91.5	[90.6, 92.3]	88.2	[87.2, 89.1]	85.0	[83.9, 86.1]	15.5	[15.1, 15.9]
2005	3,985	97.8	[97.3, 98.2]	95.5	[94.8, 96.1]	92.7	[91.9, 93.5]	90.4	[89.5, 91.3]	87.6	[86.5, 88.6]	>15	
2006	4,053	97.8	[97.2, 98.2]	95.1	[94.4, 95.7]	92.5	[91.7, 93.3]	89.8	[88.9, 90.7]	86.9	[85.8, 87.9]	>14	
2007	4,156	97.6	[97.1, 98.0]	94.7	[94.0, 95.3]	92.3	[91.5, 93.1]	89.3	[88.3, 90.2]	86.5	[85.4, 87.5]	>13	
2008	4,298	97.3	[96.8, 97.7]	95.0	[94.3, 95.6]	92.1	[91.2, 92.8]	89.3	[88.3, 90.1]	86.0	[84.9, 87.0]	>12	
2009	4,461	97.7	[97.2, 98.1]	95.3	[94.6, 95.9]	92.8	[92.0, 93.5]	89.9	[89.0, 90.7]	86.4	[85.4, 87.4]	>11	
2010	1,936	97.9	[97.1, 98.4]	95.2	[94.1, 96.1]	93.6	[92.4, 94.6]	92.2	[90.9, 93.3]	89.7	[88.2, 91.0]	>10	
2011	2,188	97.9	[97.1, 98.4]	95.7	[94.7, 96.4]	94.1	[93.0, 95.0]	92.4	[91.3, 93.5]	90.2	[88.9, 91.4]	>9	
2012	1,985	97.9	[97.1, 98.4]	95.7	[94.7, 96.5]	94.0	[92.9, 95.0]	91.6	[90.2, 92.7]	89.5	[88.0, 90.8]	>8	
2013	1,920	98.0	[97.2, 98.5]	95.8	[94.8, 96.6]	93.3	[92.1, 94.3]	91.2	[89.8, 92.4]	89.0	[87.6, 90.4]	>7	
2014	1,850	98.0	[97.2, 98.5]	95.8	[94.8, 96.7]	93.0	[91.7, 94.0]	90.9	[89.5, 92.2]	88.6	[87.1, 90.0]	>6	
2015	1,997	98.1	[97.4, 98.7]	96.9	[96.0, 97.6]	94.6	[93.5, 95.5]	92.8	[91.6, 93.9]	90.5	[88.9, 91.8]	>5	
2016	2,217	98.1	[97.4, 98.6]	96.3	[95.4, 97.0]	94.8	[93.8, 95.7]	93.1	[91.7, 94.2]	no FU	—	>4	



Unadjusted observed survival, %													
		1 year		2 year		3 year		4 year		5 year		Median survival time (year)	
Characteristic	N at risk	%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI	T	95% CI
2017	2,381	98.4	[97.9, 98.9]	96.8	[96.1, 97.5]	94.7	[93.4, 95.8]	no FU	—	no FU	—	>3	
Combined Stage III													
2004	1,155	97.6	[96.5, 98.3]	94.3	[92.8, 95.5]	89.7	[87.8, 91.3]	86.1	[84.0, 88.0]	82.2	[79.9, 84.3]	14.0	[13.1, 14.9]
2005	1,191	97.0	[95.8, 97.8]	94.5	[93.1, 95.7]	90.2	[88.3, 91.7]	85.9	[83.8, 87.7]	82.9	[80.6, 84.9]	14.9	[13.9, .]
2006	1,225	97.2	[96.1, 98.0]	94.7	[93.3, 95.8]	90.9	[89.2, 92.4]	87.1	[85.1, 88.8]	83.1	[80.8, 85.1]	14.0	[13.7, .]
2007	1,114	97.3	[96.2, 98.1]	94.2	[92.6, 95.4]	91.3	[89.5, 92.8]	87.1	[85.0, 89.0]	83.4	[81.0, 85.4]	>13	
2008	1,122	97.5	[96.4, 98.3]	94.6	[93.1, 95.7]	91.4	[89.6, 92.9]	87.3	[85.2, 89.1]	84.6	[82.3, 86.5]	>12	
2009	1,117	96.2	[94.9, 97.2]	92.6	[90.9, 94.0]	89.0	[87.0, 90.7]	84.4	[82.1, 86.4]	80.6	[78.2, 82.8]	>11	
2010	1,208	97.9	[97.0, 98.6]	94.7	[93.3, 95.8]	91.3	[89.6, 92.8]	86.5	[84.4, 88.3]	82.7	[80.4, 84.7]	>10	
2011	1,310	98.3	[97.5, 98.9]	95.3	[94.0, 96.3]	92.4	[90.8, 93.7]	88.1	[86.2, 89.7]	83.8	[81.6, 85.7]	>9	
2012	1,219	97.2	[96.1, 98.0]	93.6	[92.1, 94.8]	90.4	[88.6, 91.9]	86.8	[84.8, 88.6]	83.1	[80.9, 85.1]	>8	
2013	1,198	97.7	[96.6, 98.4]	94.1	[92.6, 95.3]	91.1	[89.4, 92.6]	86.8	[84.7, 88.6]	83.2	[80.9, 85.2]	>7	
2014	1,231	97.6	[96.5, 98.3]	94.9	[93.5, 96.0]	91.7	[90.0, 93.1]	87.1	[85.1, 88.9]	83.6	[81.4, 85.5]	>6	
2015	1,265	97.4	[96.3, 98.1]	93.9	[92.4, 95.1]	90.6	[88.8, 92.1]	87.9	[85.9, 89.5]	84.5	[82.0, 86.6]	>5	
2016	1,353	98.1	[97.2, 98.7]	94.7	[93.4, 95.8]	92.0	[90.4, 93.3]	88.2	[86.0, 90.1]	no FU	—	>4	
2017	1,604	97.1	[96.1, 97.8]	93.8	[92.5, 94.9]	89.6	[87.5, 91.5]	no FU	—	no FU	—	>3	
Combined Stage IV													
2004	582	84.9	[81.7, 87.5]	68.0	[64.1, 71.7]	56.2	[52.1, 60.1]	46.4	[42.3, 50.4]	39.0	[35.0, 42.9]	3.7	[3.2, 4.0]
2005	559	85.7	[82.5, 88.3]	69.4	[65.4, 73.0]	55.0	[50.8, 59.0]	47.3	[43.1, 51.4]	40.9	[36.8, 44.9]	3.7	[3.1, 4.2]
2006	507	86.2	[82.9, 88.9]	71.4	[67.3, 75.1]	61.7	[57.4, 65.8]	50.7	[46.3, 54.9]	45.4	[41.0, 49.6]	4.1	[3.7, 4.9]
2007	610	87.5	[84.7, 89.9]	73.4	[69.7, 76.8]	60.2	[56.2, 63.9]	51.8	[47.8, 55.7]	45.7	[41.7, 49.6]	4.2	[3.7, 4.9]
2008	625	85.4	[82.4, 88.0]	71.0	[67.3, 74.4]	59.9	[56.0, 63.6]	52.0	[48.0, 55.9]	48.6	[44.7, 52.5]	4.6	[3.7, 5.6]
2009	643	85.8	[82.9, 88.3]	70.3	[66.6, 73.7]	57.8	[53.9, 61.5]	49.1	[45.2, 52.9]	44.1	[40.2, 47.9]	3.9	[3.5, 4.6]
2010	639	82.8	[79.6, 85.5]	70.1	[66.4, 73.5]	60.1	[56.2, 63.8]	52.3	[48.3, 56.1]	46.0	[42.1, 49.8]	4.3	[3.7, 4.9]



Characteristic	N at risk	Unadjusted observed survival, %										Median survival time (year)	
		1 year		2 year		3 year		4 year		5 year			
		%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI	T	95% CI
2011	760	86.6	[83.9, 88.8]	72.6	[69.3, 75.6]	59.8	[56.2, 63.2]	52.3	[48.7, 55.8]	46.0	[42.4, 49.5]	4.3	[3.8, 5.0]
2012	789	84.5	[81.8, 86.9]	72.1	[68.8, 75.1]	61.1	[57.6, 64.4]	52.3	[48.8, 55.8]	43.7	[40.2, 47.1]	4.3	[3.9, 4.7]
2013	856	85.1	[82.6, 87.4]	70.6	[67.4, 73.5]	59.6	[56.2, 62.8]	52.5	[49.1, 55.8]	46.4	[43.1, 49.7]	4.4	[3.8, 5.0]
2014	936	86.2	[83.8, 88.3]	73.0	[70.1, 75.8]	61.8	[58.6, 64.8]	53.3	[50.0, 56.4]	44.4	[41.2, 47.5]	4.4	[4.0, 4.7]
2015	1,070	85.6	[83.3, 87.6]	74.1	[71.3, 76.6]	62.0	[59.0, 64.8]	54.0	[51.0, 57.0]	49.2	[46.0, 52.3]	4.6	[4.2, .]
2016	1,130	88.5	[86.5, 90.2]	75.0	[72.4, 77.4]	63.7	[60.9, 66.5]	54.6	[51.0, 58.1]	no FU	—	>4	
2017	1,276	88.3	[86.4, 90.0]	76.9	[74.5, 79.1]	66.2	[63.0, 69.2]	no FU	—	no FU	—	>3	



Table 171 – Prostate cancer (2004-2017), time trend relative survival with incidence year

Characteristic	1 year			2 year			3 year			4 year			5 year		
	N at risk	%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI		
All															
2004	9,582	98.2	[97.7, 98.7]	97.1	[96.4, 97.8]	96.6	[95.7, 97.4]	95.8	[94.8, 96.8]	95.3	[94.2, 96.4]				
2005	9,620	98.4	[97.9, 98.9]	97.1	[96.4, 97.8]	95.9	[95.1, 96.8]	95.2	[94.3, 96.2]	94.8	[93.7, 95.9]				
2006	9,239	98.7	[98.2, 99.1]	97.6	[96.9, 98.3]	96.7	[95.9, 97.5]	95.8	[94.9, 96.8]	95.3	[94.2, 96.4]				
2007	8,895	98.8	[98.3, 99.3]	97.4	[96.8, 98.1]	96.6	[95.7, 97.4]	95.4	[94.4, 96.3]	95.0	[93.9, 96.0]				
2008	8,809	98.5	[98.0, 99.0]	97.6	[96.9, 98.3]	96.9	[96.1, 97.7]	96.0	[95.0, 96.9]	95.8	[94.7, 96.9]				
2009	8,675	98.7	[98.2, 99.2]	97.6	[96.9, 98.3]	96.8	[95.9, 97.6]	96.0	[95.0, 97.0]	95.7	[94.6, 96.7]				
2010	8,696	98.7	[98.2, 99.2]	97.4	[96.7, 98.1]	96.8	[96.0, 97.6]	96.0	[95.0, 97.0]	95.3	[94.2, 96.4]				
2011	9,044	99.0	[98.5, 99.4]	98.0	[97.3, 98.6]	97.1	[96.3, 97.9]	96.7	[95.8, 97.6]	96.3	[95.2, 97.3]				
2012	8,255	98.4	[97.9, 98.9]	97.0	[96.3, 97.7]	96.0	[95.1, 96.8]	95.3	[94.3, 96.3]	94.4	[93.2, 95.4]				
2013	7,869	98.7	[98.2, 99.2]	97.2	[96.5, 97.9]	96.1	[95.3, 97.0]	95.6	[94.6, 96.6]	95.1	[94.0, 96.2]				
2014	7,903	98.7	[98.2, 99.2]	97.8	[97.0, 98.4]	96.3	[95.4, 97.1]	95.4	[94.4, 96.4]	94.3	[93.1, 95.4]				
2015	8,353	99.0	[98.5, 99.4]	98.1	[97.4, 98.8]	97.1	[96.2, 97.9]	96.8	[95.8, 97.8]	96.4	[95.2, 97.6]				
2016	9,026	99.4	[98.9, 99.8]	98.3	[97.6, 98.9]	97.7	[96.9, 98.5]	96.9	[95.9, 97.9]	no FU	—				
2017	9,516	99.2	[98.7, 99.6]	98.4	[97.8, 99.0]	97.5	[96.6, 98.4]	no FU	—	no FU	—				
Combined Stage I															
2004	214	100.8	[96.7, 103.1]	97.9	[92.1, 102.2]	102.1	[95.7, 106.9]	101.7	[94.1, 107.6]	101.0	[92.4, 108.2]				
2005	207	100.5	[96.6, 102.5]	101.6	[96.7, 104.7]	101.2	[95.1, 105.5]	102.4	[95.5, 107.6]	101.8	[94.0, 108.1]				
2006	181	98.5	[93.6, 101.3]	99.6	[93.7, 103.4]	100.8	[94.1, 105.5]	99.0	[91.1, 105.0]	92.9	[83.7, 100.5]				
2007	230	101.0	[97.5, 102.8]	101.2	[96.5, 104.3]	101.6	[95.8, 105.7]	100.8	[94.1, 106.1]	101.6	[94.0, 107.7]				
2008	189	99.9	[95.4, 102.2]	97.9	[91.9, 102.0]	96.7	[89.6, 102.0]	96.0	[88.0, 102.2]	96.3	[87.6, 103.4]				
2009	201	99.6	[95.4, 101.8]	98.1	[92.6, 101.8]	98.6	[92.3, 103.1]	98.3	[91.2, 103.8]	101.9	[94.3, 107.8]				
2010	2,759	101.2	[100.5, 101.8]	101.3	[100.2, 102.2]	101.8	[100.4, 103.0]	102.0	[100.4, 103.5]	101.3	[99.4, 103.1]				
2011	2,718	100.7	[99.9, 101.3]	101.0	[99.9, 102.0]	101.3	[99.9, 102.5]	101.8	[100.2, 103.3]	102.8	[101.0, 104.5]				
2012	2,579	100.5	[99.7, 101.2]	100.7	[99.6, 101.7]	100.5	[99.0, 101.8]	101.9	[100.3, 103.4]	102.5	[100.6, 104.2]				



	1 year			2 year			3 year			4 year			5 year		
Characteristic	N at risk	%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI		
2013	3,146	99.9	[99.1, 100.6]	99.6	[98.5, 100.6]	100.1	[98.7, 101.3]	100.5	[99.0, 102.0]	100.6	[98.8, 102.3]				
2014	2,590	100.1	[99.2, 100.8]	101.0	[99.9, 102.0]	100.9	[99.4, 102.2]	101.0	[99.3, 102.5]	100.8	[98.8, 102.6]				
2015	2,685	100.5	[99.7, 101.1]	100.5	[99.3, 101.5]	101.1	[99.7, 102.4]	101.9	[100.2, 103.4]	102.0	[99.9, 103.9]				
2016	2,954	100.4	[99.7, 101.1]	101.2	[100.2, 102.1]	101.9	[100.6, 103.0]	102.0	[100.3, 103.6]	no FU	—				
2017	3,496	99.8	[99.1, 100.4]	99.9	[98.9, 100.8]	100.7	[99.4, 101.9]	no FU	—	no FU	—				
Combined Stage II															
2004	4,125	101.1	[100.6, 101.5]	101.9	[101.1, 102.5]	102.4	[101.4, 103.3]	102.8	[101.6, 103.9]	103.4	[102.0, 104.6]				
2005	3,985	101.0	[100.5, 101.4]	102.0	[101.2, 102.6]	102.7	[101.7, 103.5]	103.9	[102.8, 104.9]	104.6	[103.3, 105.8]				
2006	4,053	100.8	[100.3, 101.2]	101.3	[100.6, 102.0]	102.0	[101.1, 102.9]	102.6	[101.5, 103.7]	103.0	[101.8, 104.2]				
2007	4,156	100.6	[100.1, 101.1]	100.9	[100.1, 101.6]	101.7	[100.8, 102.6]	102.0	[100.8, 103.0]	102.5	[101.3, 103.7]				
2008	4,298	100.4	[99.9, 100.9]	101.3	[100.6, 102.0]	101.6	[100.6, 102.4]	102.1	[101.0, 103.1]	102.2	[100.9, 103.4]				
2009	4,461	100.8	[100.3, 101.2]	101.7	[100.9, 102.3]	102.4	[101.5, 103.2]	103.0	[101.9, 104.0]	102.9	[101.6, 104.0]				
2010	1,936	100.2	[99.4, 100.7]	99.7	[98.6, 100.6]	100.5	[99.3, 101.6]	101.7	[100.3, 103.0]	101.7	[100.1, 103.2]				
2011	2,188	100.1	[99.4, 100.7]	100.3	[99.3, 101.1]	101.1	[100.0, 102.1]	102.0	[100.7, 103.1]	102.3	[100.8, 103.6]				
2012	1,985	100.1	[99.3, 100.6]	100.1	[99.1, 101.0]	100.8	[99.6, 101.8]	100.7	[99.3, 102.0]	101.2	[99.6, 102.6]				
2013	1,920	100.3	[99.6, 100.9]	100.6	[99.6, 101.5]	100.5	[99.2, 101.7]	101.1	[99.5, 102.4]	101.7	[100.0, 103.2]				
2014	1,850	100.4	[99.6, 100.9]	100.7	[99.6, 101.5]	100.4	[99.0, 101.5]	101.0	[99.5, 102.4]	101.6	[99.8, 103.1]				
2015	1,997	100.5	[99.8, 101.0]	101.8	[100.9, 102.5]	102.1	[100.9, 103.1]	103.3	[101.9, 104.4]	103.7	[102.0, 105.3]				
2016	2,217	100.5	[99.8, 101.0]	101.2	[100.3, 101.9]	102.5	[101.4, 103.4]	103.6	[102.2, 104.8]	no FU	—				
2017	2,381	101.1	[100.5, 101.5]	102.3	[101.5, 103.0]	103.4	[102.2, 104.4]	no FU	—	no FU	—				
Combined Stage III															
2004	1,155	100.7	[99.6, 101.5]	100.6	[99.0, 101.9]	99.1	[97.0, 100.9]	98.6	[96.1, 100.7]	97.6	[94.8, 100.1]				
2005	1,191	100.2	[99.0, 101.0]	100.9	[99.4, 102.2]	99.7	[97.7, 101.4]	98.4	[96.0, 100.5]	98.5	[95.8, 100.9]				
2006	1,225	100.3	[99.2, 101.1]	100.9	[99.4, 102.1]	100.2	[98.2, 101.8]	99.4	[97.1, 101.4]	98.3	[95.7, 100.7]				
2007	1,114	100.3	[99.2, 101.2]	100.2	[98.5, 101.5]	100.3	[98.4, 102.0]	99.1	[96.7, 101.2]	98.3	[95.5, 100.7]				
2008	1,122	100.8	[99.6, 101.5]	101.1	[99.5, 102.4]	101.2	[99.2, 102.9]	100.2	[97.8, 102.3]	100.8	[98.1, 103.1]				



Characteristic	1 year			2 year			3 year			4 year			5 year		
	N at risk	%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI		
2009	1,117	99.6	[98.3, 100.6]	99.3	[97.4, 100.8]	98.9	[96.7, 100.8]	97.4	[94.8, 99.7]	96.6	[93.7, 99.3]				
2010	1,208	101.2	[100.2, 101.9]	101.4	[99.9, 102.6]	101.3	[99.4, 102.9]	99.6	[97.3, 101.7]	98.9	[96.2, 101.4]				
2011	1,310	101.5	[100.6, 102.0]	101.6	[100.2, 102.7]	102.0	[100.3, 103.4]	100.7	[98.6, 102.6]	99.4	[96.9, 101.7]				
2012	1,219	100.3	[99.2, 101.1]	99.8	[98.1, 101.1]	99.5	[97.5, 101.2]	98.8	[96.5, 100.9]	98.2	[95.5, 100.5]				
2013	1,198	100.7	[99.6, 101.4]	100.1	[98.5, 101.4]	100.3	[98.4, 102.0]	99.0	[96.7, 101.1]	98.6	[96.0, 101.0]				
2014	1,231	100.7	[99.6, 101.4]	101.1	[99.6, 102.3]	101.2	[99.4, 102.8]	99.8	[97.5, 101.8]	99.5	[96.9, 101.9]				
2015	1,265	100.6	[99.5, 101.3]	100.3	[98.7, 101.6]	100.1	[98.2, 101.8]	100.8	[98.6, 102.7]	100.1	[97.3, 102.6]				
2016	1,353	101.3	[100.3, 101.9]	101.2	[99.8, 102.4]	101.8	[100.1, 103.3]	101.0	[98.6, 103.1]	no FU	—				
2017	1,604	100.4	[99.4, 101.1]	100.5	[99.1, 101.7]	100.3	[98.3, 102.0]	no FU	—	no FU	—				
Combined Stage IV															
2004	582	89.5	[86.1, 92.3]	75.7	[71.2, 79.7]	65.8	[61.0, 70.4]	57.3	[52.2, 62.2]	50.5	[45.4, 55.6]				
2005	559	90.5	[87.1, 93.3]	77.2	[72.7, 81.2]	64.5	[59.6, 69.2]	58.3	[53.2, 63.3]	52.8	[47.6, 58.0]				
2006	507	90.5	[87.0, 93.4]	78.8	[74.2, 82.9]	71.4	[66.3, 76.1]	61.6	[56.3, 66.8]	57.8	[52.3, 63.3]				
2007	610	91.9	[88.8, 94.4]	80.8	[76.8, 84.5]	69.4	[64.8, 73.7]	62.7	[57.8, 67.4]	57.9	[52.8, 62.8]				
2008	625	89.8	[86.6, 92.4]	78.4	[74.3, 82.1]	69.3	[64.7, 73.6]	63.1	[58.3, 67.8]	62.0	[56.9, 66.9]				
2009	643	90.4	[87.3, 92.9]	77.9	[73.9, 81.6]	67.0	[62.4, 71.3]	59.6	[54.8, 64.2]	56.0	[51.1, 60.8]				
2010	639	87.3	[83.9, 90.2]	77.7	[73.6, 81.5]	70.1	[65.5, 74.4]	64.0	[59.1, 68.6]	59.1	[54.1, 64.0]				
2011	760	91.0	[88.2, 93.3]	80.1	[76.4, 83.4]	69.1	[64.9, 73.0]	63.3	[58.9, 67.5]	58.4	[53.9, 62.8]				
2012	789	88.8	[85.9, 91.2]	79.3	[75.7, 82.6]	70.4	[66.4, 74.2]	63.2	[58.9, 67.3]	55.2	[50.8, 59.5]				
2013	856	89.3	[86.6, 91.6]	77.5	[74.1, 80.7]	68.3	[64.4, 72.0]	62.9	[58.8, 66.8]	58.2	[54.0, 62.3]				
2014	936	90.4	[87.9, 92.6]	80.3	[77.0, 83.3]	71.2	[67.5, 74.7]	64.4	[60.5, 68.2]	56.4	[52.3, 60.4]				
2015	1,070	90.0	[87.6, 92.1]	81.7	[78.7, 84.5]	71.6	[68.2, 74.9]	65.5	[61.8, 69.1]	61.0	[56.9, 65.1]				
2016	1,130	92.9	[90.8, 94.7]	82.6	[79.8, 85.3]	73.6	[70.2, 76.7]	66.7	[62.8, 70.5]	no FU	—				
2017	1,276	92.6	[90.6, 94.3]	84.5	[81.9, 87.0]	75.2	[71.6, 78.5]	no FU	—	no FU	—				



Appendix 11.1.2. Uptake of selected drugs

Table 172 – Prostate cancer stage III: proportion of patients who received at least one dose during 5-year period after diagnosis

Drug/incidence year (n)	2004 (1155)	2005 (1191)	2006 (1226)	2007 (1114)	2008 (1122)	2009 (1117)	2010 (1208)	2011 (1310)	2012 (1220)	2013 (1201)	2014 (1231)	2015 (1265)	2016 (1353)	2017 (1604)
Enzalutamide							1.7%	1.8%	3.3%	2.8%	2.9%	1.8%	1.0%	0.6%

Number in yellow indicates the first calendar year of reimbursement. Enzalutamide was first reimbursed in 2014. The columns in this table indicate the incidence year. For example, for incidence year 2013, 2.8% of patients received reimbursed enzalutamide during the five years after diagnosis. Source: BCR-IMA.

Table 173 – Prostate cancer stage IV: proportion of patients who received at least one dose during 5-year period after diagnosis

Drug/incidence year (n)	2004 (583)	2005 (559)	2006 (507)	2007 (610)	2008 (626)	2009 (643)	2010 (639)	2011 (760)	2012 (789)	2013 (856)	2014 (937)	2015 (1071)	2016 (1133)	2017 (1276)
Enzalutamide							4.1%	6.6%	11.0%	16.4%	19.2%	15.4%	11.1%	5.1%

Number in yellow indicates the first calendar year of reimbursement. Enzalutamide was first reimbursed in 2014. The columns in this table indicate the incidence year. For example, for incidence year 2013, 16.4% of patients received reimbursed enzalutamide during the five years after diagnosis. Source: BCR-IMA.

Appendix 11.2. Reimbursement criteria for selected drugs

Drug	Trade name	Date start reimbursement	Indication NI	Indication Fr
Enzalutamide	Xtandi	1/12/2014	behandeling van gemetastaseerde castratieresistente prostaatkanker bij patiënten die progressie vertonen van de ziekte tijdens of na de behandeling met een chemotherapie op basis van docetaxel	traitement du cancer métastatique de la prostate résistant à la castration chez les patients qui présentent pendant ou après une chimiothérapie à base de docétaxel une progression documentée de leur maladie
		1/10/2015	gemetastaseerde castratieresistente prostaatkanker die asymptomatisch of licht symptomatisch zijn na falen van androgeendeprivatietherapie en voor wie behandeling met chemotherapie nog niet klinisch geïndiceerd is	traitement du cancer métastatique de la prostate résistant à la castration chez les hommes adultes asymptomatiques ou peu symptomatiques, après échec d'un traitement par suppression androgénique et pour lesquels la chimiothérapie n'est pas encore cliniquement indiquée
		1/10/2019 (indication discussed)	not behandeling van volwassen mannen met hoog-risico niet-gemetastaseerde castratieresistente prostaatkanker	traitement du cancer de la prostate résistant à la castration (CPRC) non métastatique à haut risque chez les hommes adultes



Appendix 11.3. Medical literature: search for evidence

Appendix 11.3.1. Search medical literature (systematic reviews)

The search for systematic reviews in MEDLINE, PreMedline and the Cochrane library of systematic reviews (inception to search date) specifically developed for this research question, yielded 321 records (Figure 503). After de-duplication, 183 of the 320 remaining reviews were screened based on title and abstract, of which 146 were excluded. In total 37 full text articles were assessed for eligibility. Based on full text evaluation, 33 reviews were excluded (Figure 504).

Figure 330 – Prostate cancer – Selection of SRs - Study flow

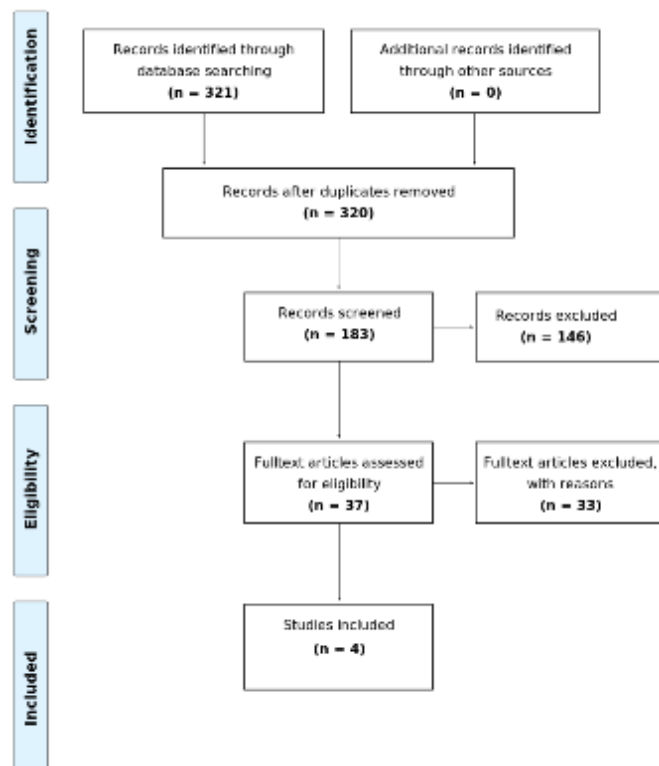



Table 174 – Prostate cancer: excluded reviews and reason for exclusion

	Year	Publication	Reason for exclusion
1	2020	Wang, X. Yang, H. Hu, X. et al. Comparing the clinical efficacy and safety of abiraterone and enzalutamide in metastatic castration-resistant prostate cancer: A systematic review and meta-analysis. J Oncol Pharm Pract 2020; doi: 10.1177/1078155220929414	cohort studies
2	2020	Sathianathen, N. J. Koschel, S. Thangasamy, I. A. et al. Indirect Comparisons of Efficacy between Combination Approaches in Metastatic Hormone-sensitive Prostate Cancer: A Systematic Review and Network Meta-analysis. Eur Urol 2020;77(3):365-372	wrong population
3	2020	Roviello, G. Gatta Michelet, M. R. D'Angelo, A. et al. Role of novel hormonal therapies in the management of non-metastatic castration-resistant prostate cancer: a literature-based meta-analysis of randomized trials. Clin Transl Oncol 2020;22(7):1033-1039	No results for enzalutamide specifically
4	2020	Rashid, M. Ramesh, M. Shamshavali, K. et al. Efficacy and Safety of Non-Steroidal Anti-Androgens in Patients with Metastatic Prostate Cancer: Meta-Analysis of Randomized Controlled Trials. Rev Recent Clin Trials 2020; 15(1):34-47	No results for enzalutamide specifically
5	2020	Pereira-Salgado, A. Kwan, E. M. Tran, B. et al. Systematic Review of Efficacy and Health Economic Implications of Real-world Treatment Sequencing in Prostate Cancer: Where Do the Newer Agents Enzalutamide and Abiraterone Fit in? Eur Urol Focus 2020;6:06	wrong research question
6	2020	Mori, K. Miura, N. Mostafaei, H. et al. Sequential therapy of abiraterone and enzalutamide in castration-resistant prostate cancer: a systematic review and meta-analysis. Prostate Cancer Prostatic Dis 2020;9:09	wrong research question
7	2020	Marchioni, M. Di Nicola, M. Primiceri, G. et al. New Antiandrogen Compounds Compared to Docetaxel for Metastatic Hormone Sensitive Prostate Cancer: Results from a Network Meta-Analysis. J Urol 2020;203(4):751-759	wrong population
8	2020	Liu, Z. Zhang, T. Ma, Z. et al. Systemic Management for Nonmetastatic Castration-resistant Prostate Cancer: A Systematic Review and Network Meta-Analysis. Am J Clin Oncol 2020;17	Included
9	2020	Kretschmer, A. Ploussard, G. Heidegger, I. et al. Health-related Quality of Life in Patients with Advanced Prostate Cancer: A Systematic Review. Eur Urol Focus 2020;20	Included
10	2020	Hird, A. E. Magee, D. E. Bhindi, B. et al. A Systematic Review and Network Meta-analysis of Novel Androgen Receptor Inhibitors in Non-metastatic Castration-resistant Prostate Cancer. Clin Genitourin Cancer 2020;6:06	No additional information
11	2020	Edmunds, K. Tuffaha, H. Galvao, D. A. et al. Incidence of the adverse effects of androgen deprivation therapy for prostate cancer: a systematic literature review. Support Care Cancer 2020;28(5):2079-2093	wrong outcome
12	2020	Di Nunno, V. Santoni, M. Mollica, V. et al. Systemic Treatment for Metastatic Hormone Sensitive Prostate Cancer: A Comprehensive Meta-Analysis Evaluating Efficacy and Safety in Specific Sub-Groups of Patients. Clin Drug Invest 2020;28	wrong patient group
13	2020	De Nunzio, C. Lombardo, R. Tema, G. et al. Adverse events related to abiraterone and enzalutamide treatment: analysis of the EudraVigilance database and meta-analysis of registrational phase III studies. Prostate Cancer Prostatic Dis 2020;23(2):199-206	wrong outcome



	Year	Publication	Reason for exclusion
14	2019	Tosco, L. Briganti, A. D'Amico A, V. et al. Systematic Review of Systemic Therapies and Therapeutic Combinations with Local Treatments for High-risk Localized Prostate Cancer. <i>Eur Urol</i> 2019;75(1):44-60	wrong patient group
15	2019	Sun, G. Chen, X. Gong, U. et al. Androgen deprivation therapy with chemotherapy or abiraterone for patients with metastatic hormone-naïve prostate cancer: a systematic review and meta-analysis. <i>Fut Oncol</i> 2019;15(10):1167-1179	wrong patient group
16	2019	Sathianathan, N. J. Koschel, S. Thangasamy, I. A. et al. Indirect Comparisons of Efficacy between Combination Approaches in Metastatic Hormone-sensitive Prostate Cancer: A Systematic Review and Network Meta-analysis. <i>Eur Urol</i> 2019;31:31	wrong patient group
17	2019	Roviello, G. Gatta Michelet, M. R. D'Angelo, A. et al. Role of novel hormonal therapies in the management of non-metastatic castration-resistant prostate cancer: a literature-based meta-analysis of randomized trials. <i>Clin Transl Oncol</i> 2019;15:15	No additional information
18	2019	Rashid, M. Ramesh, M. Shamshavali, K. et al. Efficacy and Safety of Non-Steroidal Anti-Androgens in Patients with Metastatic Prostate Cancer: Meta-Analysis of Randomized Controlled Trials. <i>Rev Recent Clin Trials</i> 2019;5:05	Full text could not be obtained
19	2019	Marchioni, M. Di Nicola, M. Primiceri, G. et al. New Antiandrogen Compounds Compared to Docetaxel in Metastatic Hormone Sensitive Prostate Cancer: Results from a Network Meta-Analysis. <i>J Urol</i> 2019; 101097JU00000000000000636	wrong patient group
20	2019	Di Nunno, V. Mollica, V. Santoni, M. et al. New Hormonal Agents in Patients With Nonmetastatic Castration-Resistant Prostate Cancer: Meta-Analysis of Efficacy and Safety Outcomes. <i>Clin Genitourin Cancer</i> 2019;17(5):e871-877	No additional information
21	2019	De Nunzio, C. Lombardo, R. Tema, G. et al. Adverse events related to abiraterone and enzalutamide treatment: analysis of the EudraVigilance database and meta-analysis of registrational phase III studies. <i>Prostate Cancer Prostatic Dis</i> 2019;4:04	wrong outcome
22	2019	Chung, D. Y. Kang, D. H. Kim, J. W. et al. Comparison of Oncologic Outcomes Between Two Alternative Sequences with Abiraterone Acetate and Enzalutamide in Patients with Metastatic Castration-Resistant Prostate Cancer: A Systematic Review and Meta-Analysis. <i>Cancers (Basel)</i> 2019;12(1):1-18	wrong research question
23	2019	Chen, W. Li, L. Ji, S. et al. Evaluation of potential surrogate endpoints for prediction of overall survival in patients with castration-resistant prostate cancer: trial-level meta-analysis. <i>Eur J Clin Pharmacol</i> 2019;75(11):1521-1532	wrong research question
24	2019	Bretoni, A. Ferrario, L. Foglia, E. HTA and innovative treatments evaluation: the case of metastatic castration-resistant prostate cancer. <i>ClinicoEcon</i> 2019;11:283-300	wrong research question
25	2018	Wang, Y. Zhang, H. Shen, W. et al. Effectiveness and tolerability of targeted drugs for the treatment of metastatic castration-resistant prostate cancer: a network meta-analysis of randomized controlled trials. <i>J Cancer Res Clin Oncol</i> 2018;144(9):1751-1768	No separate results for enzalutamide



Year	Publication	Reason for exclusion
26	2018 Tassinari, D. Cherubini, C. Roudnas, B. et al. Treatment of Metastatic, Castration-resistant, Docetaxel-resistant Prostate Cancer: A Systematic Review of Literature With a Network Meta-analysis of Randomized Clinical Trials. <i>Rev Recent Clin Trials</i> 2018;13(3):226-237	full text could not be obtained
27	2018 McCool, R. Fleetwood, K. Glanville, J. et al. Systematic Review and Network Meta-Analysis of Treatments for Chemotherapy-Naïve Patients with Asymptomatic/Mildly Symptomatic Metastatic Castration-Resistant Prostate Cancer. <i>Value Health</i> 2018;21(10):1259-1268	Included
28	2018 Ingrosso, G. Detti, B. Scartoni, D. et al. Current therapeutic options in metastatic castration-resistant prostate cancer. <i>Semin Oncol</i> 2018; 45(5):303-315	Not a systematic review
29	2017 Summers, N. Vanderpuye-Orgle, J. Reinhart, M. et al. Efficacy and safety of post-docetaxel therapies in metastatic castration-resistant prostate cancer: a systematic review of the literature. <i>Curr Med Res Opin</i> 2017;33(11):1995-2008	No additional information
30	2017 Poorthuis, M. H. F. Vernooij, R. W. M. van Moorselaar, R. J. A. de Reijke, T. M. Second-line therapy in patients with metastatic castration-resistant prostate cancer with progression after or under docetaxel: A systematic review of nine randomized controlled trials. <i>Semin Oncol</i> 2017;44(5):358-371	Included
31	2017 Fang, M. Nakazawa, M. Antonarakis, E. S. Li, C. Efficacy of Abiraterone and Enzalutamide in Pre- and Postdocetaxel Castration-Resistant Prostate Cancer: A Trial-Level Meta-Analysis. <i>prostate cancer</i> 2017; 8560827	No critical appraisal, inclusion of non-randomized studies
32	2017 Chopra, A. Georgieva, M. Lopes, G. et al. Abiraterone or Enzalutamide in Advanced Castration-Resistant Prostate Cancer: An Indirect Comparison. <i>Prostate</i> 2017;77(6): 639-646	Not a systematic review
33	2017 Bianchi, E. Fantini, M. Nicoletti, S. L. V. et al. Enzalutamide (E) vs abiraterone acetate (AA) in the treatment of metastatic, castration-resistant prostate cancer. Indirect comparisons and network meta-analysis for clinical practice. <i>Ann Oncol</i> 2017;28: vi20	conference abstract
34	2016 Roviello, G. Sigala, S. Sandhu, S. et al. Role of the novel generation of androgen receptor pathway targeted agents in the management of castration-resistant prostate cancer: A literature based meta-analysis of randomized trials. 2016;61:111-21	No additional information
35	2016 Lowrance, W. T. Roth, B. J. Kirkby, E. et al. Castration-Resistant Prostate Cancer: AUA Guideline Amendment 2015. <i>J Urol</i> 2016;195(5):1444-1452	not a systematic review
36	2016 Lebdaï, S. Basset, V. Branchereau, J. et al. What do we know about treatment sequencing of abiraterone, enzalutamide, and chemotherapy in metastatic castration-resistant prostate cancer? <i>World J Urol</i> 2016;34(5):617-24	Retrospective studies only
37	2016 Dinh, J. A. Baker, D. Chahal, M. Therapy Update for Metastatic Castration-Resistant Prostate Cancer. <i>Consult Pharm</i> 2016;31(10):581-592	Full text not obtained



Appendix 11.3.2. Critical appraisal systematic reviews

	Liu 2020 ²⁷⁶		Kretschmer 2020 ²⁷⁷	
	Score	Rationale/comment	score	Rationale/comment
1. PICO	Y		Y	
2. A priori study design	N		N	
3. Inclusion study designs	Y		Y	
4. Comprehensive literature search	Partial Y	No search of reference lists, no search of trial registers	Partial Y	No search of trial registers
5. Duplicate study selection	Y		Y	
6. Duplicate data extraction	Y		N	Unclear
7. List of excluded studies and rationale	N		N	
8. Characteristics of included studies provided	Y		Y	
9. Assessment of risk of bias	Y		Y	
10. Sources of funding reported	N		N	Funding sources of included studies not reported
11. Appropriate methods to combine findings	Y		NA	
12. Assessment of impact RoB in included studies on results MA	N		Y	
13. RoB assessment used in interpretation of results and in conclusions	N		Y	
14. Explanation for and discussion of any observed heterogeneity	NA		NA	
15. Adequate investigation of publication bias and its impact on the results	N		N	
16. Potential sources of conflict of interest reported	Y		Y	



	McCool 2018 ²⁷⁸		Poorthuis 2017 ²⁷⁹	
	Score	Rationale/comment	score	Rationale/comment
1. PICO	Y		Y	
2. A priori study design	Y		N	
3. Inclusion study designs	Y		Y	
4. Comprehensive literature search	Partial yes	no search of reference lists, no search of trial registries	Partial Y	No trial registries searched
5. Duplicate study selection	Y		Y	
6. Duplicate data extraction	Y		Y	
7. List of excluded studies and rationale	N		Y	
8. Characteristics of included studies provided	Y		N	
9. Assessment of risk of bias	Y		Y	
10. Sources of funding reported	N		N	
11. Appropriate methods to combine findings	Y		Y	
12. Assessment of impact RoB in included studies on results MA	N		N	
13. RoB assessment used in interpretation of results and in conclusions	N		N	
14. Explanation for and discussion of any observed heterogeneity	N		N	
15. Adequate investigation of publication bias and its impact on the results	N		Y	(too few studies)
16. Potential sources of conflict of interest reported	N	? Two sponsor companies in acknowledgments?	N	



Appendix 11.3.3. Search strategy

Appendix 11.3.3.1. Cochrane library of systematic reviews

Date	24/06/2020 21:10:41	
Database	Cochrane@Wiley.com	
Search strategy		
#1	[mh "Prostatic Neoplasms"]	5417
#2	(prostat* NEAR/3 (neoplasm* or cancer* or carcinoma* or adenocarcinoma* or tumour* or tumor* or malignan* or sarcoma*)):ab,ti	12333
#3	#1 or #2	12855
#4	enzalutamide:ab,ti	592
#5	93T0T9GKNU:ab,ti	0
#6	"MDV 3100":ab,ti	1
#7	MDV3100:ab,ti	35
#8	XTANDI:ab,ti	26
#9	"915087-33-1":ab,ti	20
#10	#4 or #5 or #6 or #7 or #8 or #9	609
#11	#3 and #10	570
#12	[mh "Androgen Antagonists"]	943
#13	[mh ^"Androgen Receptor Antagonists"]	30
#14	#12 or #13	943
#15	(androgen? NEAR/3 (inhibit* or antagonist? or target* or block* or against or anti or multi-targets or multi-target or multi-targeting or reduc*)):ab,ti	1020
#16	("nonsteroidal antiandrogen" or "nonsteroidal antiandrogen"):ab,ti	63
#17	("non steroidal antiandrogen" or "non steroidal antiandrogens"):ab,ti	18
#18	nsaa:ab,ti	68
#19	#15 or #16 or #17 or #18	1114
#20	#14 or #19	1869
#21	#3 and #20	1294
#22	((("new class" or "new classes" or innovative or target*) NEAR/3 (drug? or therapy or therapies or therapeutic* or treatment? or chemotherap*)):ab,ti	11940
#23	#3 and #22	251
#24	#11 or #21 or #23	1866
#25	#24 in Cochrane Reviews	8
Comments		



Appendix 11.3.3.2. Medline + PreMedline

Date	June 23, 2020	
Database	Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946 to June 23, 2020>	
Search strategy		
1	exp Colorectal Neoplasms/	200186
2	((rectum or rectal or colorectal) adj4 (cancer* or tumor* or tumour* or carcin* or adenocarcin* or metasta* or malignan* or lymphom* or leiomyosarcom* or melanom*)).ab,ti,kf.	159915
3	((colon or colonic) adj4 (cancer* or tumor* or tumour* or carcin* or adenocarcin* or metasta* or malignan* or lymphom* or leiomyosarcom* or melanom*)).ab,ti,kf.	91577
4	(sigmoid adj4 (cancer* or tumor* or tumour* or carcin* or adenocarcin* or metasta* or malignan* or lymphom* or leiomyosarcom* or melanom*)).ab,ti,kf.	2944
5	lynch syndrome.ab,ti,kf.	3172
6	(adenomatous adj3 polypos*).ab,ti,kf.	7295
7	(gardner* adj3 syndrome).ab,ti,kf.	1172
8	2 or 3 or 4 or 5 or 6 or 7	231379
9	1 or 8	277882
10	aflibercept.ab,ti,kf,rn.	2200
11	ZALTRAP.ab,ti,kf,rn.	30
12	EYLEA.ab,ti,kf,rn.	123
13	15C2VL427D.ab,ti,kf,rn.	1298
14	VEGF TRAP.ab,ti,kf,rn.	286
15	VEGF TRAP-EYE.ab,ti,kf,rn.	45
16	BAY-86-5321.ab,ti,kf,rn.	1
17	BAY-865321.ab,ti,kf,rn.	0
18	BAY86-5321.ab,ti,kf,rn.	1
19	BAY865321.ab,ti,kf,rn.	0
20	AVE-0005.ab,ti,kf,rn.	2
21	AVE0005.ab,ti,kf,rn.	3
22	vascular endothelial growth factor trap.ab,ti,kf,rn.	55
23	vasculotropin trap.ab,ti,kf,rn.	0
24	845771-78-0.ab,ti,kf,rn.	0
25	862111-32-8.ab,ti,kf,rn.	1
26	10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25	2362
27	Bevacizumab/	11513
28	bevacizumab.ab,ti,kf,rn.	18098
29	avastin.ab,ti,kf,rn.	1534
30	mvasi.ab,ti,kf,rn.	5



Date	June 23, 2020	
31	zirabev.ab,ti,kf,rn.	2
32	ainex.ab,ti,kf,rn.	1
33	altuzan.ab,ti,kf,rn.	2
34	bevax.ab,ti,kf,rn.	0
35	bryxta.ab,ti,kf,rn.	0
36	krabeva.ab,ti,kf,rn.	0
37	kyomarc.ab,ti,kf,rn.	0
38	2S9ZZM9Q9V.ab,ti,kf,rn.	11514
39	1438851-35-4.ab,ti,kf,rn.	0
40	216974-75-3.ab,ti,kf,rn.	1
41	RHUMAB.ab,ti,kf,rn.	137
42	rhuMAb-VEGF.ab,ti,kf,rn.	18
43	12-IGG1.ab,ti,kf,rn.	3
44	ABP-215.ab,ti,kf,rn.	9
45	ABP215.ab,ti,kf,rn.	1
46	AVA1.ab,ti,kf,rn.	8
47	AVA-1.ab,ti,kf,rn.	42
48	ask b1202.ab,ti,kf,rn.	0
49	askb1202.ab,ti,kf,rn.	0
50	BI 695502.ab,ti,kf,rn.	1
51	BI695502.ab,ti,kf,rn.	0
52	BS503.ab,ti,kf,rn.	0
53	BS-503.ab,ti,kf,rn.	0
54	BS-503A.ab,ti,kf,rn.	1
55	BS503A.ab,ti,kf,rn.	0
56	bat 1706.ab,ti,kf,rn.	0
57	bat1706.ab,ti,kf,rn.	2
58	"bcd 021".ab,ti,kf,rn.	0
59	bcd021.ab,ti,kf,rn.	1
60	bevz 92.ab,ti,kf,rn.	0
61	bevz92.ab,ti,kf,rn.	1
62	CHS-5217.ab,ti,kf,rn.	0
63	CHS5217.ab,ti,kf,rn.	0
64	CT-16.ab,ti,kf,rn.	120
65	CT16.ab,ti,kf,rn.	37
66	CT-P16.ab,ti,kf,rn.	1



Date	June 23, 2020	
67	CTP16.ab,ti,kf,rn.	0
68	FKB-238.ab,ti,kf,rn.	0
69	FKB238.ab,ti,kf,rn.	0
70	hd 204.ab,ti,kf,rn.	2
71	hd204.ab,ti,kf,rn.	0
72	HLX-04.ab,ti,kf,rn.	0
73	HLX04.ab,ti,kf,rn.	0
74	"mb 02".ab,ti,kf,rn.	18
75	mb02.ab,ti,kf,rn.	4
76	mil 60.ab,ti,kf,rn.	2
77	mil60.ab,ti,kf,rn.	2
78	myl 14020.ab,ti,kf,rn.	0
79	myl14020.ab,ti,kf,rn.	0
80	myl 1402o.ab,ti,kf,rn.	0
81	myl1402o.ab,ti,kf,rn.	0
82	nsc 704865.ab,ti,kf,rn.	2
83	nsc704865.ab,ti,kf,rn.	0
84	ons 1045.ab,ti,kf,rn.	0
85	ons1045.ab,ti,kf,rn.	0
86	ons 5010.ab,ti,kf,rn.	0
87	ons5010.ab,ti,kf,rn.	0
88	PF06439535.ab,ti,kf,rn.	0
89	PF-06439535.ab,ti,kf,rn.	5
90	PF6439535.ab,ti,kf,rn.	0
91	PF-6439535.ab,ti,kf,rn.	0
92	ql 1101.ab,ti,kf,rn.	0
93	ql1101.ab,ti,kf,rn.	1
94	RG-435.ab,ti,kf,rn.	1
95	RG435.ab,ti,kf,rn.	0
96	R-435.ab,ti,kf,rn.	53
97	R435.ab,ti,kf,rn.	15
98	ro 4876646.ab,ti,kf,rn.	0
99	ro4876646.ab,ti,kf,rn.	0
100	sb 8.ab,ti,kf,rn.	30
101	sb8.ab,ti,kf,rn.	19
102	stc 103.ab,ti,kf,rn.	0



Date	June 23, 2020	
103	stc103.ab,ti,kf,rn.	0
104	28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102 or 103	18733
105	27 or 104	18733
106	cetuximab/	4449
107	cetuximab.ab,ti,kf,rn.	7321
108	Erbitux.ab,ti,kf,rn.	344
109	C225.ab,ti,kf,rn.	478
110	C-225.ab,ti,kf,rn.	76
111	PQX0D8J21J.ab,ti,kf,rn.	4450
112	IMC225.ab,ti,kf,rn.	1
113	CMAB-009.ab,ti,kf,rn.	0
114	CMAB009.ab,ti,kf,rn.	3
115	ABP-494.ab,ti,kf,rn.	0
116	ABP494.ab,ti,kf,rn.	0
117	205923-56-4.ab,ti,kf,rn.	1
118	107 or 108 or 109 or 110 or 111 or 112 or 113 or 114 or 115 or 116 or 117	7696
119	106 or 118	7696
120	Panitumumab/	972
121	panitumumab.ab,ti,kf,rn.	1794
122	panitumumab.ab,ti,kf,rn.	7
123	Vectibix.ab,ti,kf,rn.	47
124	Vectibex.ab,ti,kf,rn.	0
125	abenix.ab,ti,kf,rn.	2
126	"E7.6.3".ab,ti,kf,rn.	6
127	ABX-EGF.ab,ti,kf,rn.	40
128	6A901E312A.ab,ti,kf,rn.	973
129	339177-26-3.ab,ti,kf,rn.	1
130	121 or 122 or 123 or 124 or 125 or 126 or 127 or 128 or 129	1827
131	120 or 130	1827
132	regorafenib.ab,ti,kf,rn.	1123
133	24T2A1DOYB.ab,ti,kf,rn.	494
134	STIVARGA.ab,ti,kf,rn.	32
135	BAY-734506.ab,ti,kf,rn.	0
136	BAY 73-4506.ab,ti,kf,rn.	23



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137	BAY734506.ab,ti,kf,rn.	0
138	1019206-88-2.ab,ti,kf,rn.	0
139	755037-03-7.ab,ti,kf,rn.	1
140	132 or 133 or 134 or 135 or 136 or 137 or 138 or 139	1127
141	26 or 105 or 119 or 131 or 140	27953
142	9 and 141	6991
143	(vegfr adj5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)).ab,ti,kf.	20933
144	(egfr adj5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)).ab,ti,kf.	22013
145	(vegfr* adj5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)).ab,ti,kf.	4593
146	((HER1 or HER-1) adj5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)).ab,ti,kf.	294
147	((erbb-1 or erbb1) adj5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)).ab,ti,kf.	267
148	(egf adj5 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)).ab,ti,kf.	7632
149	143 or 144 or 145 or 146 or 147 or 148	51425
150	exp Vascular Endothelial Growth Factors/ai	8313
151	exp Receptors, Vascular Endothelial Growth Factor/ai	2960
152	Epidermal Growth Factor/ai	570
153	exp ErbB Receptors/ai	11721
154	150 or 151 or 152 or 153	22460
155	149 or 154	61371
156	9 and 155	4911
157	Protein Kinase Inhibitors/	45263
158	exp Protein-Tyrosine Kinases/ai	38056
159	exp Antibodies, Monoclonal/	235325
160	157 or 158 or 159	299853
161	tki.ab,ti,kf.	7579
162	(kinase? adj3 (inhibit* or antagonist? or target* or block* or against or anti or multi-target* or reduc*)).ab,ti,kf.	118162
163	(monoclonal adj3 antibod*).ab,ti,kf.	196475
164	161 or 162 or 163	312405
165	160 or 164	468390
166	9 and 165	15716
167	((new class* or innovative or target*) adj3 (drug? or therapy or therapies or therapeutic* or treatment? or chemotherap*)).ab,ti,kf.	330433
168	9 and 167	11340
169	142 or 156 or 166 or 168	27558
170	((systematic review or systematic literature review or systematic scoping review or systematic narrative review or systematic qualitative review or systematic evidence review or systematic quantitative review or systematic meta-review	159535



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	or systematic critical review or systematic mixed studies review or systematic mapping review or systematic cochrane review or "systematic search and review" or systematic integrative review).ti. not comment.pt. not (protocol or protocols).ti. not medline.st.) or (Cochrane Database Syst Rev.ja. and review.pt.) or systematic review.pt.	
171	meta-analys*.ti.	109097
172	meta-analysis.pt.	116362
173	exp Technology Assessment, Biomedical/	11075
174	health technology assessment.ti,kf.	1925
175	HtA.ti,kf.	596
176	170 or 171 or 172 or 173 or 174 or 175	253258
177	169 and 176	414
Comments		



Appendix 11.4. Economic literature

Appendix 11.4.1. Search economic literature (HTA reports)

The search strategy in CRD's HTA database identified 253 references (Table 175). In a first round, 4 references were selected based on a review of title, keywords and abstract. The 249 remaining references were excluded for the following reasons: intervention (244), design (1), population (1) or language (3). In a second round, the full text of the 4 selected references was reviewed. One reference was excluded (design (1)). Three references were retained. These references are indicated in Table 42 with an asterisk (*).

Furthermore, in May 2020, the website of the National Institute for Health Research (NIHR) was searched for relevant reports. The following search term was used: enzalutamide (5 hits, 3 with a focus on prostate cancer, 3 not previously identified).

Finally, also in May 2020, the website of the National Institute for Health and Care Excellence (NICE) was searched. The following search term was used: enzalutamide (21 hits, 3 relevant Technology Assessments (TAs), 1 not previously identified).

An overview of the identified references is provided in Table 176.

Table 175 – Search strategy and results for CRD: HTA

Date			
Date covered	All		
Search Strategy	1	MeSH DESCRIPTOR Prostatic Neoplasms EXPLODE ALL TREES	709
	2	* IN HTA	17351
	3	#1 AND #2	253 references
Note	/		

**Table 176 – Prostate cancer – Identified HTA reports for the selected drugs****Selected reports****Enzalutamide**

- All Wales Therapeutics and Toxicology Centre (AWTTC) secretariat of the All Wales Medicines Strategy Group (AWMSG). Enzalutamide (Xtandi®). 2015.*²⁸⁰
- NICE, TA580. May 2019. Enzalutamide for hormone-relapsed non-metastatic prostate cancer.^{β281}
 - Robertson C, Chong H, Scotland G, Cooper D, Ramsay C, Urquhart G, Aucott L. Enzalutamide for treating non-metastatic hormone-relapsed prostate cancer. Aberdeen HTA Group, 2018.^{α282}
- NICE, TA377. January 2016. Enzalutamide for treating metastatic hormone-relapsed prostate cancer before chemotherapy is indicated.*^{β283}
 - Robertson C, Cummins E, Fielding S, Lam T, Fraser C, Ramsay CR. Enzalutamide for treating metastatic hormone-relapsed prostate cancer not previously treated with chemotherapy: a single technology appraisal. Aberdeen HTA Group, 2015.^{α284}
- NICE, TA316. July 2014. Enzalutamide for metastatic hormone-relapsed prostate cancer previously treated with a docetaxel-containing regimen.*^{β285}
 - Enzalutamide for the treatment of metastatic hormone relapsed prostate cancer previously treated with a docetaxel-containing regimen (ID600). → No link to full report. Only link to TA316.^α

* These references were identified in CRD's HTA database. α References identified on NIHR's website. β References identified on NICE's website.



Appendix 11.4.2. Results economic literature (HTA reports)

Appendix 11.4.2.1. AWMSG (2015): enzalutamide

- QoL:
 - “Utility values for the PFS state are based on EQ-5D data collected during the PREVAIL study. A utility increment over BSC while on first-line enzalutamide or abiraterone treatment is assumed. Disutilities associated with SREs are also derived from the PREVAIL data, while (dis)utility values for progressed states, and for the AEs and their assumed durations, are based on several sources from the literature and the technology appraisal of abiraterone in the post-chemotherapy setting.”²⁸⁶”²⁸⁰
 - “Utility data for PFS states are derived from EQ-5D data collected in the PREVAIL study. Trial-based EQ-5D data are normally preferred over other external sources; however, the baseline utility value of [commercial in confidence data removed], which is applied throughout the PFS state, is somewhat greater than the usually-quoted mean estimates of population norms for this age group (mean values in range 0.78 to 0.75 for males aged 65 to > 75 years²⁸⁷).”²⁸⁰
- Results:
 - “Compared with the primary comparator BSC, enzalutamide had an incremental cost per QALY gained of [commercial in confidence data removed], based on additional costs of around [commercial in confidence data removed] and a gain of [commercial in confidence data removed] QALYs.”²⁸⁰
 - “In probabilistic sensitivity analyses, the probability of enzalutamide having an incremental cost per QALY gained below £20,000 was 0%, and below £30,000 was 57% compared with BSC.”²⁸⁰
- Uncertainty/sensitivity:
 - “The main drivers of the results are the greater acquisition cost of enzalutamide and the longer PFS with enzalutamide, which as modelled maintains patients at a higher quality of life for longer than the comparator.”²⁸⁰
 - “Uncertainties in the modelled efficacy of enzalutamide and BSC relate to the use of TTD as a proxy for duration of PFS, and OS data are adjusted for treatment crossover and extrapolated over the long-term; sensitivity and scenario analyses demonstrate the ICER estimates are sensitive to the approaches employed to model these. Other uncertainties, which individually have the potential to increase the ICER estimate above £30,000/QALY, include the assumed duration of enzalutamide treatment and the baseline utility value assumed for progression-free patients.”²⁸⁰
 - “Treatment crossover has the potential to confound the OS data. Different methods of handling treatment crossover have been explored and the ICER estimates are sensitive to these.”²⁸⁰
 - “The company has used TTD as a proxy for PFS on the basis that rPFS alone (a co-primary endpoint of the PREVAIL study) would not adequately determine disease progression and prompt treatment switching in practice; however, a large proportion of patients in the PREVAIL study discontinued treatment for reasons other than progression (only 70.4% on enzalutamide and 73.7% on BSC discontinued due to progression²⁸⁸), which introduces uncertainty into the assumed time in a PFS state in the model and time to initiation of second-line docetaxel.”²⁸⁰
 - “Relatively short-term survival data are extrapolated in the long-term.”²⁸⁰



- “Second- and subsequent lines of therapy also contribute to the overall ICER estimates.”²⁸⁰
- “Utility data for PFS states are derived from EQ-5D data collected in the PREVAIL study. Trial-based EQ-5D data are normally preferred over other external sources; however, the baseline utility value of [commercial in confidence data removed], which is applied throughout the PFS state, is somewhat greater than the usually-quoted mean estimates of population norms for this age group (mean values in range 0.78 to 0.75 for males aged 65 to > 75 years²⁸⁷). A key driver of the ICER is the longer PFS with enzalutamide, which as modelled maintains patients at a higher quality of life for longer than the comparator.”²⁸⁰
- “Alternative discount on list price of enzalutamide demonstrates the sensitivity of the ICER estimate to assumed price of enzalutamide. However, the PAS price of enzalutamide is fixed”²⁸⁰
- Conclusions:
 - No explicit conclusion is formulated in this document
- (Confidential) prices:
 - “Enzalutamide acquisition costs are based on a Department of Health agreed Patient Access Scheme (PAS), which provides a confidential discount on the list price.”²⁸⁰



Reference Costs (list prices & remarks)	Population, Intervention & comparator IC, IE and ICERs	Remarks on use of generic utility instrument (e.g. EQ- 5D) to measure impact on QoL in economic evaluations	Most uncertain variables or important variables in sensitivity analysis
Enzalutamide			
AWMSG, 2015 ²⁸⁰	Patients with metastatic castration-resistant prostate cancer who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy (ADT) in whom chemotherapy is not yet clinically indicated. Enzalutamide versus best supportive care (BSC; including gonadotrophin-releasing hormone analogues (if not surgically castrated), and corticosteroids, blood transfusion, bisphosphonates, radiotherapy, analgesics and palliative surgery to treat skeletal-related events, when needed).		
List prices, negotiated discounts are hidden. Based on its current list price, enzalutamide would have an annual cost per patient treated of £35,650 (excluding VAT).	Results are commercial in confidence. Medicine acquisition cost, total costs, life-years gained, QALYs gained and ICERs are commercial in confidence. Probability ICER < £20 000/QALY: 0% Probability ICER < £30 000/QALY: 57% Remark: A comparison against abiraterone, which is also licensed for this indication, ²⁸⁹ has been conducted as a secondary comparison; however, as abiraterone is not recommended by AWMSG for use in NHS Wales, ²⁹⁰ the primary comparison against BSC is most relevant to the decision problem and is the focus of the discussion of the company's economic evidence.	EQ-5D data was collected in the underlying PREVAIL study, but utility information was removed since it was considered to be commercial in confidence data.	Acquisition costs & treatment duration PFS & QoL OS (cross-over adjustment) & extrapolation.

AWMSG: All Wales Medicines Strategy Group.



Appendix 11.4.2.2. NICE, TA580 (2019): enzalutamide

- QoL:
 - “The company presented health-related quality-of-life data from PROSPER measured after 22 months of follow up using various quality-of-life instruments. These included the Brief Pain Inventory, the European Organisation for Research and Treatment of Cancer prostate cancer module (EORTC), Functional Assessment of Cancer Therapy – Prostate (FACT-P) and the EQ-5D. The only statistically significant ($p < 0.05$) differences between treatments were detected using the EORTC in hormonal-treatment related symptoms and the FACT-P social wellbeing instruments. The committee concluded that there was not enough evidence from PROSPER to show that enzalutamide improved quality of life compared with placebo. In response to consultation, the company stated that enzalutamide increased the time until deterioration of quality of life compared with placebo rather than improving quality of life. The committee noted that data from PROSPER supported this, but that the company did not reflect this benefit in its economic model.”²⁸¹
 - “There were no statistically significant differences between the enzalutamide and placebo groups, with the exception of hormonal treatment-related symptoms (measured by the EORTC QLQ PR25) and social wellbeing (measured by FACT-P) in favour of enzalutamide. Changes in pain scores favoured enzalutamide and median time to worsening of pain symptoms and pain progression was also longer in the enzalutamide arm than the placebo arm, as measured by the FACT-P and BPI-SF, although only the BPI-SF measure was statistically significant (HR: 0.75, 95% CI [0.57, 0.97]. Time to deterioration favoured enzalutamide over placebo for other HRQOL dimensions, with the exception of the physical wellbeing dimension of the FACT-P, although this was statistically non-significant, and time to worsening in hormonal treatment-related symptoms (33.15 vs 36.83 months; HR: 1.29, 95% CI [1.02, 1.63]). Statistically significant differences favouring enzalutamide were reported for EORTC-QLQ-PR25 bowel (33.15 vs 25.89 months; HR: 0.72, 95% CI [0.59, 0.89]), and urinary symptoms (36.86 vs 25.86 months; HR: 0.56, 95% CI [0.46, 0.72]), FACT-P emotional well-being (HR 0.69 [95% CI 0.55, 0.86]), physical composite score (HR 0.79 [95% CI 0.67, 0.93]), FACT P total score (HR 0.83 [95% CI 0.69, 0.99]), and the EQ-5D visual analogue scale (HR 0.75 [95% CI 0.63, 0.90]). The ERG notes that enzalutamide is associated with an earlier deterioration in HRQOL due treatment-related symptoms compared to placebo, for example hormonal treatment-related symptoms, but, overall, enzalutamide is associated with a delay in the worsening of HRQOL.”²⁸²
 - Mean changes for the EQ-5D VAS scores from baseline to week 97 were presented as confidential in the HTA report.
- Results:
 - “The company’s base-case cost-effectiveness results are presented ... It demonstrates that enzalutamide is associated with a cost increase of ***** and **** QALY gain, as compared to ADT. The ICER comes to £28,853 per QALY gained.”²⁸²
 - “The committee considered whether enzalutamide would be a cost-effective use of NHS resources for non-metastatic hormone resistant prostate cancer, taking into account the patient access scheme (discount) associated with enzalutamide. The company presented a base-case deterministic incremental cost-effectiveness ratio (ICER) of £28,853 per quality-adjusted life year (QALY) gained. However, this value was uncertain and included several assumptions that the committee considered inappropriate, notably, that enzalutamide prolongs survival when used in non-metastatic disease. The ERG presented a base-case ICER of £56,168 per QALY gained”²⁸¹



- Uncertainty/sensitivity:
 - “Clinical trial evidence shows that adding in enzalutamide extends the time until the cancer starts spreading to other parts of the body. But there is no evidence that it increases how long people live.”²⁸¹
 - “The company presented 2 of 3 planned interim analyses of overall survival: the first after 135 deaths (coinciding with the final analysis for metastasis-free survival; see section 3.7), and the second after 285 deaths (about 1 year later). The company stated that it intends to do another interim analysis and a final analysis. The committee appreciated that, in its amended statistical plan, the company planned the final analysis for when 596 deaths had occurred. It agreed that the overall survival data from PROSPER presented by the company were immature and provided too few deaths to detect a statistically significant difference between treatment arms. For example, at the second interim analysis, the median overall survival had not been reached and the hazard ratio between the 2 treatment arms was not statistically significant as predefined (HR 0.83, 95% CI 0.65 to 1.06; p=0.134). In response to consultation, the company agreed that the overall survival data were immature because the study was statistically powered to detect a benefit in metastasis-free survival rather than overall survival. The committee noted this comment but agreed that overall survival was clinically important and key to populating the economic model.”²⁸¹
 - “the company suggested that it was difficult to show a statistically significant benefit in this population because, over time, people may die from causes other than prostate cancer. However, the committee agreed that, in a randomised trial, mortality from causes other than prostate cancer would be similar in both treatment arms. In the absence of new evidence, the committee did not change its conclusions about enzalutamide's survival benefit compared with placebo.”²⁸¹
 - “The committee reiterated that both the company's and ERG's ICERs were associated with substantial uncertainty. This mainly arose from: the immaturity of the overall survival data; the lack of evidence of a survival benefit or quality-of-life improvement by delaying metastasis; and the disconnect between the costs and benefits of subsequent treatments in the model. Furthermore, splitting survival into before and after metastasis in the model introduced an additional layer of uncertainty.”²⁸¹
- Conclusions:
 - “Clinical trial evidence shows that adding in enzalutamide extends the time until the cancer starts spreading to other parts of the body. But there is no evidence that it increases how long people live.
 - Cost-effectiveness estimates comparing enzalutamide plus androgen deprivation therapy with androgen deprivation therapy alone are uncertain. This is because:
 - it is not possible to estimate accurately how long people who take enzalutamide live
 - the costs and benefits of treatments used after enzalutamide in the economic analysis do not reflect NHS practice.
 - The estimates are not within the range that NICE usually considers a cost-effective use of NHS resources. Therefore, enzalutamide is not recommended in the NHS for treating hormone-relapsed non-metastatic prostate cancer.”²⁸¹



- (Confidential) prices:
 - “The company has a commercial arrangement which would apply if the technology had been recommended.”²⁸¹

Reference Costs (list prices & remarks)	Population, Intervention & comparator IC, IE and ICERs	Remarks on use of generic utility instrument (e.g. EQ- 5D) to measure impact on QoL in economic evaluations	Most uncertain variables or important variables in sensitivity analysis
Enzalutamide			
NICE, TA580 (2019) ²⁸¹	Patients with hormone-relapsed non-metastatic prostate cancer whose disease is at 'high risk' of metastasis.		
Robertson (2018) ²⁸²	Enzalutamide plus androgen deprivation therapy (ADT) or placebo plus ADT.		
List prices, negotiated discounts are hidden. Enzalutamide is administered orally at a dose of 160 mg (4×40 mg soft capsules) daily.	Results of the incremental analysis (with confidential prices): - company's base-case ICER: £28 853 per QALY gained - ERG's base-case ICER: £56 168 per QALY gained Incremental costs and effects are confidential.	EQ-5D data are collected in the underlying PROSPER trial.	OS and HRQoL data Costs and benefits of subsequent treatments.
£2734.67 per 112 capsules (excluding VAT; British national formulary online, accessed December 2018). The daily dose comprises 4 capsules and costs £97.67			



Appendix 11.4.2.3. NICE, TA377 (2016): enzalutamide

- QoL:
 - “The Committee agreed that the model predicted that people having enzalutamide had more time with better utility than people on best supportive care, but it was unclear whether the benefit of delaying chemotherapy had been fully captured by the utility values included in the modelling.”²⁸³
 - “The company measured quality of life using the Functional Assessment of Cancer Therapy – Prostate (FACT-P) and European quality-of-life 5-domain scale (EQ-5D) questionnaires at baseline and again at weeks 5, 13 and then every 12 weeks until disease progression as defined by radiographic evidence or a skeletal-related event. These outcomes were exploratory because they had not been specified in the study protocol. People in both the enzalutamide and placebo arms showed a decrease in FACT-P scores from baseline (meaning a worsening of quality of life). However, the company stated that a 'clinically meaningful deterioration', which it defined as a decrease in FACT-P score of more than 6 points, was seen only in the placebo group. To estimate a treatment effect for enzalutamide relative to placebo, the company produced a mixed repeated measures model to estimate the change from baseline in utility value (derived from EQ-5D) in people who remained on treatment. Over the course of the study, the utility value for people taking enzalutamide was 0.02 higher than for people taking placebo.”²⁸³
 - “As the investigators in PREVAIL collected EQ-5D only from people on treatment (enzalutamide or placebo before chemotherapy) who by definition did not have progressed disease, the company estimated utility values in the progressed health states from the published literature.”²⁸³
 - “The Committee discussed the utility values that had been calculated from EQ-5D data collected in PREVAIL for best supportive care and enzalutamide. It noted that, in PREVAIL, quality of life had decreased over time while people had best supportive care or enzalutamide, but it did so to a lesser extent with enzalutamide.”²⁸³
 - “The Committee agreed that the benefit of delaying chemotherapy may not have been fully captured by the utility values included in the modelling”²⁸³
 - “A mixed model was used to compare differences between treatment arms. The treatment effect on the EQ5D utility favoured enzalutamide at week 61 (LS mean 0.03+/-0.02), but did not reach statistical significance ($p = 0.080$). However, a lower decrease in the VAS score by week 61 was observed for patients treatment with enzalutamide compared to placebo (LS mean: 4.58 +/- 1.39, $p = 0.001$). Time to EQ5D deterioration was also assessed, defined as reduction of 0.14 in utility score, or reduction of 11 points on the VAS score. Median time to deterioration of the utility score was 19.2 months on enzalutamide and 11.1 months on placebo, and $HR = 0.62$ (0.52, 0.73), $p < 0.001$. In the case of the VAS, median time to deterioration was 22.1 months on enzalutamide and 13.8 months on placebo, and $HR = 0.67$ (0.56, 0.80), $p < 0.001$. The treatment effect of enzalutamide over the whole study was analysed using the mixed model and showed a utility gain of 0.02. Data beyond week 61 were not included in the model by the company because of the low numbers in the placebo arm (falling below 10%).”²⁸⁴
- Results:
 - Without patient access scheme (PAS): “The ERG revised base case quite considerably worsens the cost effectiveness estimates. For the comparison of enzalutamide with BSC the company estimate of £78,587 per QALY worsen to £113k per QALY.”²⁸⁴
 - With PAS: “The most plausible ICER for enzalutamide compared with best supportive care was nearer to £31,600 than to £34,800 per QALY gained. The Committee also concluded that enzalutamide is innovative and taking into account factors, which had not been fully accounted for in the modelling, agreed that the ICER for enzalutamide compared with best supportive care was below £30,000 per QALY gained.”²⁸³



- Uncertainty/sensitivity:
 - “There is considerable uncertainty around the modelled survival gains due to the PREVAIL Kaplan Meier overall survival curves being quite incomplete. Whether the extrapolated curves and their tails are realistic representations of what will happen in practice is unclear.”²⁸⁴
 - “The model structure was appropriate in terms of the sequence of treatments people would have in clinical practice in England, but there was uncertainty about whether time spent on treatments after enzalutamide reflected clinical practice. The Committee was concerned that the company had not further checked the validity of the extrapolated data. This was particularly important because of the immaturity of the trial data and because of the small population at risk at the end of the trial follow-up (those who had not died or had been otherwise censored). This meant that a large proportion of the estimated survival benefit was based on the extrapolated period rather than the trial data.”²⁸³
 - “What are the key drivers of cost effectiveness? The data cut-offs from PREVAIL that are used in the modelling and the utility value estimates.”²⁸³
- Conclusions:
 - “The Committee noted that the NICE guide to the methods of technology appraisal states that, if a technology has a most plausible ICER above £30,000 per QALY gained, the Committee will need to identify an increasingly stronger case for supporting the technology as an effective use of NHS resources. The Committee noted that:
 - The company had chosen a conservative parametric distribution to model overall survival, and this reduced the level of uncertainty around the ICER
 - The utility values in the model may not fully capture the benefit to patients of delaying cytotoxic chemotherapy.
 - Enzalutamide provides an active treatment option for some people whose only alternative is best supportive care, and in that respect enzalutamide is a step change in treatment at this point in the treatment pathway.
 - Taking all of these factors into account, the Committee agreed that the ICER for enzalutamide compared with best supportive care would likely fall below £30,000 per QALY gained, and it considered enzalutamide to be a cost-effective use of NHS resources.”²⁸³
- (Confidential) prices:
 - “The company has agreed a patient access scheme with the Department of Health. This is a simple discount to the list price of enzalutamide. The level of the discount is commercial in confidence”²⁸³



Reference Costs (list prices & remarks)	Population, Intervention & comparator IC, IE and ICERs	Remarks on use of generic utility instrument (e.g. EQ- 5D) to measure impact on QoL in economic evaluations	Most uncertain variables or important variables in sensitivity analysis																																				
Enzalutamide																																							
NICE, TA377 (2016) ²⁸³ Robertson (2015) ²⁸⁴	Patients with metastatic hormone-relapsed prostate cancer who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy, before chemotherapy is indicated. Enzalutamide compared with best supportive care (BSC).																																						
List prices, negotiated discounts are hidden. The cost (list price) of enzalutamide is £2734.67 for a 112-capsule pack of 40 mg enzalutamide. The daily dose of enzalutamide is 160 mg and costs £97.67 per day.	Results of the incremental analysis (without patient access scheme): A) Company deterministic base case (exclusive PAS): <table><tr><td></td><td>Costs</td><td>IC</td><td>QALYs</td><td>IE</td><td>ICER</td></tr><tr><td>BSC</td><td>£36 296</td><td></td><td>1.657</td><td></td><td></td></tr><tr><td>Enzalutamide</td><td>£84 840</td><td>£48 543</td><td>2.274</td><td>0.618</td><td>£78 587</td></tr></table> B) ERG revised base case (exclusive PAS): <table><tr><td></td><td>Costs</td><td>IC</td><td>QALYs</td><td>IE</td><td>ICER</td></tr><tr><td>BSC</td><td>£37 309</td><td></td><td>1.672</td><td></td><td></td></tr><tr><td>Enzalutamide</td><td>£98 420</td><td>£61 110</td><td>2.213</td><td>0.541</td><td>£112 878</td></tr></table> Results of the incremental analysis (with patient access scheme): <ul style="list-style-type: none">- Including the ERG assumptions on luteinising hormone-releasing hormone analogue, docetaxel and outpatient costs and monitoring, but keeping the company's assumption on post-docetaxel utility values, resulted in an ICER of £31,579 per QALY gained.- Applying the two-stage method, including the ERG's assumptions on luteinising hormone-releasing hormone analogue, docetaxel and outpatient costs and monitoring, but keeping the company's assumption on post-docetaxel utility value resulted in an ICER of £34,759 per QALY gained. Remark: The company did not present the comparison between enzalutamide and abiraterone with its new PAS because the Committee had concluded in a previous meeting that best supportive care was the key comparator to enzalutamide.		Costs	IC	QALYs	IE	ICER	BSC	£36 296		1.657			Enzalutamide	£84 840	£48 543	2.274	0.618	£78 587		Costs	IC	QALYs	IE	ICER	BSC	£37 309		1.672			Enzalutamide	£98 420	£61 110	2.213	0.541	£112 878	EQ-5D data are collected in the underlying PREVAIL trial.	OS & extrapolation HRQoL
	Costs	IC	QALYs	IE	ICER																																		
BSC	£36 296		1.657																																				
Enzalutamide	£84 840	£48 543	2.274	0.618	£78 587																																		
	Costs	IC	QALYs	IE	ICER																																		
BSC	£37 309		1.672																																				
Enzalutamide	£98 420	£61 110	2.213	0.541	£112 878																																		



Appendix 11.4.2.4. NICE, TA316 (2014): enzalutamide

- QoL:
 - “or health-related quality of life, investigators collected data during AFFIRM using the EQ-5D and Functional Assessment of Cancer Therapy-Prostate (FACT-P) questionnaires. However, EQ-5D utility data were collected only at study sites in France, Germany, Italy, Spain and the UK. In total, 179 patients provided EQ-5D data (15.8% and 13.3% of patients randomised to enzalutamide and placebo respectively).”²⁸⁵
 - “Because a limited number of patients completed the EQ-5D questionnaire, the manufacturer used a mapping algorithm to transform the FACT-P responses into EQ-5D data. However, because mapping utility values introduces uncertainty, the manufacturer used the EQ-5D data collected from AFFIRM in the model, and applied the mapped values only when it considered the number of EQ-5D responses insufficient. The manufacturer derived the EQ-5D utility values by applying UK valuations of health states estimated using the time trade-off method. For the baseline utility value in the model, the manufacturer presented the EQ-5D value collected from the trial and the mapped value (both are academic in confidence), but used the former because it considered the sample size to be reasonable (n=209).”²⁸⁵
 - “For the decrease in utility associated with disease progression, the manufacturer derived a value from a published study, Sandblom et al. (2004), because no health-related quality-of-life data were collected in AFFIRM after a patient's disease had progressed.”²⁸⁵
- Results:
 - “For patients who had received 1 course of cytotoxic chemotherapy, the Committee noted that the analysis reflecting its preferred assumptions, but not the actual patient access scheme discount for abiraterone, gave an incremental cost effectiveness ratio (ICER) of £22,600 per quality-adjusted life year (QALY) gained for enzalutamide compared with abiraterone. The Committee accepted that this ICER was associated with uncertainty but, on balance, it was satisfied that it would remain below £30,000 per QALY gained. The Committee noted that taking into account the correct patient access scheme for abiraterone would not change its conclusion.
 - For patients who had received 2 or more courses of chemotherapy, the Committee noted that the ICERs for enzalutamide compared with best supportive care were between £45,500 and £48,000 per QALY gained. The Committee agreed that enzalutamide would be considered an end-of-life treatment as defined by NICE for this subgroup and that the magnitude of the additional weight that would need to be assigned to the QALY benefits would justify enzalutamide being recommended as a cost-effective use of NHS resources.”²⁸⁵
- Uncertainty/sensitivity:
 - “The ERG agreed that, given the uncertainty around mapping utility values, it was appropriate for the manufacturer to have chosen the baseline EQ-5D utility value collected from AFFIRM. However, the ERG regarded this value as uncertain, because only a small proportion of patients completed the EQ-5D questionnaire (209 out of 1199 patients) and of those, a considerable proportion had missing values.”²⁸⁵
 - “The manufacturer stated that, compared with abiraterone or best supportive care, the cost effectiveness of enzalutamide was most sensitive to the hazard ratios for overall survival and treatment discontinuation, and the degree to which health-related quality of life improved while taking enzalutamide or abiraterone (that is, the degree to which utility increased 'on-treatment').”²⁸⁵
- Conclusions:



- “End-of-life considerations
- The Committee considered the subgroup of patients who had received 2 or more courses of cytotoxic chemotherapy under the 'end-of-life' criteria.
- The Committee concluded that enzalutamide fulfilled the criterion for short life expectancy. ...
- the Committee was satisfied that enzalutamide was likely to extend life by more than 3 months in the subgroup. It therefore concluded that enzalutamide fulfilled the criterion for life extension.
- The Committee concluded that enzalutamide fulfilled the criterion for small patient populations and would be considered an end-of-life treatment as defined by NICE for patients who have previously received 2 or more cytotoxic chemotherapy regimens.”²⁸⁵
- “The Committee agreed that taking into account the correct patient access scheme for abiraterone would not change its conclusion. It therefore concluded that enzalutamide could be recommended as an option for treating hormone-relapsed metastatic prostate cancer in adults whose disease has progressed during or after 1 docetaxel-containing cytotoxic chemotherapy regimen, only if the manufacturer provides enzalutamide with the discount agreed in the patient access scheme.”²⁸⁵
- (Confidential) prices:
 - “The manufacturer of enzalutamide has agreed a patient access scheme with the Department of Health. This scheme provides a simple discount to the price listed above, with the discount applied at the point of purchase or invoice. The level of the discount is commercial in confidence.”²⁸⁵
 - “The Committee discussed the estimates of costs and resource use chosen by the manufacturer. It noted that the manufacturer had to assume the patient access scheme discount for abiraterone in the model because the discount is commercial in confidence, and was not provided by the manufacturer of abiraterone for this appraisal. The Committee would have preferred a situation in which the manufacturer of enzalutamide could have applied the actual discount for abiraterone in its economic model. The Committee acknowledged that both the manufacturer and the ERG provided sensitivity analyses varying the discount in the model.”²⁸⁵



Reference Costs (list prices & remarks)	Population, Intervention & comparator IC, IE and ICERs	Remarks on use of generic utility instrument (e.g. EQ- 5D) to measure impact on QoL in economic evaluations	Most uncertain variables or important variables in sensitivity analysis
Enzalutamide			
NICE, TA316 (2014) ²⁸⁵	Patients with metastatic hormone-relapsed prostate cancer previously treated with a docetaxel-containing regimen. Enzalutamide, compared with abiraterone and with best supportive care (BSC).		
List prices, negotiated discounts are hidden. Enzalutamide costs £2734.67 for 1 pack of 112 40-mg capsules, (excluding VAT; 'British national formulary' [BNF] website accessed March 2014). Assuming a daily dose of 160 mg and a mean length of treatment of 8.5 months, the manufacturer estimated that the average cost of treatment with enzalutamide, based on the list price, is £25 269.	Results of the incremental analysis (with patient access scheme (PAS) for enzalutamide, but without PAS for the comparator): - Enzalutamide compared with abiraterone: £22 604 per QALY gained. - Enzalutamide compared with best supportive care: £45 898 per QALY gained.	EQ-5D data are collected in the underlying AFFIRM trial (but only for a limited number of patients and not after disease progression).	Overall survival Treatment discontinuation Health-related quality of life



APPENDIX 12. RENAL CELL CARCINOMA (RCC)

Appendix 12.1. BCR data

Appendix 12.1.1. Descriptive statistics

Appendix 12.1.1.1. Renal Cell Carcinoma, exploration

Table 177 – Renal cell carcinoma (2004-2017): Frequency table of patient and tumour characteristics

Characteristic	Incidence period			
	Total	2004-2008	2009-2013	2014-2017
Overall	19,607	6,404	7,153	6,050
Gender				
Male	12,555 (64.0)	4,011 (62.6)	4,567 (63.8)	3,977 (65.7)
Female	7,052 (36.0)	2,393 (37.4)	2,586 (36.2)	2,073 (34.3)
Age at diagnosis (year)				
<50 years	2,189 (11.2)	719 (11.2)	813 (11.4)	657 (10.9)
50-59 years	3,764 (19.2)	1,260 (19.7)	1,373 (19.2)	1,131 (18.7)
60-69 years	5,820 (29.7)	1,764 (27.5)	2,170 (30.3)	1,886 (31.2)
70-79 years	5,696 (29.1)	2,013 (31.4)	1,986 (27.8)	1,697 (28.0)
80+ years	2,138 (10.9)	648 (10.1)	811 (11.3)	679 (11.2)
WHO - Performance Status				
0 – Asymptomatic	5,978 (30.5)	1,410 (22.0)	2,419 (33.8)	2,149 (35.5)
1 – Symptomatic but completely ambulatory	7,096 (36.2)	1,741 (27.2)	2,860 (40.0)	2,495 (41.2)
2 – Symptomatic, <50% in bed during the day	665 (3.4)	237 (3.7)	222 (3.1)	206 (3.4)
3 – Symptomatic, >50% in bed, but not bedbound	166 (0.8)	59 (0.9)	68 (1.0)	39 (0.6)
4 – Bedbound	53 (0.3)	14 (0.2)	24 (0.3)	15 (0.2)
Not reported	5,649 (28.8)	2,943 (46.0)	1,560 (21.8)	1,146 (18.9)
Combined stage				



I	10,162 (51.8)	2,764 (43.2)	3,876 (54.2)	3,522 (58.2)
II	1,898 (9.7)	667 (10.4)	701 (9.8)	530 (8.8)
III	3,103 (15.8)	993 (15.5)	1,137 (15.9)	973 (16.1)
IV	2,681 (13.7)	926 (14.5)	934 (13.1)	821 (13.6)
X	1,763 (9.0)	1,054 (16.5)	505 (7.1)	204 (3.4)

Note: the values between parentheses are column percentages.

Table 178 – Renal cell carcinoma (2004-2017): Frequency table of patient and tumour characteristics (cut-off point: 2006)

Characteristic	Incidence period		
	Total	2004-2005	2007-2017
Overall	18 332	2 462	15 870
Gender			
Male	11 761 (64.2)	1 513 (61.5)	10 248 (64.6)
Female	6 571 (35.8)	949 (38.5)	5 622 (35.4)
Age at diagnosis (year)			
<50 years	2 053 (11.2)	291 (11.8)	1 762 (11.1)
50-59 years	3 513 (19.2)	485 (19.7)	3 028 (19.1)
60-69 years	5 475 (29.9)	686 (27.9)	4 789 (30.2)
70-79 years	5 292 (28.9)	770 (31.3)	4 522 (28.5)
80+ years	1 999 (10.9)	230 (9.3)	1 769 (11.1)
WHO - Performance Status			
0 – Asymptomatic	5 754 (31.4)	476 (19.3)	5 278 (33.3)
1 – Symptomatic but completely ambulatory	6 769 (36.9)	641 (26.0)	6 128 (38.6)
2 – Symptomatic, <50% in bed during the day	583 (3.2)	66 (2.7)	517 (3.3)
3 – Symptomatic, >50% in bed, but not bedbound	145 (0.8)	22 (0.9)	123 (0.8)
4 – Bedbound	51 (0.3)	6 (0.2)	45 (0.3)
Not reported	5 030 (27.4)	1 251 (50.8)	3 779 (23.8)
Combined stage			



I	9 608 (52.4)	988 (40.1)	8 620 (54.3)
II	1 792 (9.8)	273 (11.1)	1 519 (9.6)
III	2 914 (15.9)	377 (15.3)	2 537 (16.0)
IV	2 496 (13.6)	351 (14.3)	2 145 (13.5)
X	1 522 (8.3)	473 (19.2)	1 049 (6.6)

Note: the values between parentheses are column percentages.

Table 179 – Renal cell carcinoma (2004-2017), Combined stage I, Frequency table of patient and tumour characteristics

Characteristic	Total	Incidence period		
		2004-2008	2009-2013	2014-2017
Overall	10,162	2,764	3,876	3,522
Gender				
Male	6,361 (62.6)	1,665 (60.2)	2,424 (62.5)	2,272 (64.5)
Female	3,801 (37.4)	1,099 (39.8)	1,452 (37.5)	1,250 (35.5)
Age at diagnosis (year)				
<50 years	1,355 (13.3)	368 (13.3)	528 (13.6)	459 (13.0)
50-59 years	2,105 (20.7)	589 (21.3)	815 (21.0)	701 (19.9)
60-69 years	3,006 (29.6)	752 (27.2)	1,172 (30.2)	1,082 (30.7)
70-79 years	2,813 (27.7)	820 (29.7)	1,034 (26.7)	959 (27.2)
80+ years	883 (8.7)	235 (8.5)	327 (8.4)	321 (9.1)
WHO - Performance Status				
0 – Asymptomatic	4,000 (39.4)	826 (29.9)	1,644 (42.4)	1,530 (43.4)
1 – Symptomatic but completely ambulatory	3,265 (32.1)	663 (24.0)	1,348 (34.8)	1,254 (35.6)
2 – Symptomatic, <50% in bed during the day	176 (1.7)	54 (2.0)	61 (1.6)	61 (1.7)
3 – Symptomatic, >50% in bed, but not bedbound	34 (0.3)	15 (0.5)	18 (0.5)	1 (0.0)
4 – Bedbound	15 (0.1)	2 (0.1)	5 (0.1)	8 (0.2)
Not reported	2,672 (26.3)	1,204 (43.6)	800 (20.6)	668 (19.0)

Note: the values between parentheses are column percentages.



Table 180 – Renal cell carcinoma (2004-2017), Combined stage I, Frequency table of patient and tumour characteristics (cut-off point: 2006)

Characteristic	Total	Incidence period	
		2004-2005	2007-2017
Overall	9 608	988	8 620
Gender			
Male	6 031 (62.8)	608 (61.5)	5 423 (62.9)
Female	3 577 (37.2)	380 (38.5)	3 197 (37.1)
Age at diagnosis (year)			
<50 years	1 293 (13.5)	141 (14.3)	1 152 (13.4)
50-59 years	1 982 (20.6)	208 (21.1)	1 774 (20.6)
60-69 years	2 856 (29.7)	268 (27.1)	2 588 (30.0)
70-79 years	2 654 (27.6)	293 (29.7)	2 361 (27.4)
80+ years	823 (8.6)	78 (7.9)	745 (8.6)
WHO - Performance Status			
0 – Asymptomatic	3 869 (40.3)	267 (27.0)	3 602 (41.8)
1 – Symptomatic but completely ambulatory	3 113 (32.4)	232 (23.5)	2 881 (33.4)
2 – Symptomatic, <50% in bed during the day	153 (1.6)	12 (1.2)	141 (1.6)
3 – Symptomatic, >50% in bed, but not bedbound	29 (0.3)	5 (0.5)	24 (0.3)
4 – Bedbound	14 (0.1)	1 (0.1)	13 (0.2)
Not reported	2 430 (25.3)	471 (47.7)	1 959 (22.7)

Note: the values between parentheses are column percentages.

**Table 181 – Renal cell carcinoma (2004-2017), Combined stage II, Frequency table of patient and tumour characteristics**

Characteristic	Incidence period			
	Total	2004-2008	2009-2013	2014-2017
Overall	1,898	667	701	530
Gender				
Male	1,221 (64.3)	443 (66.4)	429 (61.2)	349 (65.8)
Female	677 (35.7)	224 (33.6)	272 (38.8)	181 (34.2)
Age at diagnosis (year)				
<50 years	245 (12.9)	81 (12.1)	88 (12.6)	76 (14.3)
50-59 years	390 (20.5)	131 (19.6)	141 (20.1)	118 (22.3)
60-69 years	568 (29.9)	186 (27.9)	221 (31.5)	161 (30.4)
70-79 years	482 (25.4)	201 (30.1)	168 (24.0)	113 (21.3)
80+ years	213 (11.2)	68 (10.2)	83 (11.8)	62 (11.7)
WHO - Performance Status				
0 – Asymptomatic	591 (31.1)	190 (28.5)	215 (30.7)	186 (35.1)
1 – Symptomatic but completely ambulatory	788 (41.5)	215 (32.2)	337 (48.1)	236 (44.5)
2 – Symptomatic, <50% in bed during the day	59 (3.1)	20 (3.0)	23 (3.3)	16 (3.0)
3 – Symptomatic, >50% in bed, but not bedbound	8 (0.4)	3 (0.4)	4 (0.6)	1 (0.2)
4 – Bedbound	3 (0.2)	1 (0.1)	2 (0.3)	0 (0.0)
Not reported	449 (23.7)	238 (35.7)	120 (17.1)	91 (17.2)

Note: the values between parentheses are column percentages.

Table 182 – Renal cell carcinoma (2004-2017), Combined stage II, Frequency table of patient and tumour characteristics (cut-off point: 2006)

Characteristic	Incidence period		
	Total	2004-2005	2007-2017
Overall	1 792	273	1 519
Gender			
Male	1 146 (64.0)	177 (64.8)	969 (63.8)



Female	646 (36.0)	96 (35.2)	550 (36.2)
Age at diagnosis (year)			
<50 years	235 (13.1)	33 (12.1)	202 (13.3)
50-59 years	368 (20.5)	55 (20.1)	313 (20.6)
60-69 years	544 (30.4)	76 (27.8)	468 (30.8)
70-79 years	444 (24.8)	86 (31.5)	358 (23.6)
80+ years	201 (11.2)	23 (8.4)	178 (11.7)
WHO - Performance Status			
0 – Asymptomatic	566 (31.6)	79 (28.9)	487 (32.1)
1 – Symptomatic but completely ambulatory	756 (42.2)	86 (31.5)	670 (44.1)
2 – Symptomatic, <50% in bed during the day	55 (3.1)	6 (2.2)	49 (3.2)
3 – Symptomatic, >50% in bed, but not bedbound	6 (0.3)	0 (0.0)	6 (0.4)
4 – Bedbound	3 (0.2)	0 (0.0)	3 (0.2)
Not reported	406 (22.7)	102 (37.4)	304 (20.0)

Note: the values between parentheses are column percentages.


Table 183 – Renal cell carcinoma (2004-2017), Combined stage III, Frequency table of patient and tumour characteristics

Characteristic	Incidence period			
	Total	2004-2008	2009-2013	2014-2017
Overall	3,103	993	1,137	973
Gender				
Male	2,081 (67.1)	655 (66.0)	759 (66.8)	667 (68.6)
Female	1,022 (32.9)	338 (34.0)	378 (33.2)	306 (31.4)
Age at diagnosis (year)				
<50 years	221 (7.1)	83 (8.4)	77 (6.8)	61 (6.3)
50-59 years	491 (15.8)	163 (16.4)	177 (15.6)	151 (15.5)
60-69 years	947 (30.5)	278 (28.0)	359 (31.6)	310 (31.9)
70-79 years	993 (32.0)	342 (34.4)	337 (29.6)	314 (32.3)
80+ years	451 (14.5)	127 (12.8)	187 (16.4)	137 (14.1)
WHO - Performance Status				
0 – Asymptomatic	829 (26.7)	213 (21.5)	349 (30.7)	267 (27.4)
1 – Symptomatic but completely ambulatory	1,333 (43.0)	341 (34.3)	517 (45.5)	475 (48.8)
2 – Symptomatic, <50% in bed during the day	106 (3.4)	29 (2.9)	42 (3.7)	35 (3.6)
3 – Symptomatic, >50% in bed, but not bedbound	18 (0.6)	5 (0.5)	8 (0.7)	5 (0.5)
4 – Bedbound	8 (0.3)	2 (0.2)	3 (0.3)	3 (0.3)
Not reported	809 (26.1)	403 (40.6)	218 (19.2)	188 (19.3)

Note: the values between parentheses are column percentages.

Table 184 – Renal cell carcinoma (2004-2017), Combined stage III, Frequency table of patient and tumour characteristics (cut-off point: 2006)

Characteristic	Incidence period		
	Total	2004-2005	2007-2017
Overall	2 914	377	2 537
Gender			
Male	1 958 (67.2)	237 (62.9)	1 721 (67.8)



Female	956 (32.8)	140 (37.1)	816 (32.2)
Age at diagnosis (year)			
<50 years	200 (6.9)	41 (10.9)	159 (6.3)
50-59 years	461 (15.8)	65 (17.2)	396 (15.6)
60-69 years	893 (30.6)	113 (30.0)	396 (30.7)
70-79 years	934 (32.1)	119 (31.6)	815 (32.1)
80+ years	426 (14.6)	39 (10.3)	387 (15.3)
WHO - Performance Status			
0 – Asymptomatic	790 (27.1)	75 (19.9)	715 (28.2)
1 – Symptomatic but completely ambulatory	1 275 (43.8)	122 (32.4)	1 153 (45.4)
2 – Symptomatic, <50% in bed during the day	93 (3.2)	6 (1.6)	87 (3.4)
3 – Symptomatic, >50% in bed, but not bedbound	15 (0.5)	2 (0.5)	13 (0.5)
4 – Bedbound	8 (0.3)	1 (0.3)	7 (0.3)
Not reported	733 (25.2)	171 (45.4)	562 (22.2)

Note: the values between parentheses are column percentages.

**Table 185 – Renal cell carcinoma (2004-2017), Combined stage IV, Frequency table of patient and tumour characteristics**

Characteristic	Incidence period			
	Total	2004-2008	2009-2013	2014-2017
Overall	2,681	926	934	821
Gender				
Male	1,774 (66.2)	595 (64.3)	627 (67.1)	552 (67.2)
Female	907 (33.8)	331 (35.7)	307 (32.9)	269 (32.8)
Age at diagnosis (year)				
<50 years	175 (6.5)	68 (7.3)	63 (6.7)	44 (5.4)
50-59 years	496 (18.5)	183 (19.8)	173 (18.5)	140 (17.1)
60-69 years	825 (30.8)	269 (29.0)	290 (31.0)	266 (32.4)
70-79 years	845 (31.5)	316 (34.1)	278 (29.8)	251 (30.6)
80+ years	340 (12.7)	90 (9.7)	130 (13.9)	120 (14.6)
WHO - Performance Status				
0 – Asymptomatic	402 (15.0)	133 (14.4)	146 (15.6)	123 (15.0)
1 – Symptomatic but completely ambulatory	1,512 (56.4)	455 (49.1)	567 (60.7)	490 (59.7)
2 – Symptomatic, <50% in bed during the day	292 (10.9)	123 (13.3)	83 (8.9)	86 (10.5)
3 – Symptomatic, >50% in bed, but not bedbound	91 (3.4)	31 (3.3)	32 (3.4)	28 (3.4)
4 – Bedbound	23 (0.9)	8 (0.9)	11 (1.2)	4 (0.5)
Not reported	361 (13.5)	176 (19.0)	95 (10.2)	90 (11.0)

Note: the values between parentheses are column percentages.

Table 186 – Renal cell carcinoma (2004-2017), Combined stage IV, Frequency table of patient and tumour characteristics (cut-off point: 2006)

Characteristic	Incidence period		
	Total	2004-2005	2007-2017
Overall	2 496	351	2 145
Gender			
Male	1 655 (66.3)	212 (60.4)	1 443 (67.3)



Female	841 (33.7)	139 (39.6)	702 (32.7)
Age at diagnosis (year)			
<50 years	161 (6.5)	24 (6.8)	137 (6.4)
50-59 years	465 (18.6)	71 (20.2)	394 (18.4)
60-69 years	770 (30.8)	100 (28.5)	670 (31.2)
70-79 years	771 (30.9)	122 (34.8)	649 (30.3)
80+ years	329 (13.2)	34 (9.7)	295 (13.8)
WHO - Performance Status			
0 – Asymptomatic	380 (15.2)	43 (12.3)	337 (15.7)
1 – Symptomatic but completely ambulatory	1 439 (57.7)	177 (50.4)	1 262 (58.8)
2 – Symptomatic, <50% in bed during the day	252 (10.1)	39 (11.1)	213 (9.9)
3 – Symptomatic, >50% in bed, but not bedbound	82 (3.3)	12 (3.4)	70 (3.3)
4 – Bedbound	22 (0.9)	3 (0.9)	19 (0.9)
Not reported	321 (12.9)	77 (21.9)	244 (11.4)

Note: the values between parentheses are column percentages.



Appendix 12.1.1.2. Renal cell carcinoma, Observed and Relative Survival graphs

Renal Cell Carcinoma (2004-2017)

Figure 331 – Renal cell carcinoma (2004-2017), Kaplan-Meier graphs observed survival by incidence period

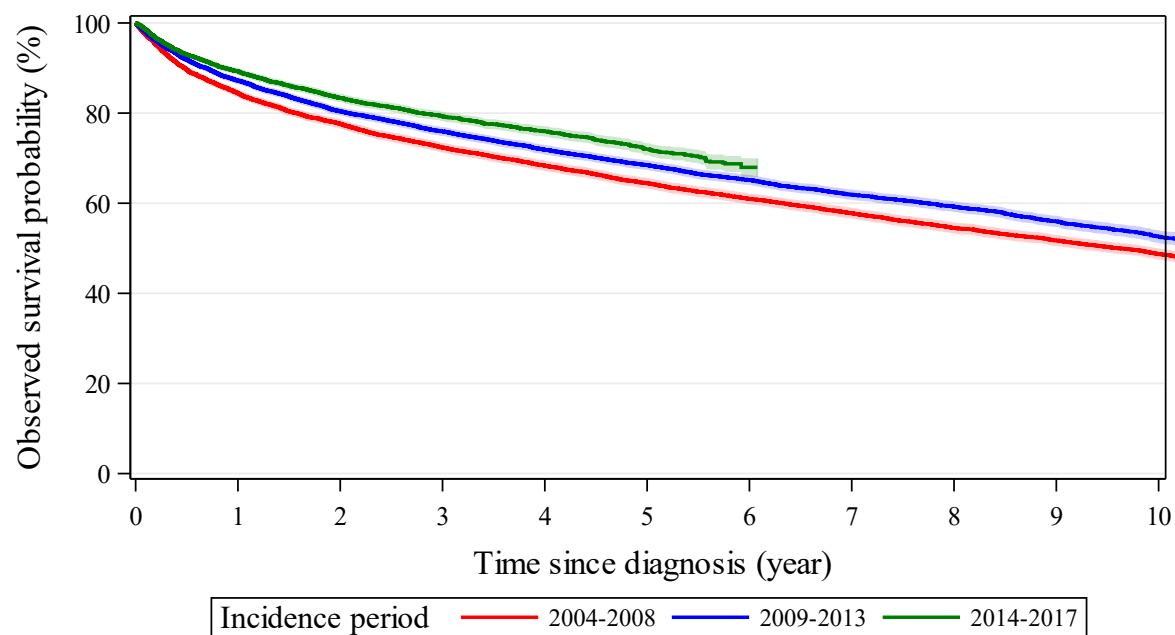




Figure 332 – Renal cell carcinoma (2004-2017), Kaplan-Meier graphs observed survival by incidence period (cut-off point: 2006)

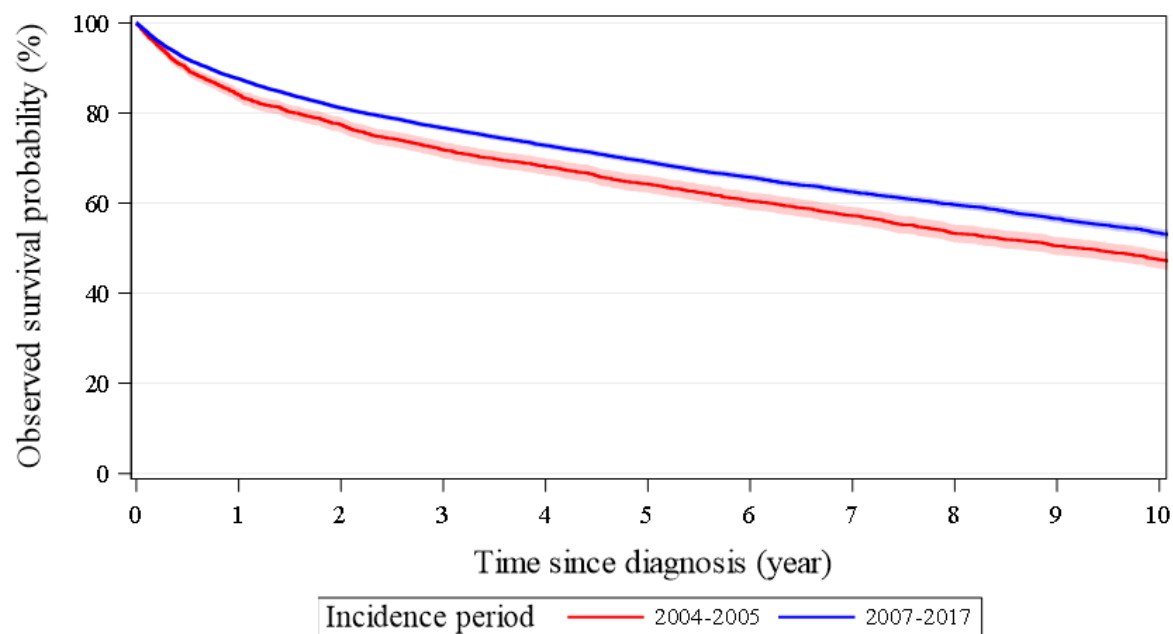




Figure 333 – Renal cell carcinoma (2004-2017), relative survival graphs by incidence period

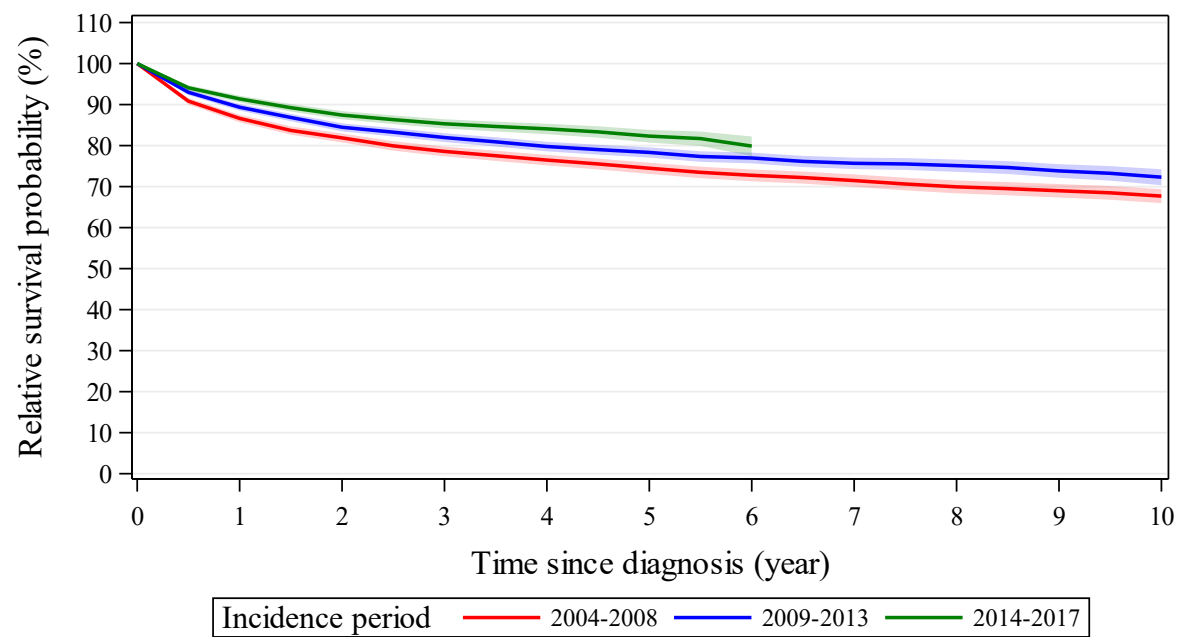
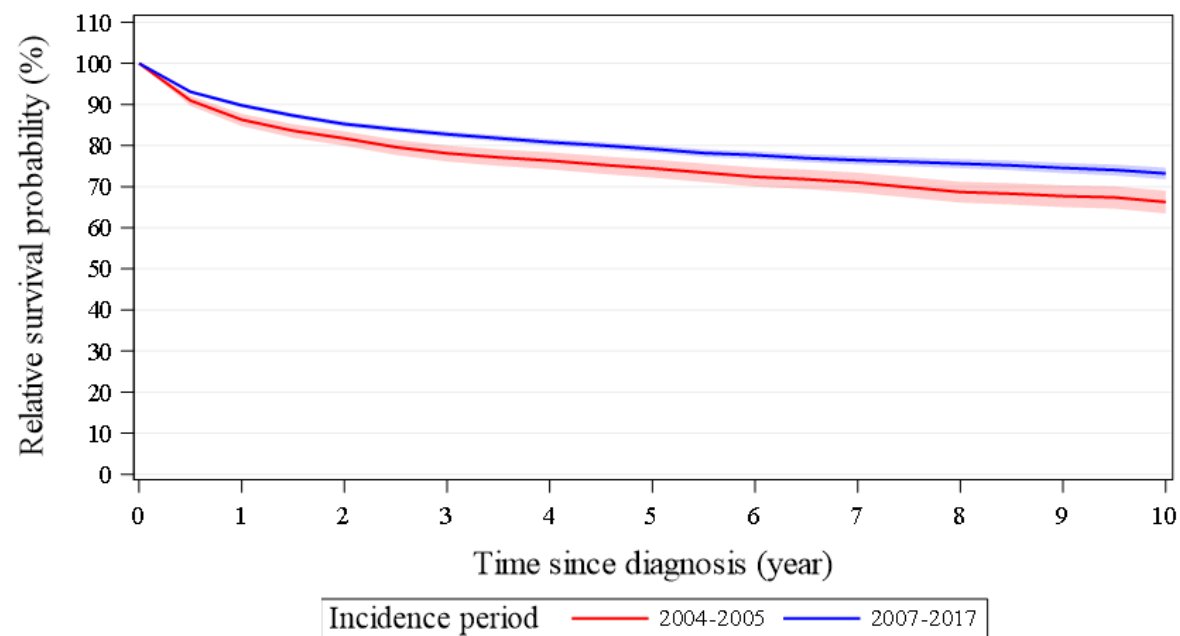




Figure 334 – Renal cell carcinoma (2004-2017), relative survival graphs by incidence period (cut-off point: 2006)



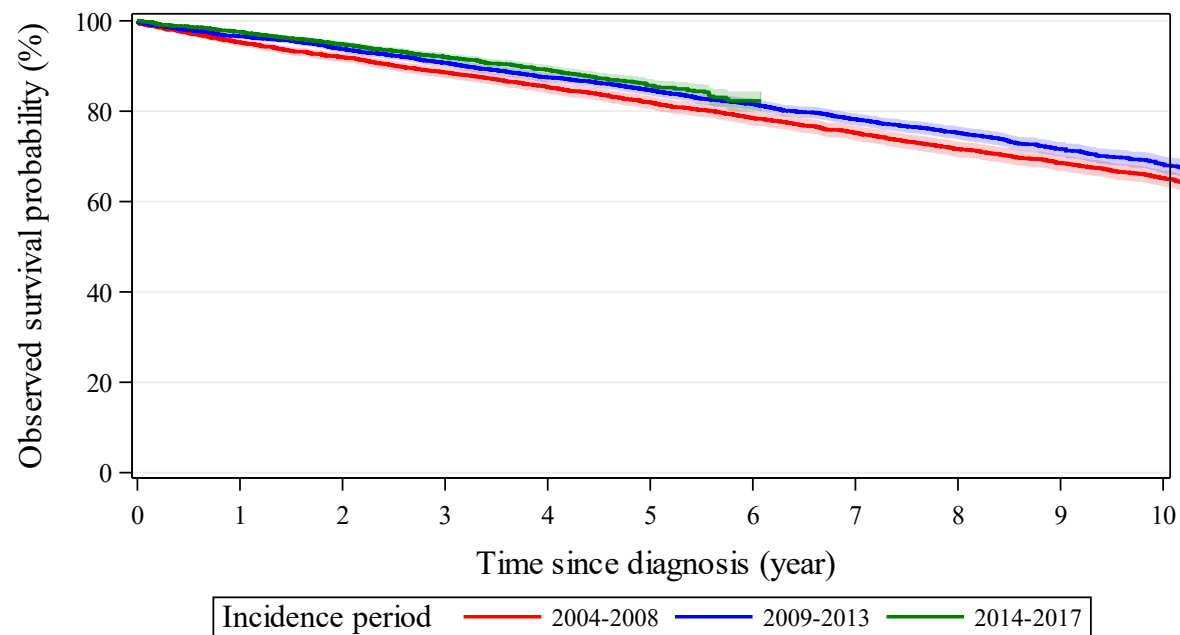
**Renal Cell Carcinoma, combined stage I (2004-2017)****Figure 335 – Renal cell carcinoma (2004-2017), combined stage I, Kaplan-Meier graphs observed survival by incidence period**



Figure 336 – Renal cell carcinoma (2004-2017), combined stage I, Kaplan-Meier graphs observed survival by incidence period (cut-off point: 2006)

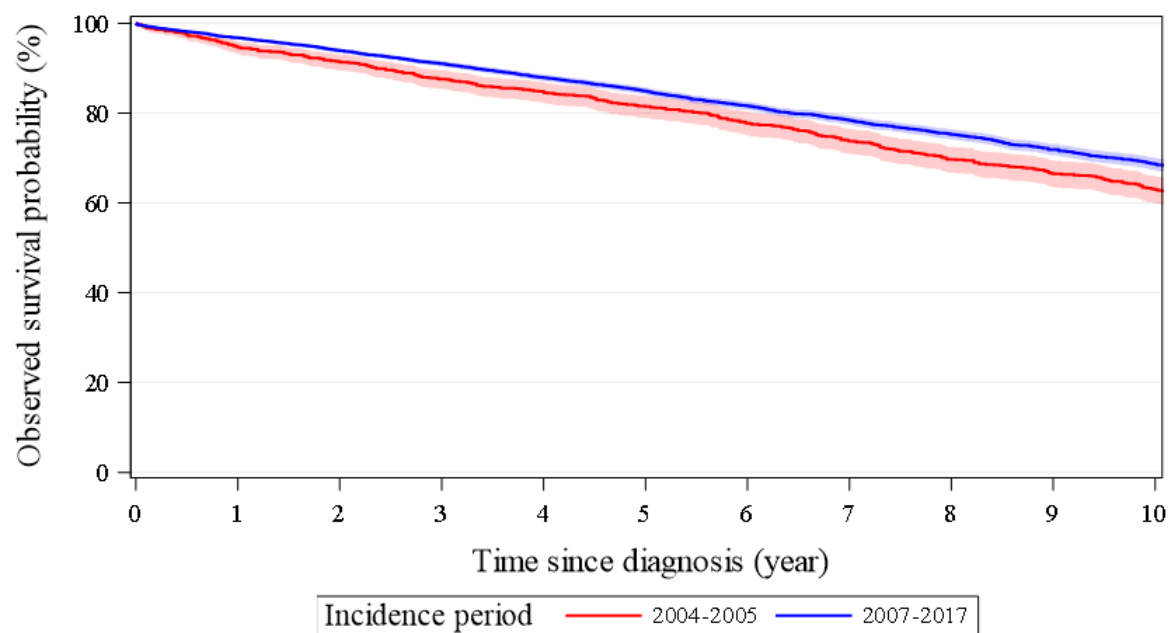




Figure 337 – Renal cell carcinoma (2004-2017), combined stage I, relative survival graphs by incidence period

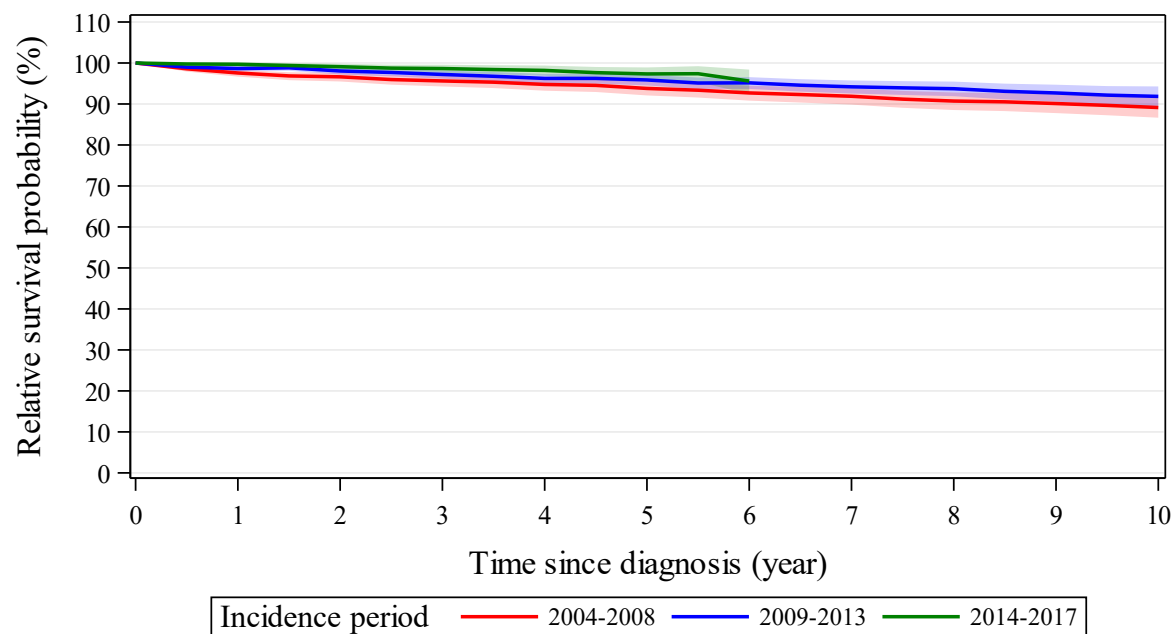
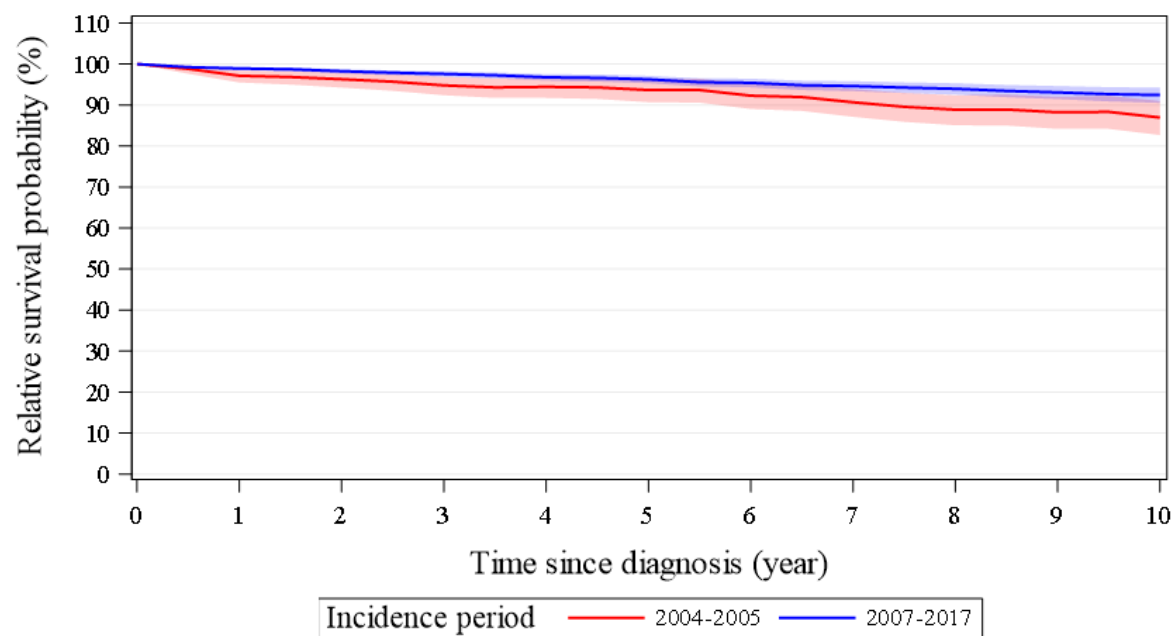




Figure 338 – Renal cell carcinoma (2004-2017), combined stage I, relative survival graphs by incidence period (cut-off point: 2006)



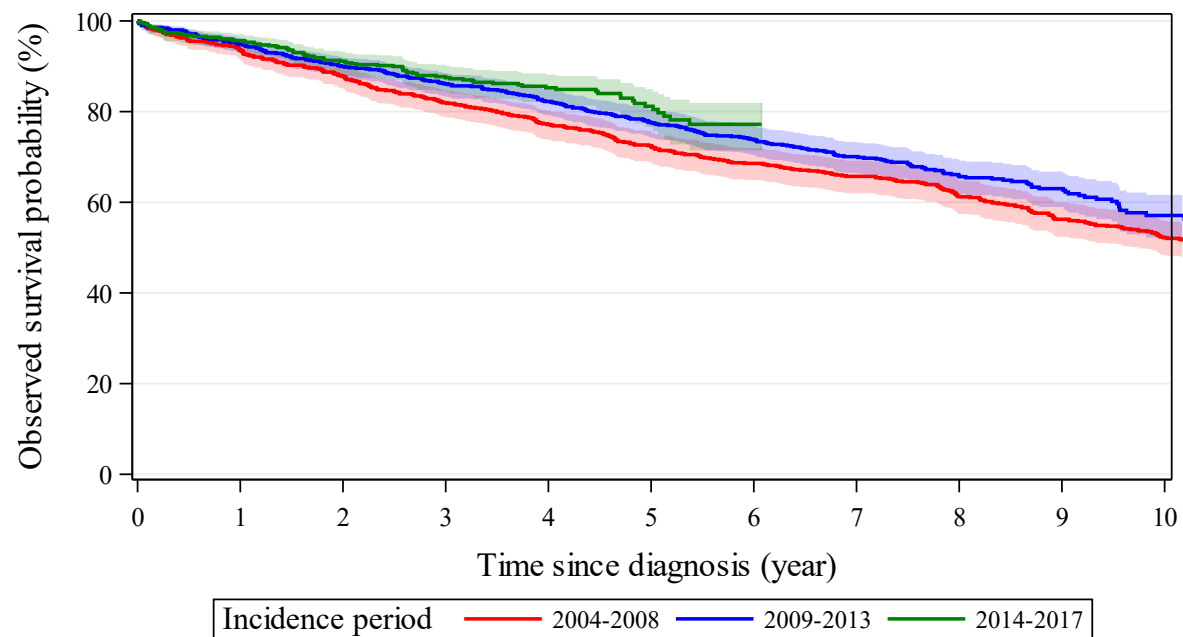
**Renal Cell Carcinoma, combined stage II (2004-2017)****Figure 339 – Renal cell carcinoma (2004-2017), combined stage II, Kaplan-Meier graphs observed survival by incidence period**



Figure 340 – Renal cell carcinoma (2004-2017), combined stage II, Kaplan-Meier graphs observed survival by incidence period (cut-off point: 2006)

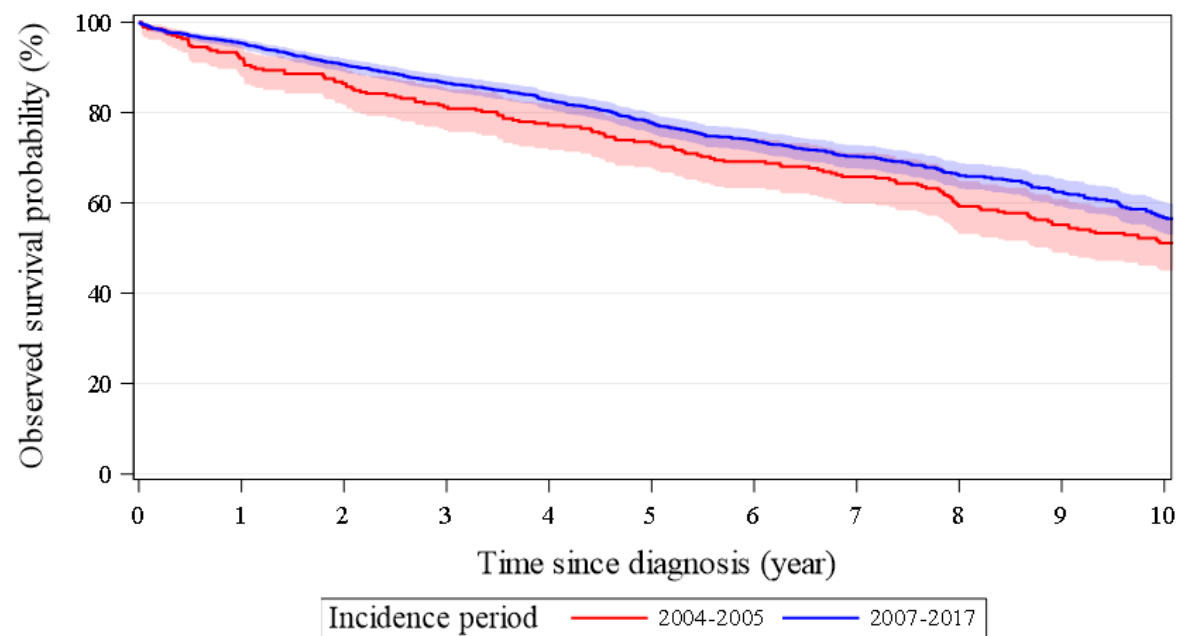




Figure 341 – Renal cell carcinoma (2004-2017), combined stage II, relative survival graphs by incidence period

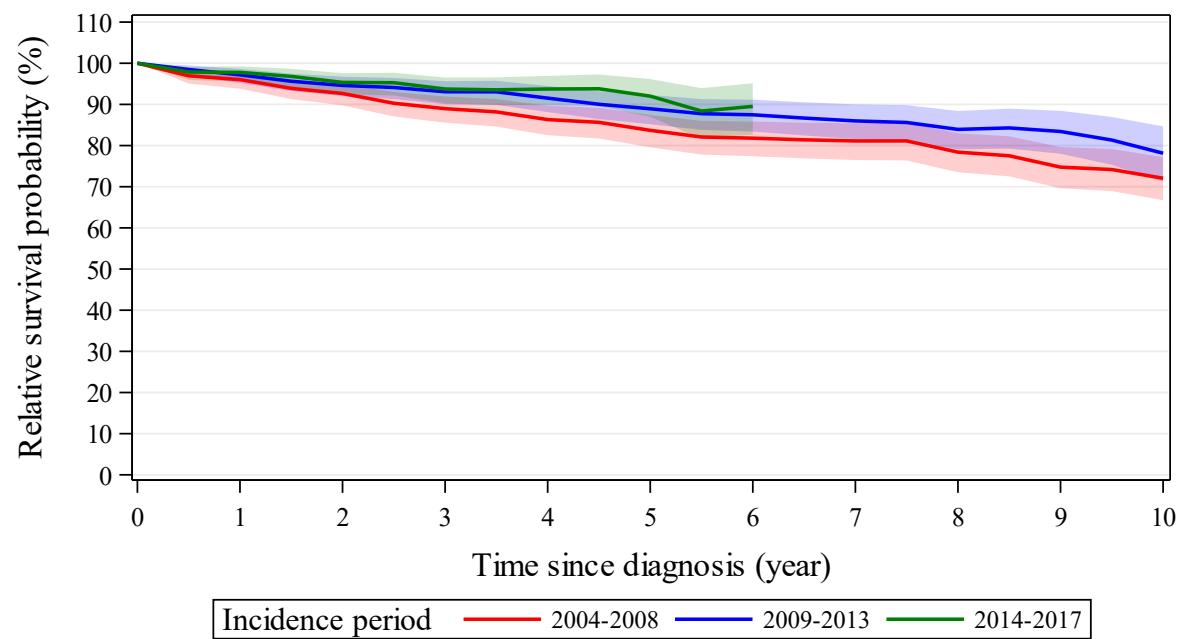
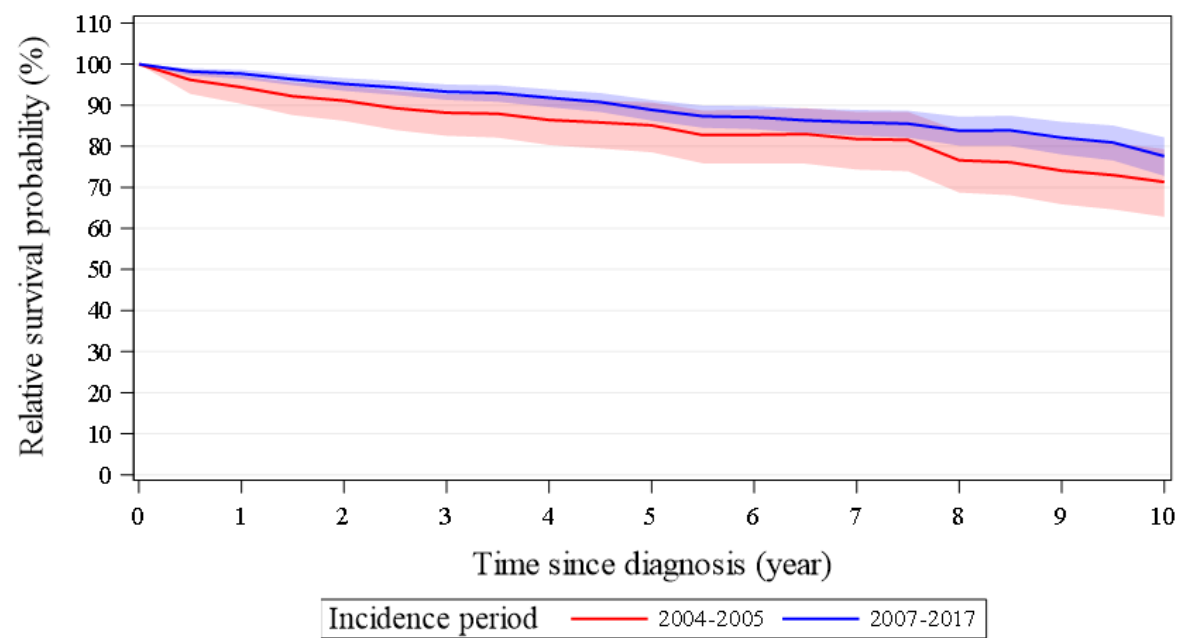




Figure 342 – Renal cell carcinoma (2004-2017), combined stage II, relative survival graphs by incidence period (cut-off point: 2006)



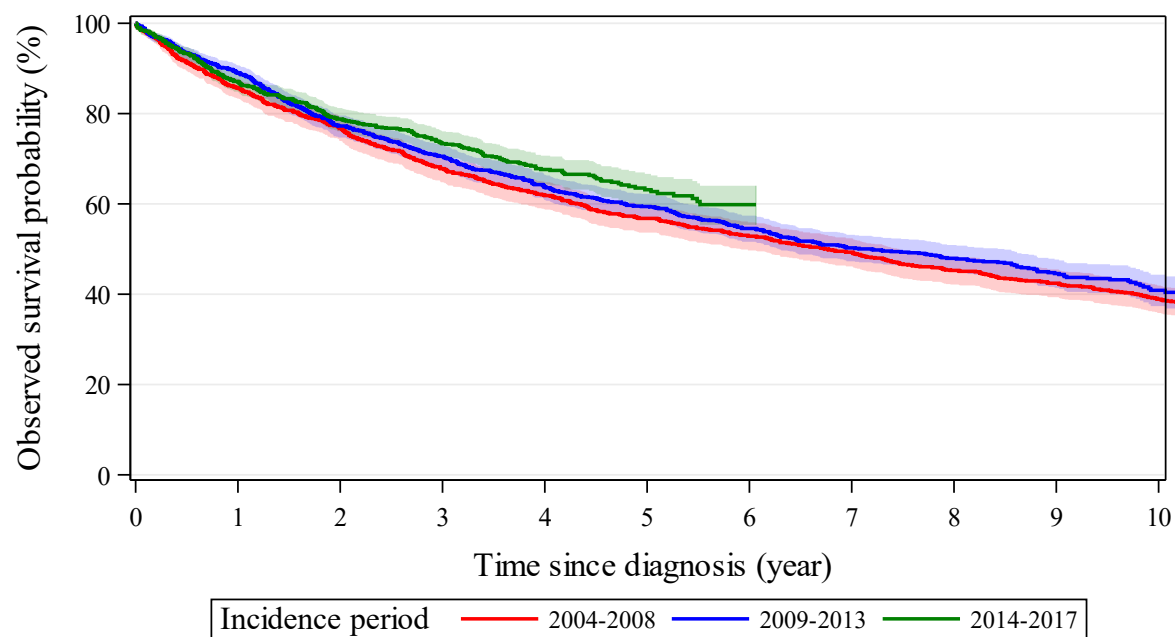
**Renal Cell Carcinoma, combined stage III (2004-2017)****Figure 343 – Renal cell carcinoma (2004-2017), combined stage III, Kaplan-Meier graphs observed survival by incidence period**



Figure 344 – Renal cell carcinoma (2004-2017), combined stage III, Kaplan-Meier graphs observed survival by incidence period (cut-off point: 2006)

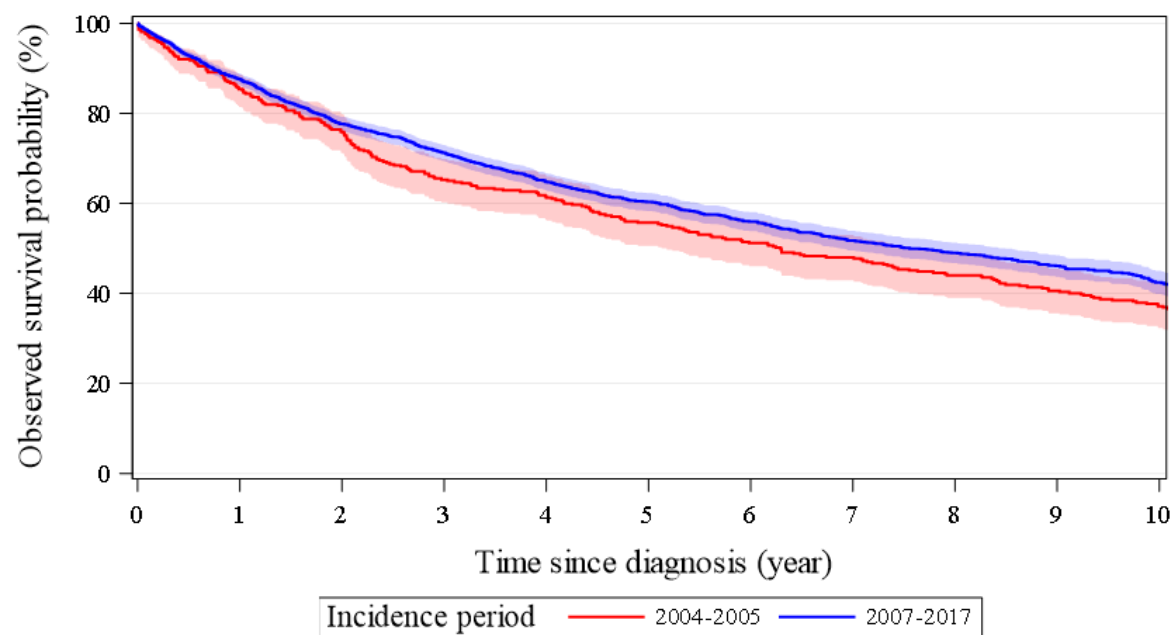




Figure 345 – Renal cell carcinoma (2004-2017), combined stage III, relative survival graphs by incidence period

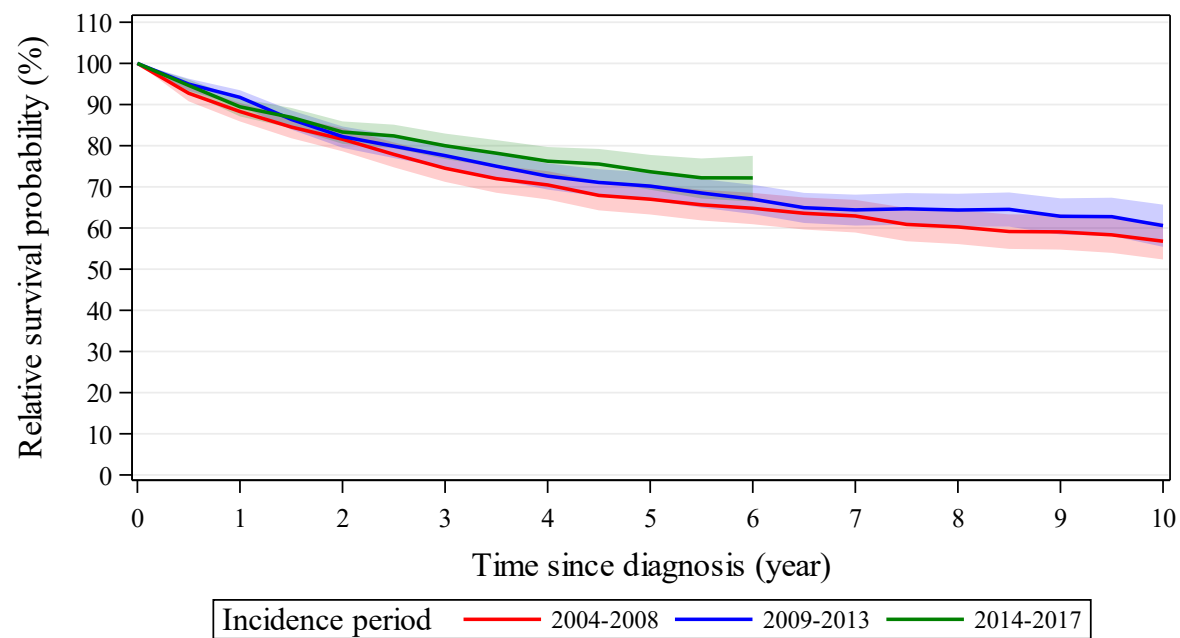
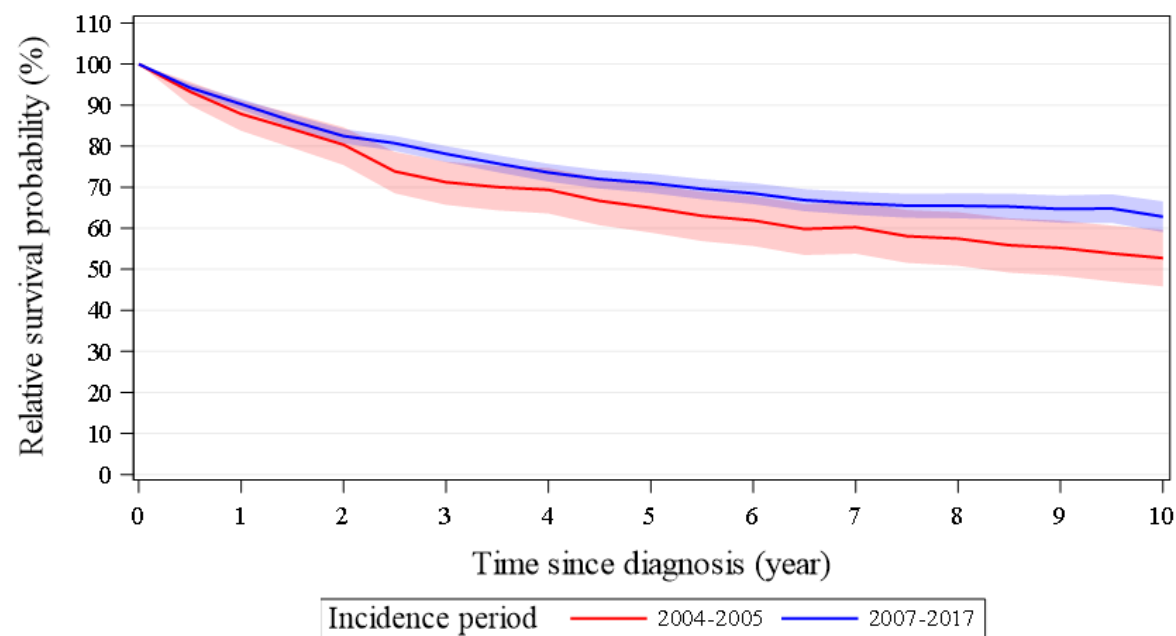




Figure 346 – Renal cell carcinoma (2004-2017), combined stage III, relative survival graphs by incidence period (cut-off point: 2006)



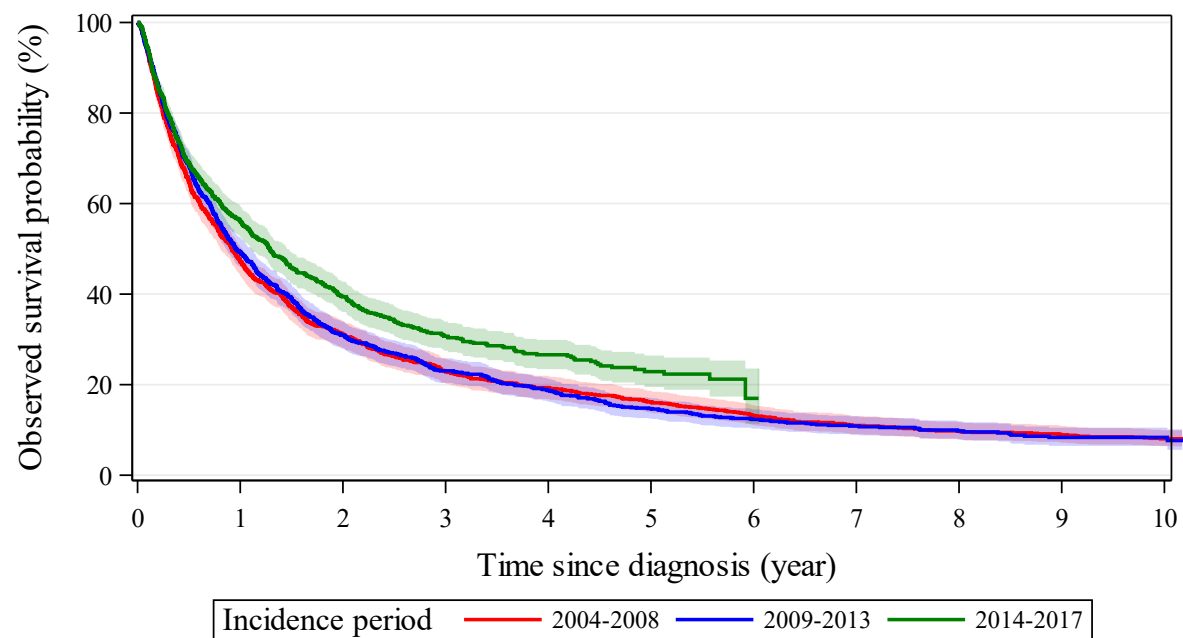
**Renal Cell Carcinoma, combined stage IV (2004-2017)****Figure 347 – Renal cell carcinoma (2004-2017), combined stage IV, Kaplan-Meier graphs observed survival by incidence period**



Figure 348 – Renal cell carcinoma (2004-2017), combined stage IV, Kaplan-Meier graphs observed survival by incidence period (cut-off point: 2006)

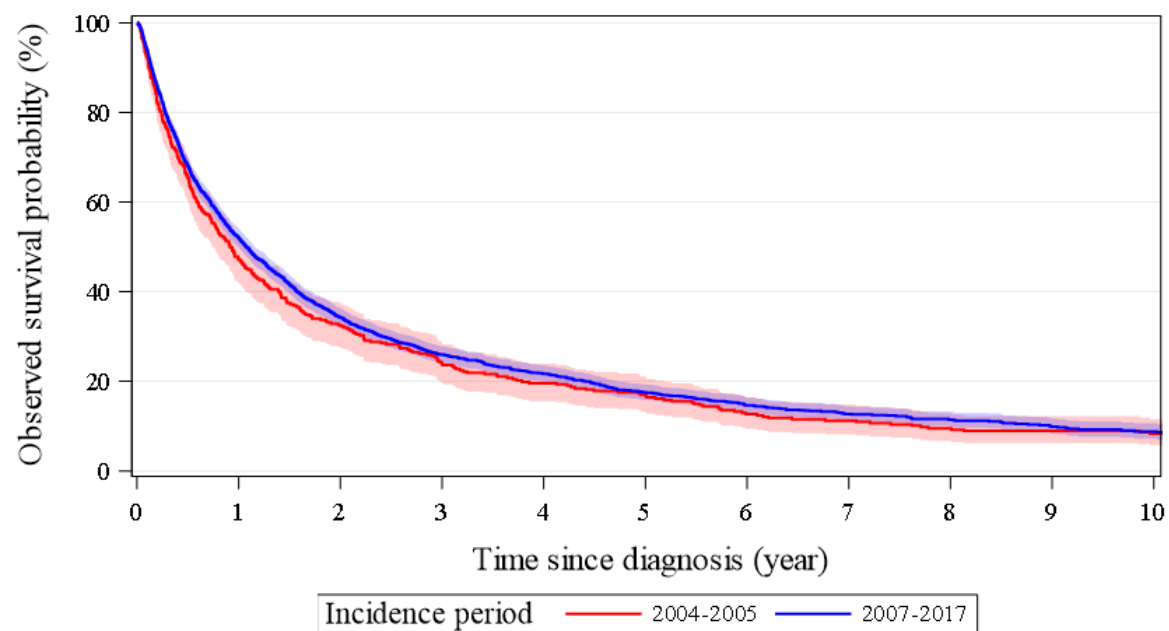




Figure 349 – Renal cell carcinoma (2004-2017), combined stage IV, relative survival graphs by incidence period

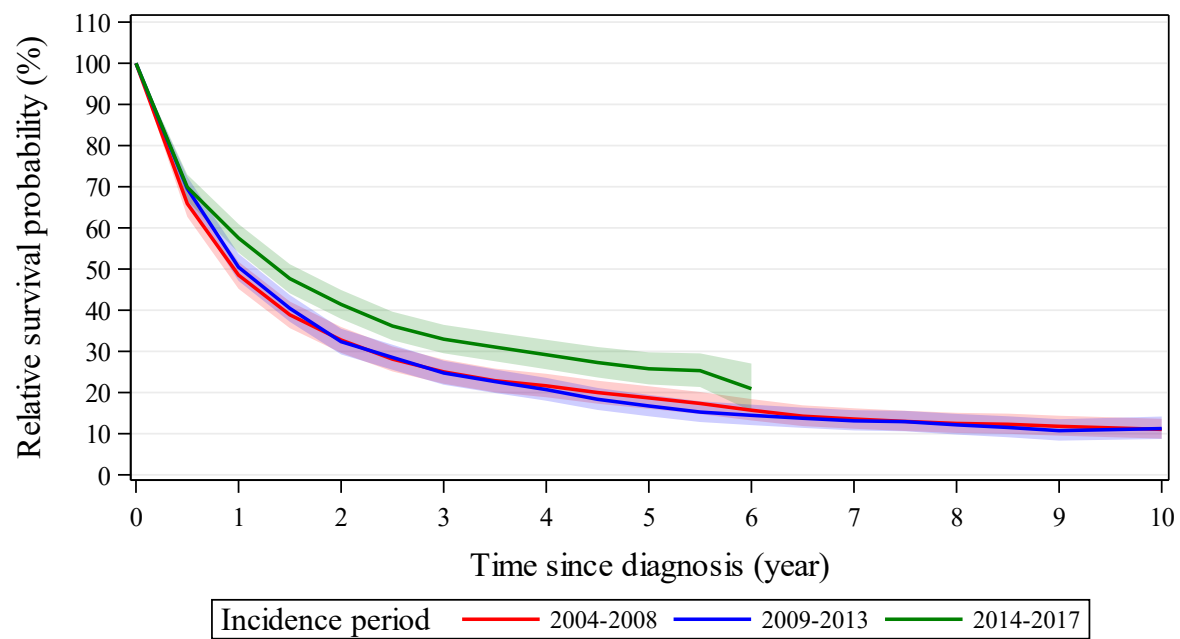
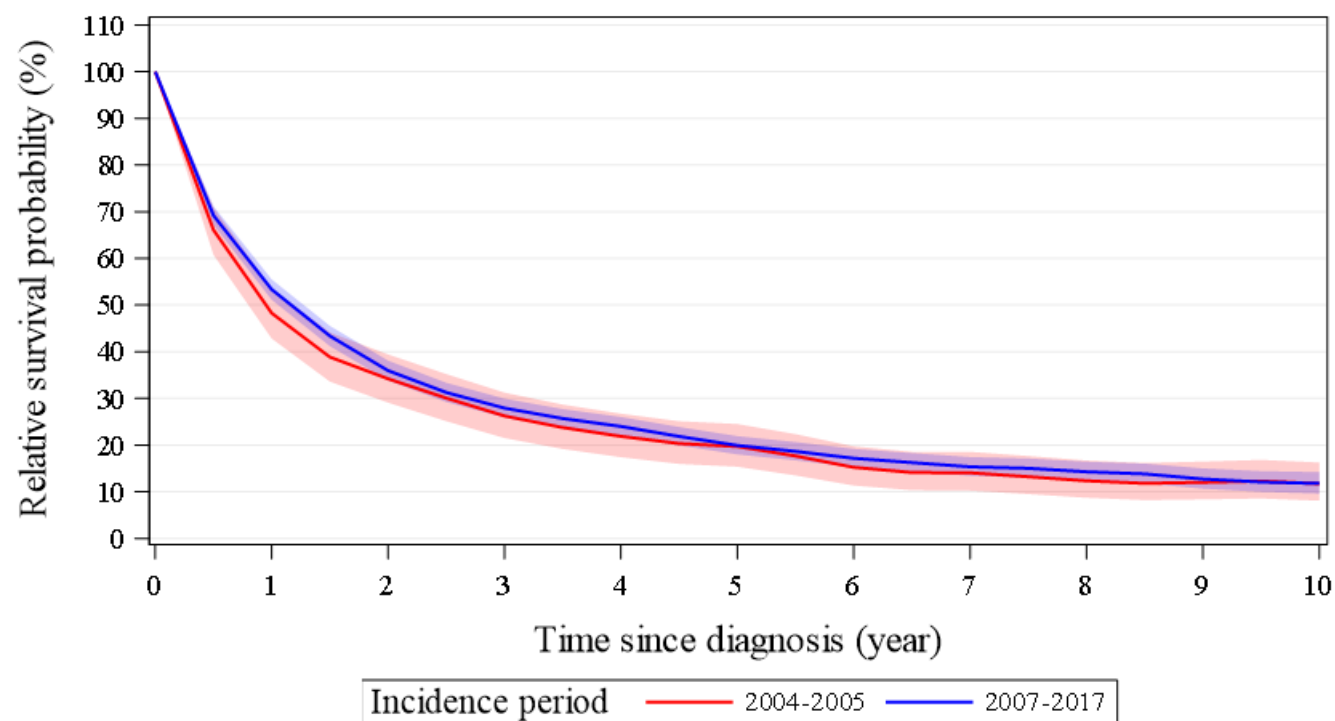




Figure 350 – Renal cell carcinoma (2004-2017), combined stage IV, relative survival graphs by incidence period

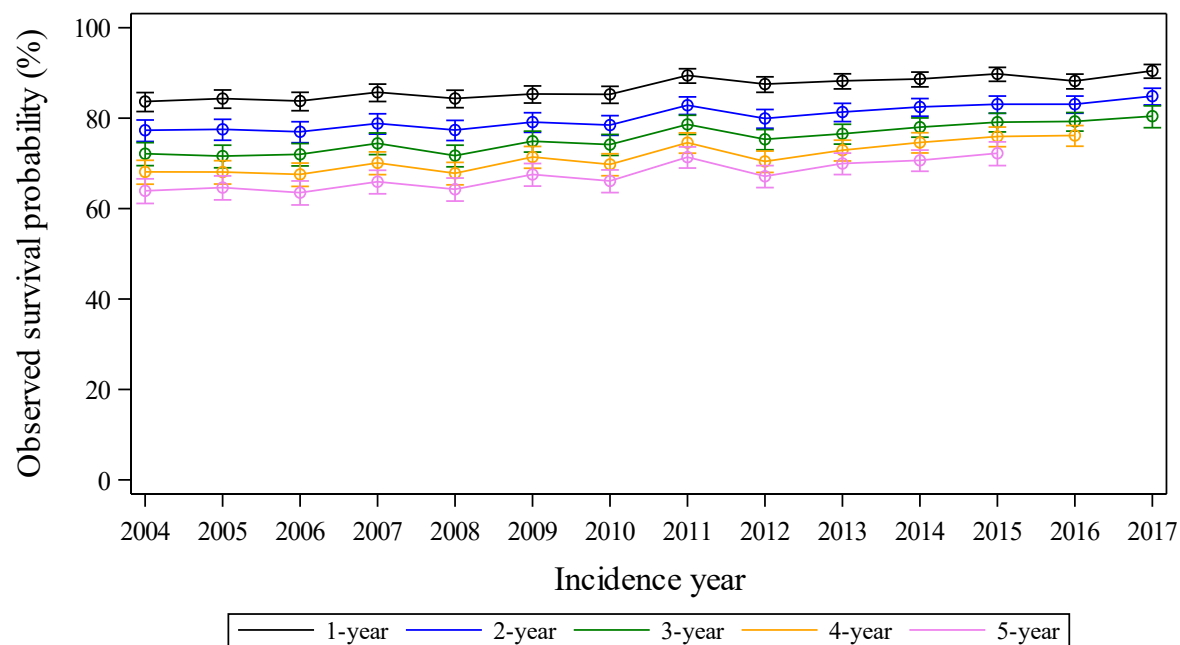




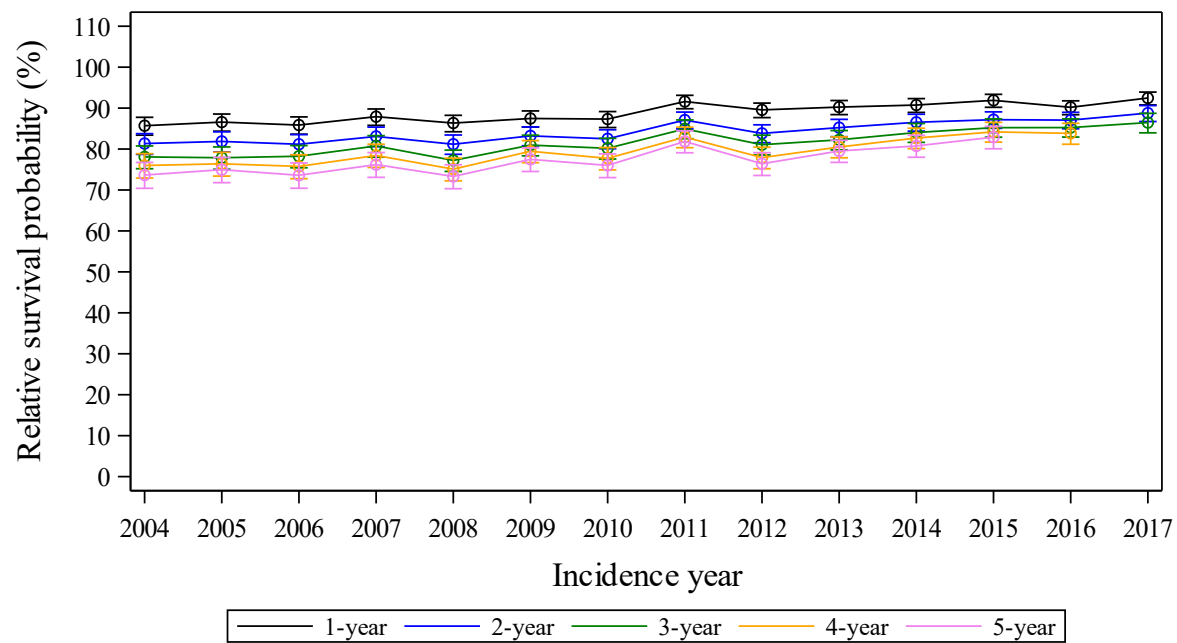
Appendix 12.1.1.3. Renal Cell Carcinoma, time trend Observed and Relative Survival

Renal Cell Carcinoma (2004-2017)

Figure 351 – Renal cell carcinoma (2004-2017), time trend observed survival with incidence year

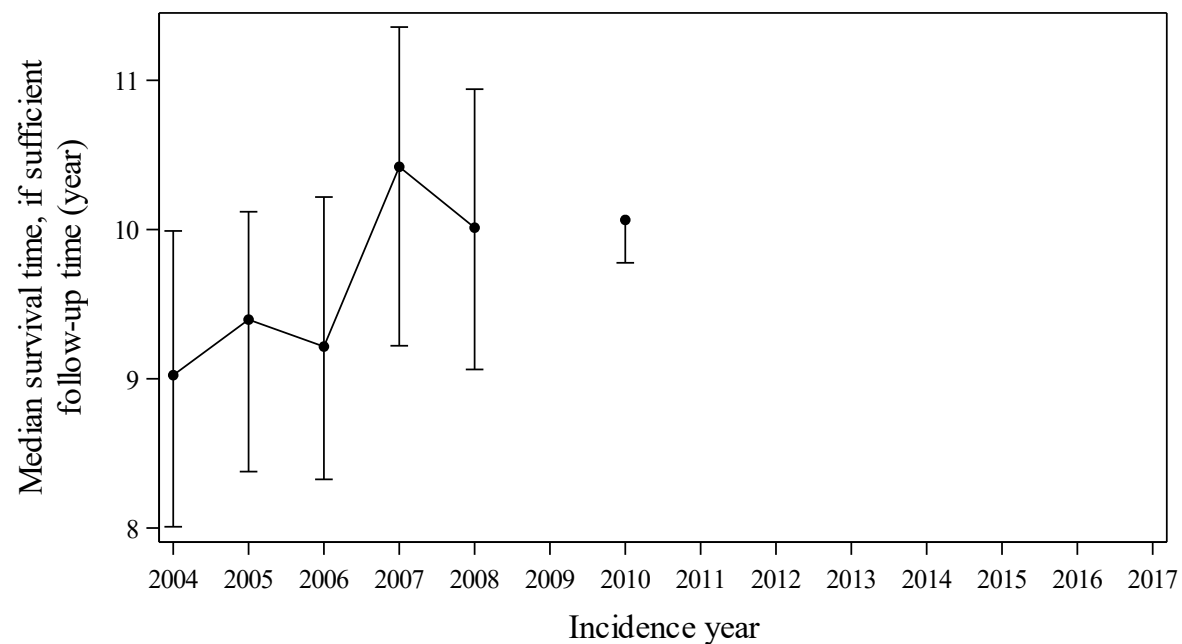


Note: the error bars represent the 95% CI.

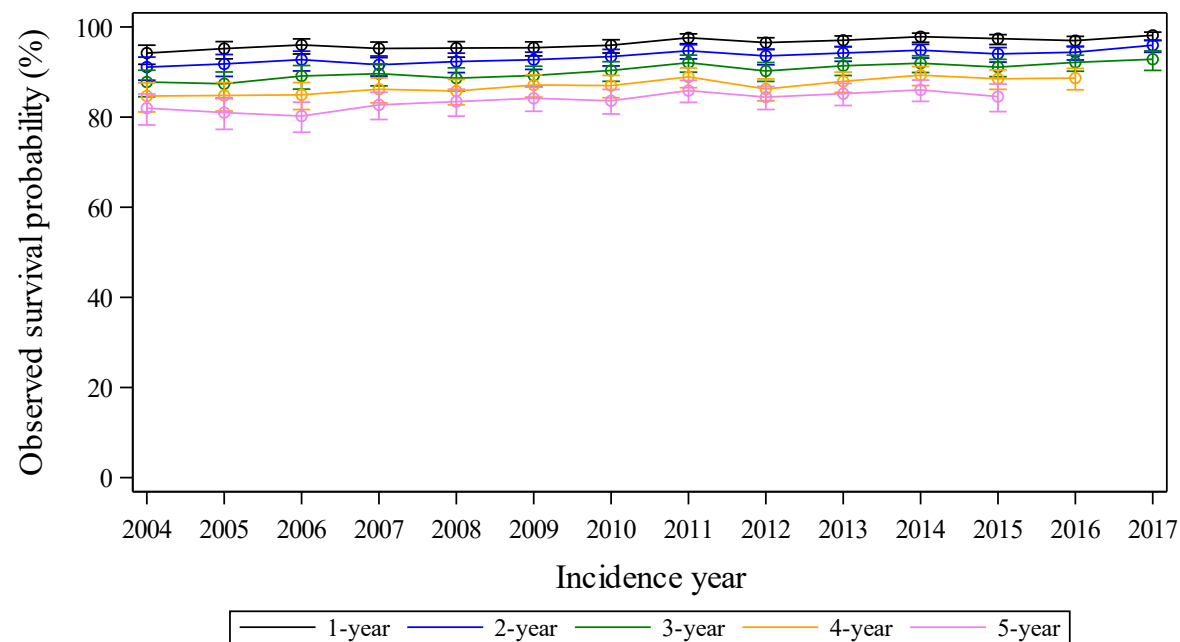
**Figure 352 – Renal cell carcinoma (2004-2017), time trend relative survival with incidence year**

Note: the error bars represent the 95% CI.

Figure 353 – Renal cell carcinoma (2004-2017), Median time observed survival



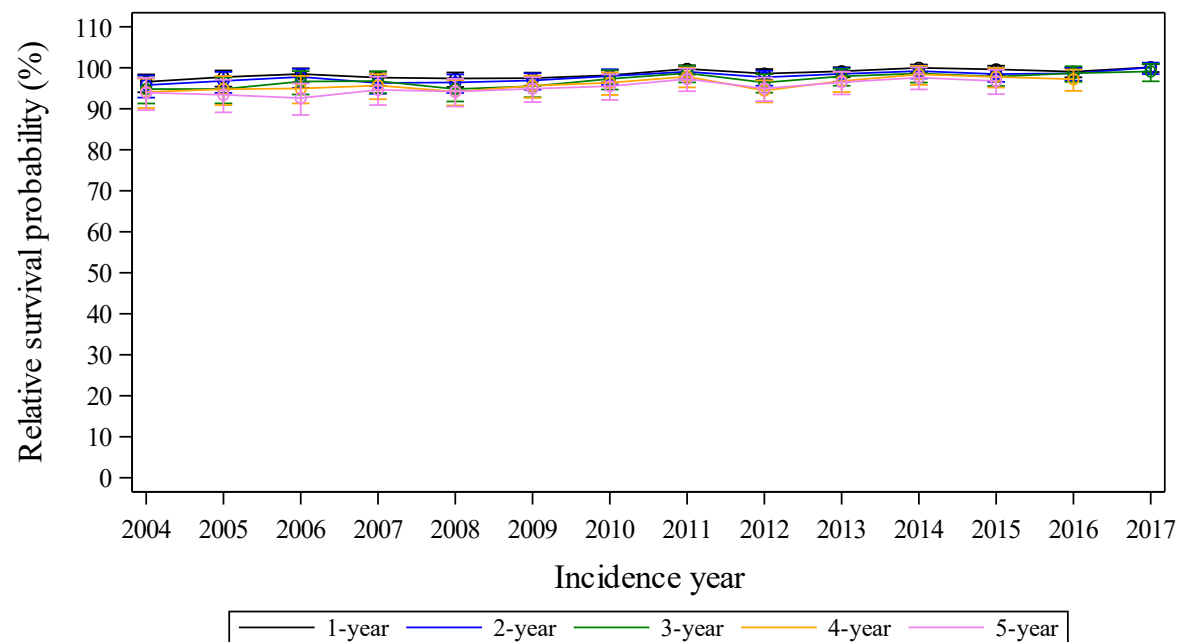
Note: the error bars represent the 95% CI. When the upper error is not plotted, the upper limit could not be determined with the follow-up available.

**Renal Cell Carcinoma, combined stage I (2004-2017)****Figure 354 – Renal cell carcinoma (2004-2017), combined stage I, time trend observed survival with incidence year**

Note: the error bars represent the 95% CI.



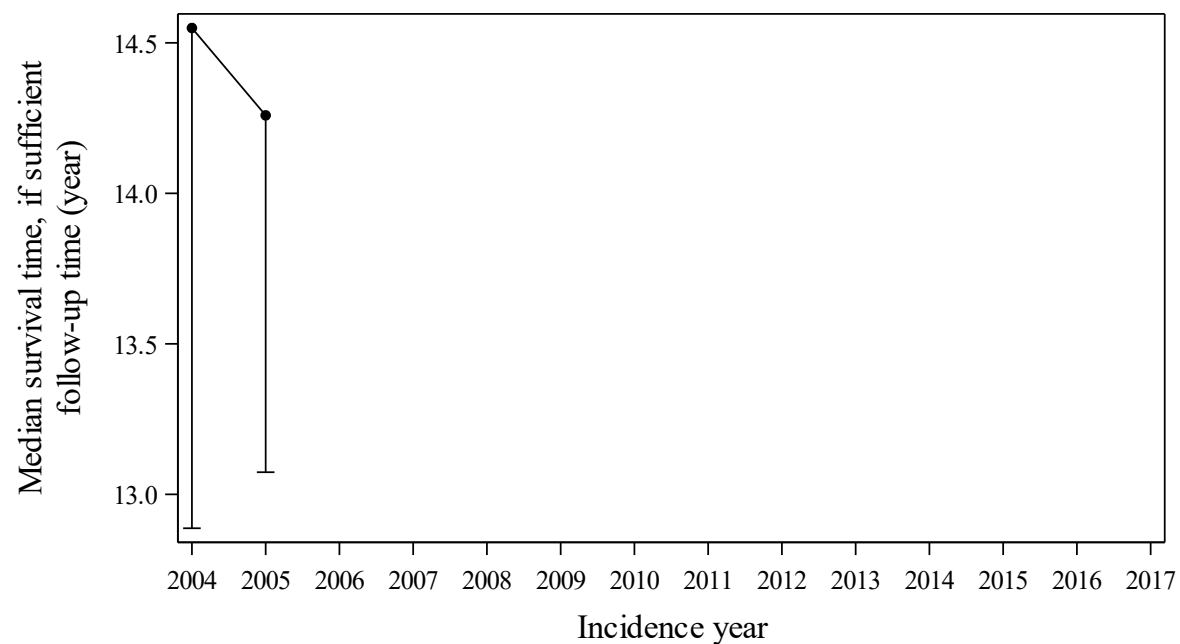
Figure 355 – Renal cell carcinoma (2004-2017), combined stage I, time trend relative survival with incidence year



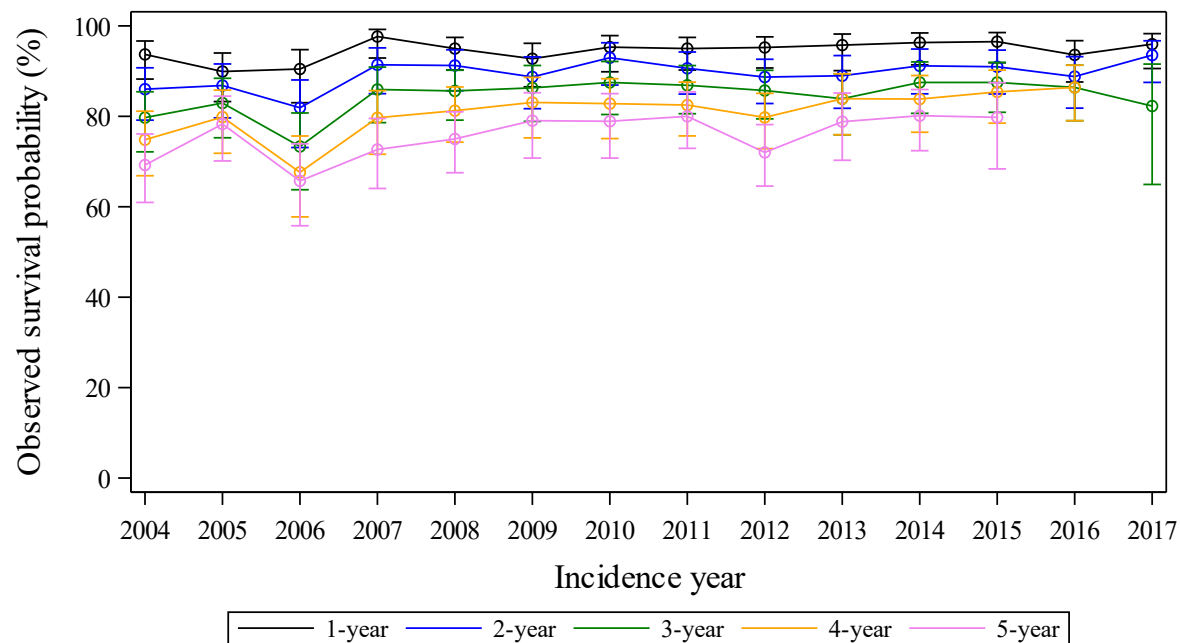
Note: the error bars represent the 95% CI.



Figure 356 – Renal cell carcinoma (2004-2017), combined stage I, median time observed survival



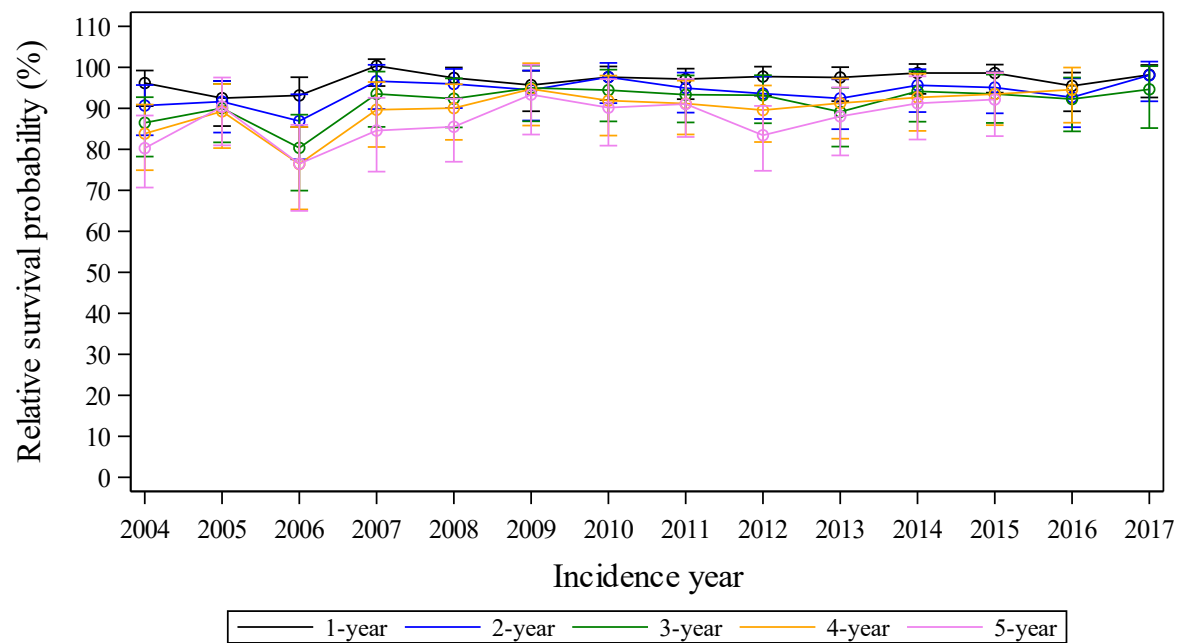
Note: the error bars represent the 95% CI. When the upper error is not plotted, the upper limit could not be determined with the follow-up available.

**Renal Cell Carcinoma, combined stage II (2004-2017)****Figure 357 – Renal cell carcinoma (2004-2017), combined stage II, time trend observed survival with incidence year**

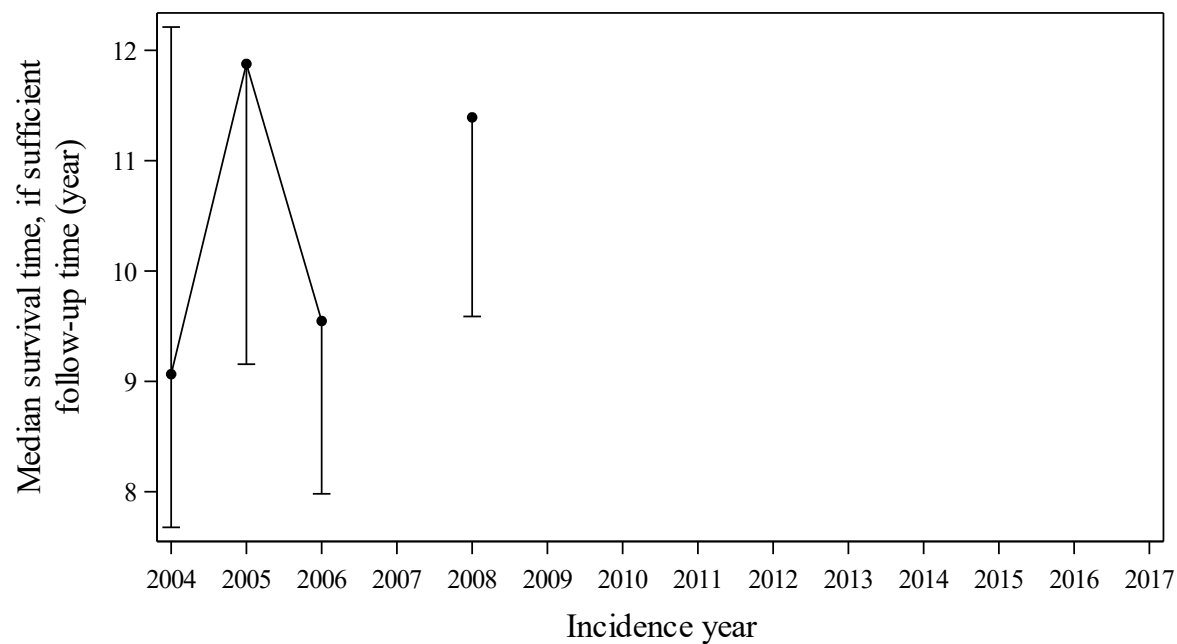
Note: the error bars represent the 95% CI.



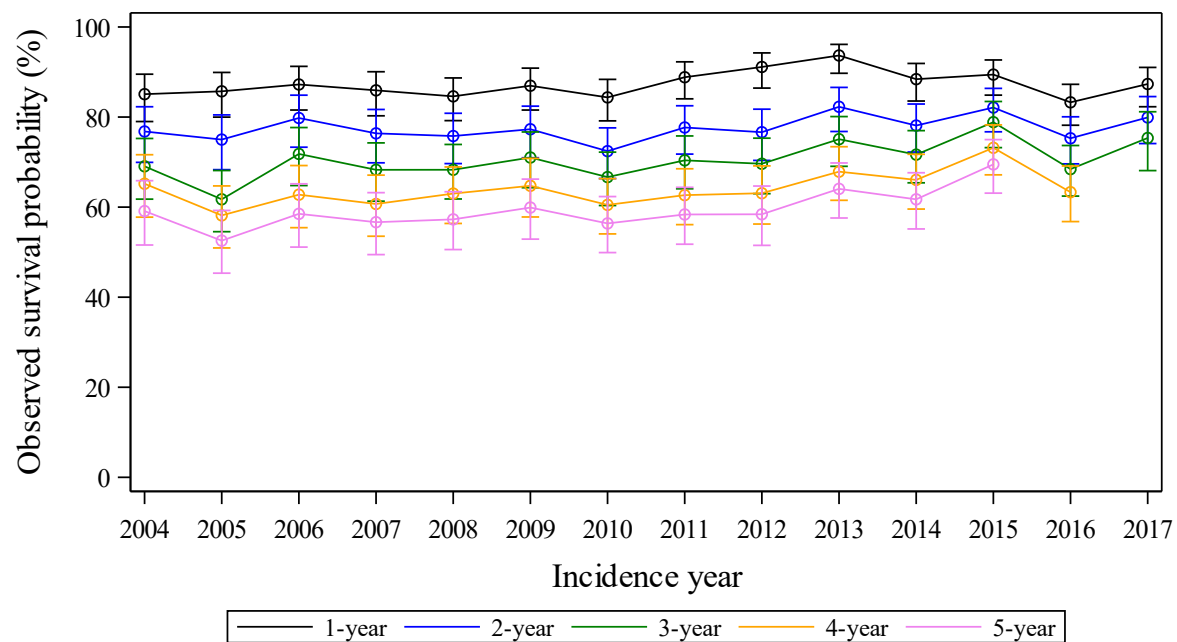
Figure 358 – Renal cell carcinoma (2004-2017), combined stage II, time trend relative survival with incidence year



Note: the error bars represent the 95% CI.

**Figure 359 – Renal cell carcinoma (2004-2017), combined stage II, median time observed survival**

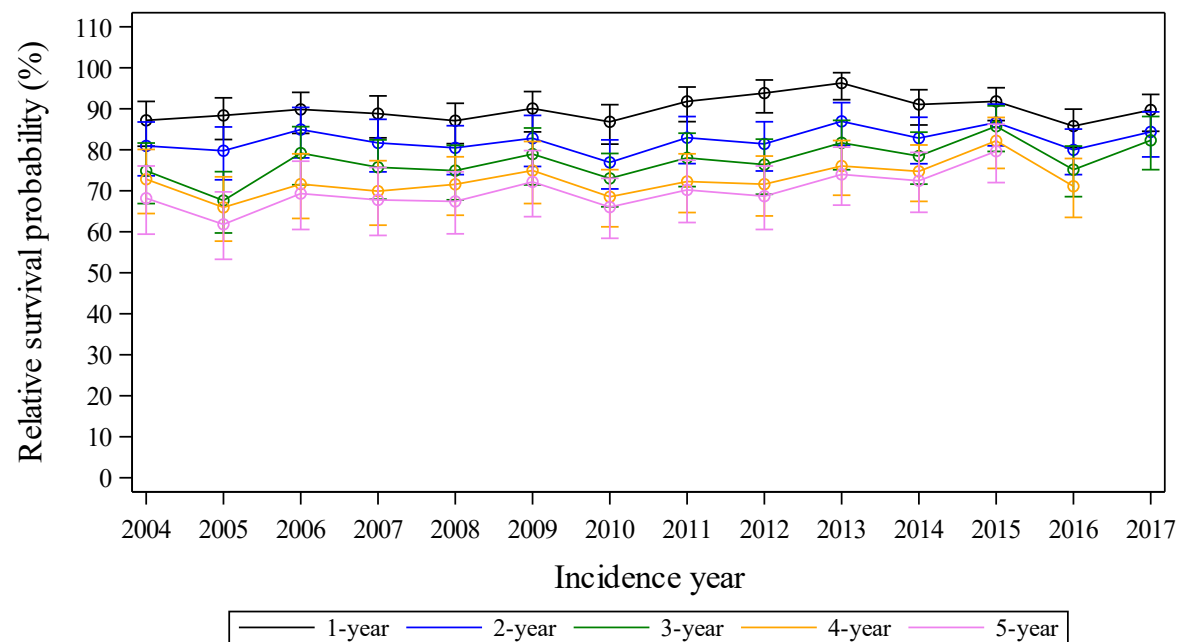
Note: the error bars represent the 95% CI. When the upper error is not plotted, the upper limit could not be determined with the follow-up available.

**Renal Cell Carcinoma, combined stage III (2004-2017)****Figure 360 – Renal cell carcinoma (2004-2017), combined stage III, time trend observed survival with incidence year**

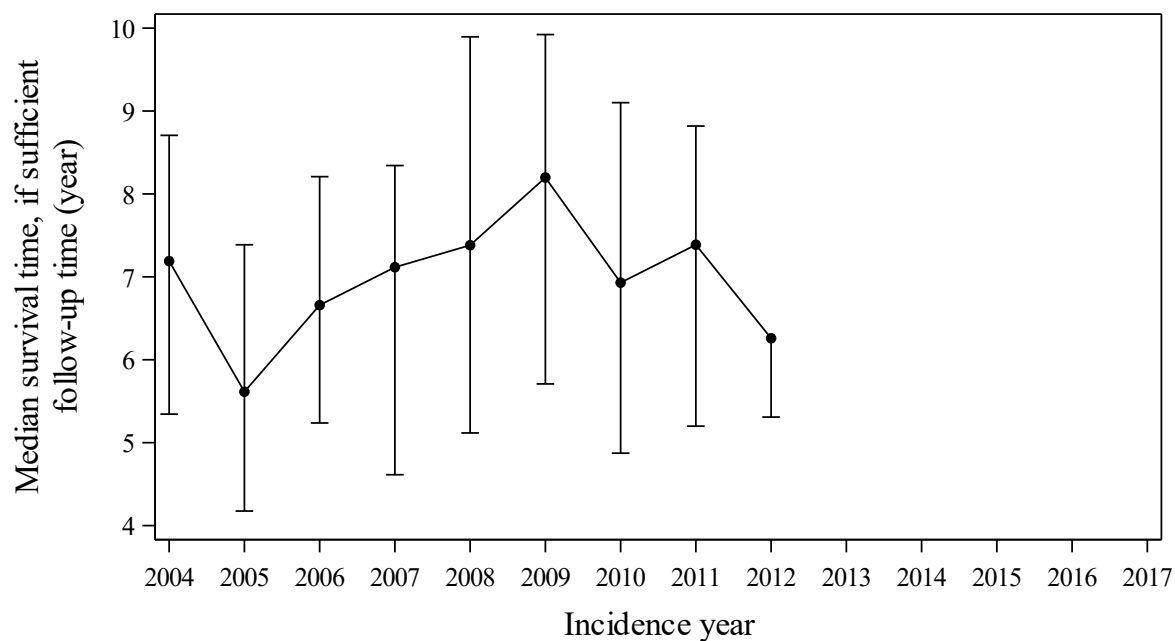
Note: the error bars represent the 95% CI.



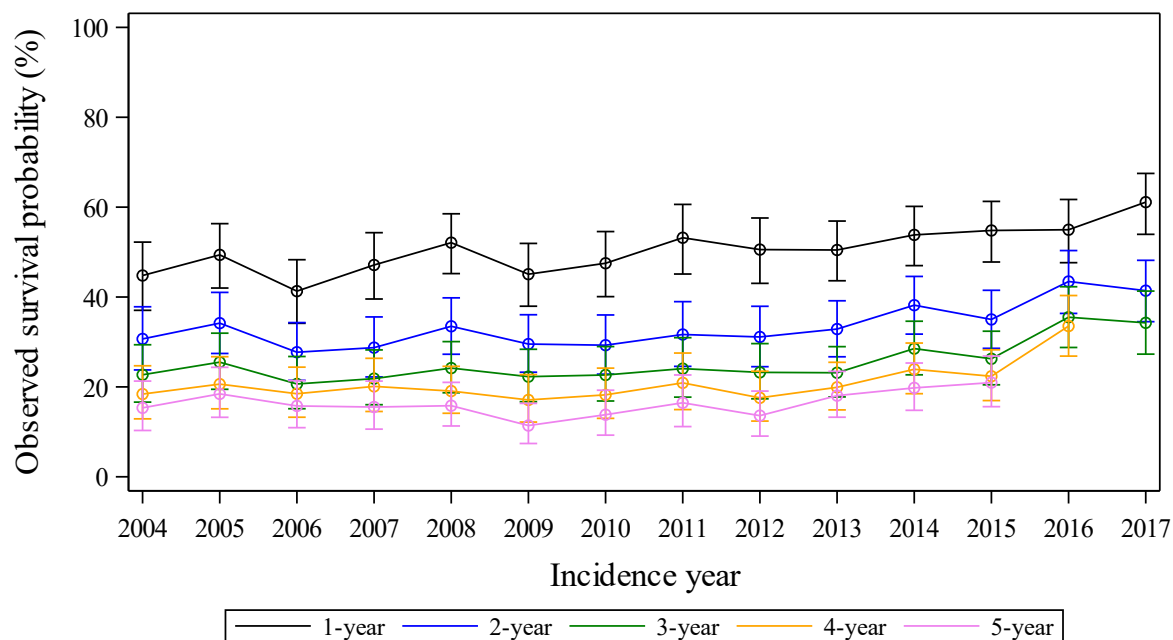
Figure 361 – Renal cell carcinoma (2004-2017), combined stage III, time trend relative survival with incidence year



Note: the error bars represent the 95% CI.

**Figure 362 – Renal cell carcinoma (2004-2017), combined stage III, median time observed survival**

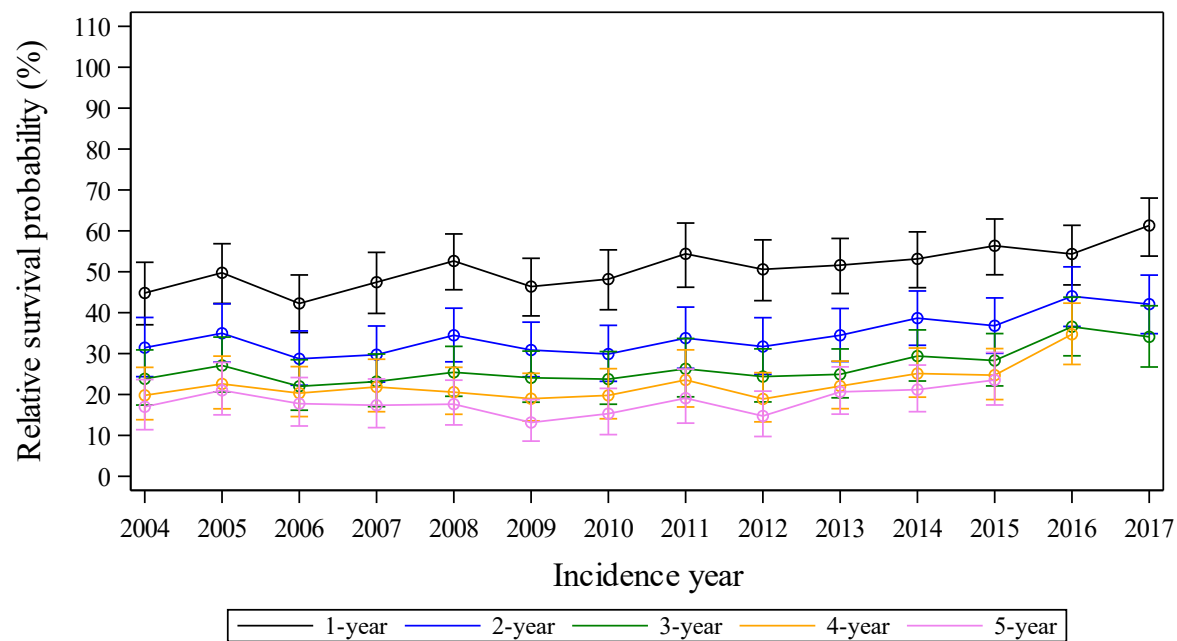
Note: the error bars represent the 95% CI. When the upper error is not plotted, the upper limit could not be determined with the follow-up available.

**Renal Cell Carcinoma, combined stage IV (2004-2017)****Figure 363 – Renal cell carcinoma (2004-2017), combined stage IV, time trend observed survival with incidence year**

Note: the error bars represent the 95% CI.

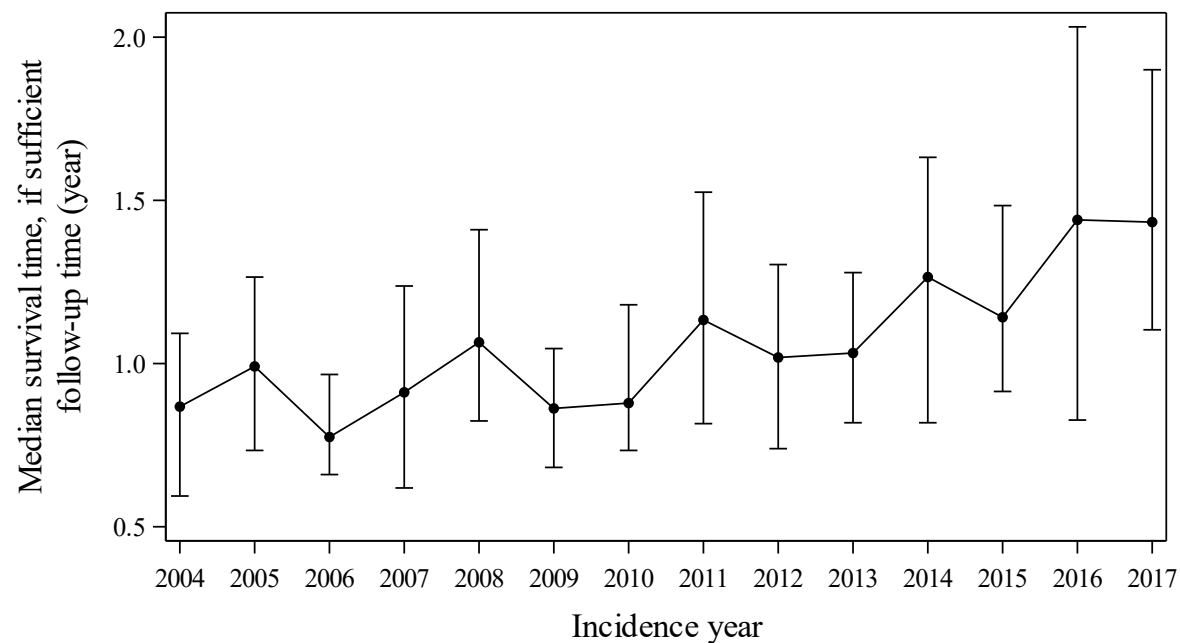


Figure 364 – Renal cell carcinoma (2004-2017), combined stage IV, time trend relative survival with incidence year



Note: the error bars represent the 95% CI.

Figure 365 – Renal cell carcinoma (2004-2017), combined stage IV, median time observed survival



Note: the error bars represent the 95% CI. When the upper error is not plotted, the upper limit could not be determined with the follow-up available.



Appendix 12.1.1.4. Renal Cell Carcinoma, time trend tables Observed and Relative Survival

Table 187 – Renal cell carcinoma (2004-2017), time trend observed survival with incidence year

Unadjusted observed survival, %													
Characteristic	N at risk	1 year		2 year		3 year		4 year		5 year		Median survival time (year)	
		%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI	T	95% CI
All													
2004	1,195	83.7	[81.5, 85.7]	77.3	[74.8, 79.6]	72.1	[69.5, 74.6]	68.1	[65.4, 70.7]	63.9	[61.1, 66.6]	9.0	[8.0, 10.0]
2005	1,251	84.3	[82.2, 86.2]	77.5	[75.1, 79.7]	71.6	[69.0, 74.0]	68.1	[65.4, 70.6]	64.6	[61.9, 67.2]	9.4	[8.4, 10.1]
2006	1,265	83.8	[81.6, 85.7]	77.0	[74.6, 79.2]	72.0	[69.4, 74.4]	67.6	[64.9, 70.1]	63.5	[60.8, 66.1]	9.2	[8.3, 10.2]
2007	1,275	85.7	[83.7, 87.5]	78.8	[76.5, 81.0]	74.4	[71.9, 76.7]	70.1	[67.5, 72.5]	65.9	[63.3, 68.5]	10.4	[9.2, 11.4]
2008	1,362	84.4	[82.3, 86.2]	77.4	[75.1, 79.5]	71.7	[69.2, 74.0]	67.8	[65.3, 70.2]	64.3	[61.7, 66.8]	10.0	[9.1, 10.9]
2009	1,352	85.3	[83.3, 87.1]	79.1	[76.9, 81.2]	74.9	[72.5, 77.1]	71.4	[68.9, 73.7]	67.5	[65.0, 70.0]	>11	
2010	1,371	85.3	[83.3, 87.0]	78.5	[76.2, 80.6]	74.2	[71.8, 76.4]	69.8	[67.3, 72.1]	66.1	[63.5, 68.6]	10.1	[9.8, .]
2011	1,443	89.4	[87.7, 90.9]	82.9	[80.8, 84.7]	78.6	[76.4, 80.6]	74.6	[72.2, 76.7]	71.4	[69.0, 73.6]	>9	
2012	1,436	87.5	[85.7, 89.1]	79.9	[77.8, 81.9]	75.3	[73.0, 77.5]	70.4	[68.0, 72.7]	67.1	[64.6, 69.5]	>8	
2013	1,439	88.2	[86.5, 89.8]	81.4	[79.2, 83.3]	76.5	[74.3, 78.6]	72.9	[70.5, 75.1]	70.0	[67.5, 72.3]	>7	
2014	1,458	88.7	[86.9, 90.2]	82.5	[80.4, 84.3]	78.0	[75.8, 80.0]	74.6	[72.3, 76.8]	70.7	[68.3, 72.9]	>6	
2015	1,491	89.8	[88.1, 91.2]	83.1	[81.1, 84.9]	79.1	[77.0, 81.1]	75.9	[73.7, 78.0]	72.2	[69.5, 74.8]	>5	
2016	1,503	88.2	[86.5, 89.7]	83.1	[81.1, 84.9]	79.3	[77.1, 81.2]	76.2	[73.8, 78.4]	no FU	—	>4	
2017	1,449	90.5	[88.8, 91.9]	84.9	[82.9, 86.6]	80.4	[77.9, 82.7]	no FU	—	no FU	—	>3	
Combined Stage I													
2004	483	94.2	[91.7, 96.0]	91.1	[88.2, 93.3]	87.8	[84.5, 90.4]	84.7	[81.1, 87.6]	82.0	[78.3, 85.1]	14.5	[12.9, .]
2005	500	95.2	[92.9, 96.8]	91.8	[89.0, 93.9]	87.4	[84.2, 90.0]	84.8	[81.3, 87.7]	81.0	[77.3, 84.2]	14.3	[13.1, .]
2006	552	96.0	[94.0, 97.4]	92.7	[90.2, 94.6]	89.1	[86.2, 91.4]	84.9	[81.7, 87.7]	80.2	[76.6, 83.3]	>14	
2007	608	95.2	[93.2, 96.7]	91.6	[89.1, 93.6]	89.6	[86.9, 91.8]	86.2	[83.2, 88.7]	82.7	[79.5, 85.5]	>13	
2008	599	95.3	[93.3, 96.7]	92.3	[89.9, 94.2]	88.6	[85.8, 90.9]	85.8	[82.7, 88.3]	83.4	[80.2, 86.2]	>12	



Unadjusted observed survival, %														
		1 year			2 year		3 year		4 year		5 year		Median survival time (year)	
Characteristic	N at risk	%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI	T	95% CI	
2009	716	95.4	[93.6, 96.7]	92.7	[90.6, 94.4]	89.2	[86.7, 91.3]	87.1	[84.4, 89.4]	84.2	[81.3, 86.7]	>11		
2010	716	95.9	[94.2, 97.2]	93.4	[91.4, 95.0]	90.3	[87.9, 92.3]	87.0	[84.3, 89.2]	83.6	[80.7, 86.1]	>10		
2011	797	97.6	[96.3, 98.5]	94.7	[92.9, 96.1]	92.1	[90.0, 93.8]	88.9	[86.5, 90.9]	85.9	[83.3, 88.1]	>9		
2012	779	96.5	[95.0, 97.6]	93.6	[91.6, 95.1]	90.2	[87.9, 92.1]	86.2	[83.6, 88.5]	84.4	[81.7, 86.8]	>8		
2013	815	97.1	[95.6, 98.0]	94.2	[92.4, 95.6]	91.4	[89.2, 93.1]	87.9	[85.5, 90.0]	85.2	[82.6, 87.5]	>7		
2014	836	97.8	[96.6, 98.6]	94.8	[93.1, 96.1]	92.0	[89.9, 93.6]	89.3	[87.0, 91.2]	86.0	[83.5, 88.2]	>6		
2015	855	97.4	[96.1, 98.3]	94.0	[92.2, 95.4]	91.1	[89.0, 92.8]	88.5	[86.2, 90.5]	84.6	[81.2, 87.3]	>5		
2016	893	97.0	[95.6, 97.9]	94.4	[92.7, 95.7]	92.1	[90.2, 93.7]	88.7	[86.1, 90.8]	no FU	—	>4		
2017	865	98.1	[97.0, 98.9]	95.9	[94.4, 97.1]	92.8	[90.4, 94.7]	no FU	—	no FU	—	>3		
Combined Stage II														
2004	143	93.7	[88.3, 96.7]	86.0	[79.2, 90.7]	79.7	[72.2, 85.4]	74.8	[66.9, 81.1]	69.2	[61.0, 76.1]	9.1	[7.7, 12.2]	
2005	129	89.9	[83.3, 94.0]	86.8	[79.7, 91.6]	82.9	[75.3, 88.4]	79.8	[71.8, 85.8]	78.3	[70.1, 84.5]	11.9	[9.2, .]	
2006	105	90.5	[83.0, 94.8]	81.9	[73.1, 88.1]	73.3	[63.8, 80.7]	67.6	[57.8, 75.7]	65.7	[55.8, 73.9]	9.5	[8.0, .]	
2007	128	97.7	[92.9, 99.2]	91.4	[85.0, 95.1]	85.9	[78.6, 90.9]	79.7	[71.6, 85.7]	72.7	[64.0, 79.5]	>13		
2008	160	95.0	[90.3, 97.5]	91.3	[85.7, 94.7]	85.6	[79.2, 90.2]	81.3	[74.3, 86.5]	75.0	[67.5, 81.0]	11.4	[9.6, .]	
2009	125	92.8	[86.5, 96.2]	88.7	[81.7, 93.2]	86.3	[78.9, 91.3]	83.1	[75.2, 88.6]	79.0	[70.8, 85.2]	>11		
2010	128	95.3	[89.9, 97.9]	93.0	[86.9, 96.3]	87.5	[80.4, 92.1]	82.8	[75.1, 88.3]	78.9	[70.8, 85.0]	>10		
2011	160	95.0	[90.3, 97.5]	90.6	[84.9, 94.2]	86.9	[80.6, 91.2]	82.5	[75.7, 87.6]	80.0	[72.9, 85.4]	>9		
2012	168	95.2	[90.7, 97.6]	88.7	[82.8, 92.6]	85.7	[79.4, 90.2]	79.8	[72.9, 85.1]	72.0	[64.6, 78.2]	>8		
2013	118	95.8	[90.1, 98.2]	89.0	[81.8, 93.4]	83.9	[75.9, 89.4]	83.9	[75.9, 89.4]	78.8	[70.3, 85.2]	>7		
2014	136	96.3	[91.4, 98.5]	91.2	[85.0, 94.9]	87.5	[80.7, 92.0]	83.8	[76.5, 89.0]	80.1	[72.4, 85.9]	>6		
2015	144	96.5	[91.9, 98.5]	91.0	[85.0, 94.7]	87.5	[80.9, 91.9]	85.4	[78.5, 90.2]	79.8	[68.4, 87.4]	>5		
2016	126	93.6	[87.6, 96.7]	88.8	[81.8, 93.2]	86.4	[79.0, 91.3]	86.4	[79.0, 91.3]	no FU	—	>4		



Characteristic	N at risk	Unadjusted observed survival, %											T	95% CI
		1 year		2 year		3 year		4 year		5 year		Median survival time (year)		
		%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI			
2017	124	96.0	[90.6, 98.3]	93.5	[87.5, 96.7]	82.3	[64.9, 91.6]	no FU	—	no FU	—	>3		
Combined Stage III														
2004	181	85.1	[79.0, 89.5]	76.8	[69.9, 82.3]	69.1	[61.8, 75.2]	65.2	[57.8, 71.6]	59.1	[51.6, 65.9]	7.2	[5.3, 8.7]	
2005	196	85.7	[80.0, 89.9]	75.0	[68.3, 80.5]	61.7	[54.5, 68.1]	58.2	[50.9, 64.7]	52.6	[45.3, 59.3]	5.6	[4.2, 7.4]	
2006	188	87.2	[81.6, 91.3]	79.8	[73.3, 84.9]	71.8	[64.8, 77.7]	62.8	[55.4, 69.2]	58.5	[51.1, 65.2]	6.7	[5.2, 8.2]	
2007	199	85.9	[80.3, 90.1]	76.4	[69.8, 81.7]	68.3	[61.3, 74.3]	60.7	[53.5, 67.1]	56.6	[49.5, 63.2]	7.1	[4.6, 8.3]	
2008	228	84.6	[79.2, 88.7]	75.8	[69.7, 80.8]	68.3	[61.8, 73.9]	63.0	[56.4, 68.9]	57.3	[50.6, 63.4]	7.4	[5.1, 9.9]	
2009	207	87.0	[81.6, 90.9]	77.3	[71.0, 82.4]	71.0	[64.3, 76.7]	64.7	[57.8, 70.8]	59.9	[52.9, 66.2]	8.2	[5.7, 9.9]	
2010	243	84.4	[79.2, 88.4]	72.4	[66.3, 77.6]	66.7	[60.4, 72.2]	60.5	[54.1, 66.3]	56.4	[49.9, 62.3]	6.9	[4.9, 9.1]	
2011	233	88.8	[84.0, 92.3]	77.7	[71.8, 82.5]	70.4	[64.1, 75.8]	62.7	[56.1, 68.5]	58.4	[51.8, 64.4]	7.4	[5.2, 8.8]	
2012	214	91.1	[86.4, 94.2]	76.6	[70.4, 81.7]	69.6	[63.0, 75.3]	63.1	[56.2, 69.2]	58.4	[51.5, 64.7]	6.3	[5.3, .]	
2013	237	93.7	[89.7, 96.1]	82.3	[76.8, 86.6]	75.1	[69.1, 80.1]	67.9	[61.5, 73.4]	64.1	[57.6, 69.8]	>7		
2014	233	88.4	[83.6, 91.9]	78.1	[72.2, 82.9]	71.7	[65.4, 77.0]	66.0	[59.6, 71.7]	61.7	[55.2, 67.6]	>6		
2015	246	89.4	[84.9, 92.7]	82.1	[76.7, 86.4]	78.9	[73.2, 83.5]	73.2	[67.2, 78.3]	69.5	[63.1, 75.0]	>5		
2016	263	83.3	[78.2, 87.3]	75.3	[69.6, 80.1]	68.4	[62.4, 73.7]	63.3	[56.8, 69.1]	no FU	—	>4		
2017	229	87.3	[82.3, 91.0]	79.9	[74.1, 84.5]	75.4	[68.1, 81.2]	no FU	—	no FU	—	>3		
Combined Stage IV														
2004	163	44.8	[37.0, 52.2]	30.7	[23.8, 37.8]	22.7	[16.6, 29.4]	18.4	[12.9, 24.7]	15.3	[10.3, 21.3]	0.9	[0.6, 1.1]	
2005	186	49.4	[42.0, 56.3]	34.2	[27.4, 41.0]	25.5	[19.5, 32.0]	20.6	[15.1, 26.7]	18.4	[13.2, 24.4]	1.0	[0.7, 1.3]	
2006	184	41.3	[34.2, 48.3]	27.7	[21.5, 34.3]	20.7	[15.1, 26.8]	18.5	[13.3, 24.4]	15.8	[10.9, 21.4]	0.8	[0.7, 1.0]	
2007	174	47.1	[39.6, 54.3]	28.7	[22.2, 35.6]	21.8	[16.0, 28.2]	20.1	[14.5, 26.4]	15.5	[10.6, 21.3]	0.9	[0.6, 1.2]	
2008	215	52.1	[45.2, 58.5]	33.5	[27.3, 39.8]	24.2	[18.7, 30.1]	19.1	[14.1, 24.6]	15.8	[11.3, 21.0]	1.1	[0.8, 1.4]	
2009	193	45.1	[38.0, 51.9]	29.5	[23.3, 36.1]	22.3	[16.7, 28.4]	17.1	[12.2, 22.7]	11.4	[7.4, 16.3]	0.9	[0.7, 1.0]	



Characteristic	N at risk	Unadjusted observed survival, %										Median survival time (year)	
		1 year		2 year		3 year		4 year		5 year			
		%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI	T	95% CI
2010	181	47.5	[40.1, 54.6]	29.3	[22.8, 36.0]	22.7	[16.9, 29.0]	18.2	[13.0, 24.2]	13.8	[9.3, 19.3]	0.9	[0.7, 1.2]
2011	159	53.2	[45.1, 60.6]	31.7	[24.6, 39.0]	24.1	[17.7, 31.0]	20.9	[15.0, 27.5]	16.5	[11.2, 22.7]	1.1	[0.8, 1.5]
2012	180	50.6	[43.0, 57.6]	31.1	[24.5, 37.9]	23.2	[17.4, 29.6]	17.6	[12.4, 23.5]	13.6	[9.1, 19.1]	1.0	[0.7, 1.3]
2013	216	50.5	[43.6, 56.9]	32.9	[26.7, 39.2]	23.1	[17.8, 29.0]	19.9	[14.9, 25.5]	18.1	[13.3, 23.5]	1.0	[0.8, 1.3]
2014	219	53.8	[47.0, 60.2]	38.2	[31.7, 44.6]	28.5	[22.7, 34.6]	23.9	[18.5, 29.8]	19.8	[14.8, 25.3]	1.3	[0.8, 1.6]
2015	208	54.8	[47.8, 61.3]	35.0	[28.6, 41.5]	26.3	[20.5, 32.4]	22.4	[17.0, 28.3]	21.0	[15.6, 26.9]	1.1	[0.9, 1.5]
2016	191	55.0	[47.6, 61.7]	43.5	[36.4, 50.3]	35.5	[28.8, 42.3]	33.5	[26.9, 40.3]	no FU	—	1.4	[0.8, 2.0]
2017	198	61.1	[53.9, 67.5]	41.4	[34.5, 48.2]	34.3	[27.3, 41.3]	no FU	—	no FU	—	1.4	[1.1, 1.9]

Table 188 – Renal cell carcinoma (2004-2017), time trend relative survival with incidence year

Unadjusted relative survival, %											
Characteristic	N at risk	1 year		2 year		3 year		4 year		5 year	
		%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI
All											
2004	1,195	85.7	[83.4, 87.8]	81.4	[78.7, 83.8]	78.1	[75.2, 80.8]	76.0	[72.9, 78.9]	73.7	[70.4, 76.7]
2005	1,251	86.6	[84.4, 88.6]	81.9	[79.3, 84.2]	77.9	[75.1, 80.5]	76.4	[73.4, 79.2]	75.0	[71.8, 78.0]
2006	1,265	85.9	[83.6, 87.9]	81.2	[78.6, 83.6]	78.2	[75.4, 80.9]	75.8	[72.8, 78.6]	73.6	[70.4, 76.6]
2007	1,275	87.9	[85.8, 89.8]	83.1	[80.6, 85.4]	80.8	[78.0, 83.3]	78.4	[75.5, 81.2]	76.2	[73.1, 79.1]
2008	1,362	86.4	[84.2, 88.3]	81.2	[78.7, 83.4]	77.2	[74.5, 79.7]	75.1	[72.2, 77.8]	73.3	[70.3, 76.2]
2009	1,352	87.5	[85.4, 89.3]	83.2	[80.8, 85.4]	81.0	[78.4, 83.4]	79.5	[76.7, 82.1]	77.5	[74.5, 80.3]
2010	1,371	87.3	[85.3, 89.2]	82.5	[80.1, 84.7]	80.2	[77.6, 82.6]	77.7	[74.9, 80.4]	76.0	[73.0, 78.8]
2011	1,443	91.6	[89.9, 93.1]	87.1	[84.9, 89.0]	84.9	[82.5, 87.1]	82.9	[80.3, 85.3]	81.9	[79.1, 84.5]



Characteristic	N at risk	Unadjusted relative survival, %									
		1 year		2 year		3 year		4 year		5 year	
		%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI
2012	1,436	89.6	[87.7, 91.2]	83.8	[81.6, 85.9]	81.1	[78.6, 83.4]	77.9	[75.2, 80.5]	76.4	[73.6, 79.1]
2013	1,439	90.3	[88.4, 91.9]	85.2	[83.0, 87.3]	82.3	[79.8, 84.5]	80.5	[77.9, 83.0]	79.5	[76.7, 82.1]
2014	1,458	90.8	[89.0, 92.3]	86.6	[84.4, 88.5]	84.0	[81.6, 86.3]	82.7	[80.1, 85.1]	80.8	[78.0, 83.4]
2015	1,491	91.9	[90.2, 93.4]	87.2	[85.1, 89.1]	85.2	[82.9, 87.4]	84.2	[81.7, 86.5]	82.9	[80.1, 85.5]
2016	1,503	90.2	[88.4, 91.8]	87.1	[85.0, 89.0]	85.3	[82.9, 87.4]	83.8	[81.2, 86.3]	no FU	—
2017	1,449	92.5	[90.8, 93.9]	88.8	[86.7, 90.6]	86.5	[84.0, 88.7]	no FU	—	no FU	—
Combined Stage I											
2004	483	96.6	[94.0, 98.4]	95.8	[92.7, 98.1]	94.8	[91.3, 97.6]	94.1	[90.2, 97.4]	93.9	[89.7, 97.5]
2005	500	97.7	[95.4, 99.3]	96.8	[93.9, 99.0]	94.8	[91.3, 97.6]	94.8	[90.9, 98.0]	93.4	[89.1, 97.1]
2006	552	98.5	[96.4, 99.9]	97.8	[95.1, 99.8]	96.7	[93.5, 99.2]	95.0	[91.3, 98.0]	92.6	[88.5, 96.2]
2007	608	97.6	[95.5, 99.1]	96.3	[93.7, 98.4]	96.8	[93.8, 99.1]	95.7	[92.3, 98.5]	94.6	[90.9, 97.8]
2008	599	97.4	[95.3, 98.9]	96.4	[93.9, 98.4]	94.8	[91.8, 97.3]	94.2	[90.8, 97.0]	94.2	[90.5, 97.3]
2009	716	97.5	[95.6, 98.8]	96.9	[94.6, 98.7]	95.5	[92.8, 97.7]	95.6	[92.7, 98.1]	94.9	[91.6, 97.7]
2010	716	98.2	[96.4, 99.4]	98.0	[95.8, 99.6]	97.3	[94.7, 99.4]	96.4	[93.4, 98.9]	95.5	[92.2, 98.4]
2011	797	99.7	[98.4, 100.6]	99.0	[97.2, 100.5]	98.7	[96.4, 100.5]	97.9	[95.2, 100.0]	97.3	[94.3, 99.8]
2012	779	98.6	[97.0, 99.7]	97.7	[95.6, 99.3]	96.4	[93.9, 98.4]	94.5	[91.6, 96.9]	95.0	[91.9, 97.6]
2013	815	99.2	[97.7, 100.1]	98.5	[96.6, 100.0]	97.9	[95.6, 99.8]	96.8	[94.1, 99.0]	96.5	[93.5, 99.0]
2014	836	100.0	[98.7, 100.8]	99.2	[97.4, 100.6]	98.6	[96.4, 100.4]	98.4	[95.8, 100.5]	97.6	[94.7, 100.1]
2015	855	99.6	[98.3, 100.5]	98.5	[96.6, 99.9]	97.9	[95.6, 99.7]	97.8	[95.2, 100.0]	96.8	[93.6, 99.5]
2016	893	99.1	[97.7, 100.0]	98.6	[96.8, 100.0]	98.7	[96.6, 100.4]	97.2	[94.4, 99.6]	no FU	—
2017	865	100.1	[99.0, 100.9]	100.1	[98.5, 101.3]	99.1	[96.7, 101.0]	no FU	—	no FU	—
Combined Stage II											
2004	143	96.2	[90.5, 99.2]	90.7	[83.4, 95.7]	86.5	[78.2, 92.7]	83.8	[74.9, 90.9]	80.3	[70.7, 88.3]
2005	129	92.5	[85.7, 96.7]	91.6	[84.1, 96.7]	90.0	[81.7, 96.0]	89.3	[80.3, 95.9]	90.4	[81.0, 97.5]



Characteristic	N at risk	Unadjusted relative survival, %									
		1 year		2 year		3 year		4 year		5 year	
		%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI
2006	105	93.1	[85.4, 97.6]	86.9	[77.6, 93.4]	80.4	[69.9, 88.5]	76.4	[65.3, 85.4]	76.5	[65.0, 86.0]
2007	128	100.4	[95.4, 102.0]	96.6	[89.8, 100.6]	93.5	[85.5, 99.0]	89.7	[80.6, 96.4]	84.6	[74.6, 92.6]
2008	160	97.4	[92.5, 100.0]	95.9	[90.1, 99.6]	92.3	[85.3, 97.3]	90.1	[82.3, 95.9]	85.5	[77.0, 92.4]
2009	125	95.7	[89.3, 99.2]	94.5	[87.0, 99.2]	95.0	[86.8, 100.4]	94.7	[85.8, 101.0]	93.3	[83.6, 100.6]
2010	128	97.6	[92.0, 100.2]	97.6	[91.3, 101.1]	94.4	[86.8, 99.4]	91.9	[83.4, 98.0]	90.2	[80.9, 97.1]
2011	160	97.1	[92.2, 99.7]	94.9	[89.0, 98.7]	93.3	[86.6, 98.0]	91.2	[83.6, 96.7]	91.0	[83.0, 97.2]
2012	168	97.8	[93.1, 100.2]	93.6	[87.4, 97.8]	93.2	[86.4, 98.1]	89.6	[81.8, 95.6]	83.4	[74.8, 90.6]
2013	118	97.5	[91.7, 100.0]	92.4	[84.9, 97.1]	89.1	[80.7, 95.0]	91.3	[82.6, 97.3]	88.0	[78.5, 95.1]
2014	136	98.6	[93.5, 100.8]	95.6	[89.1, 99.5]	94.1	[86.7, 99.1]	92.6	[84.5, 98.4]	91.2	[82.4, 97.8]
2015	144	98.6	[93.8, 100.7]	95.1	[88.8, 98.9]	93.5	[86.4, 98.2]	93.5	[85.9, 98.7]	92.2	[83.2, 98.6]
2016	126	95.5	[89.3, 98.7]	92.7	[85.4, 97.3]	92.3	[84.4, 97.5]	94.6	[86.5, 100.0]	no FU	—
2017	124	98.2	[92.6, 100.6]	98.1	[91.7, 101.4]	94.6	[85.2, 100.3]	no FU	—	no FU	—
Combined Stage III											
2004	181	87.2	[80.9, 91.8]	80.9	[73.7, 86.8]	74.9	[66.9, 81.6]	72.8	[64.5, 80.1]	68.2	[59.4, 76.0]
2005	196	88.4	[82.5, 92.7]	79.8	[72.7, 85.6]	67.6	[59.7, 74.7]	65.9	[57.7, 73.4]	61.8	[53.3, 69.7]
2006	188	89.9	[84.0, 94.0]	84.9	[78.0, 90.3]	79.2	[71.5, 85.6]	71.6	[63.2, 79.0]	69.3	[60.6, 77.2]
2007	199	88.8	[82.9, 93.1]	81.7	[74.6, 87.4]	75.7	[67.9, 82.4]	69.9	[61.6, 77.3]	67.8	[59.1, 75.7]
2008	228	87.1	[81.5, 91.3]	80.5	[73.9, 85.9]	74.9	[67.8, 81.1]	71.6	[64.0, 78.3]	67.4	[59.5, 74.6]
2009	207	90.1	[84.4, 94.2]	82.8	[75.9, 88.4]	78.9	[71.4, 85.3]	74.9	[66.9, 82.0]	72.2	[63.7, 79.8]
2010	243	86.8	[81.4, 91.0]	76.9	[70.5, 82.4]	73.0	[66.1, 79.1]	68.5	[61.2, 75.2]	66.0	[58.4, 73.0]
2011	233	91.8	[86.9, 95.3]	82.9	[76.6, 88.1]	78.0	[71.0, 84.0]	72.3	[64.7, 79.0]	70.2	[62.3, 77.5]
2012	214	93.8	[89.0, 97.0]	81.4	[74.8, 86.8]	76.4	[69.2, 82.6]	71.6	[63.9, 78.5]	68.7	[60.6, 76.0]
2013	237	96.3	[92.2, 98.8]	86.9	[81.1, 91.5]	81.7	[75.1, 87.2]	76.0	[68.9, 82.3]	74.0	[66.5, 80.6]
2014	233	91.1	[86.1, 94.6]	82.8	[76.6, 87.9]	78.5	[71.6, 84.3]	74.7	[67.4, 81.2]	72.4	[64.7, 79.4]



Characteristic	N at risk	Unadjusted relative survival, %									
		1 year		2 year		3 year		4 year		5 year	
		%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI
2015	246	91.8	[87.1, 95.1]	86.7	[81.0, 91.1]	85.7	[79.6, 90.7]	82.2	[75.5, 87.9]	79.6	[72.0, 86.2]
2016	263	85.8	[80.5, 89.9]	80.0	[73.9, 85.0]	75.1	[68.6, 80.9]	71.1	[63.5, 77.9]	no FU	—
2017	229	89.7	[84.5, 93.5]	84.4	[78.3, 89.2]	82.3	[75.1, 88.1]	no FU	—	no FU	—
Combined Stage IV											
2004	163	44.8	[37.0, 52.3]	31.4	[24.4, 38.8]	23.8	[17.4, 30.9]	19.8	[13.8, 26.6]	17.0	[11.4, 23.6]
2005	186	49.7	[42.2, 56.8]	35.0	[27.9, 42.2]	27.1	[20.6, 34.0]	22.6	[16.5, 29.4]	21.0	[15.0, 27.8]
2006	184	42.2	[35.1, 49.2]	28.7	[22.3, 35.5]	22.0	[16.1, 28.5]	20.3	[14.6, 26.8]	17.8	[12.3, 24.1]
2007	174	47.4	[39.8, 54.7]	29.7	[23.0, 36.7]	23.1	[17.0, 29.9]	21.8	[15.8, 28.6]	17.4	[11.9, 23.8]
2008	215	52.6	[45.6, 59.2]	34.5	[28.0, 41.1]	25.4	[19.6, 31.8]	20.6	[15.2, 26.6]	17.6	[12.6, 23.5]
2009	193	46.4	[39.2, 53.3]	30.9	[24.3, 37.7]	24.1	[18.1, 30.6]	19.0	[13.6, 25.2]	13.1	[8.6, 18.8]
2010	181	48.2	[40.7, 55.3]	29.9	[23.2, 36.9]	23.7	[17.6, 30.5]	19.8	[14.1, 26.3]	15.3	[10.2, 21.5]
2011	159	54.4	[46.2, 61.9]	33.8	[26.4, 41.4]	26.3	[19.4, 33.7]	23.6	[16.9, 30.9]	19.1	[13.0, 26.2]
2012	180	50.6	[42.9, 57.8]	31.7	[24.9, 38.8]	24.4	[18.2, 31.1]	18.9	[13.3, 25.3]	14.7	[9.7, 20.8]
2013	216	51.6	[44.7, 58.1]	34.5	[28.0, 41.0]	24.9	[19.2, 31.1]	22.0	[16.5, 28.2]	20.6	[15.2, 26.8]
2014	219	53.1	[46.1, 59.7]	38.7	[32.0, 45.3]	29.4	[23.3, 35.8]	25.1	[19.3, 31.4]	21.2	[15.8, 27.2]
2015	208	56.3	[49.3, 62.9]	36.8	[30.1, 43.6]	28.3	[22.1, 34.9]	24.7	[18.8, 31.2]	23.5	[17.4, 30.3]
2016	191	54.3	[46.8, 61.3]	44.0	[36.6, 51.2]	36.6	[29.4, 43.8]	34.7	[27.3, 42.3]	no FU	—
2017	198	61.3	[53.8, 68.0]	42.1	[34.9, 49.2]	34.1	[26.7, 41.7]	no FU	—	no FU	—



Appendix 12.1.2. Uptake of selected drugs

Table 189 – Proportion of patients who received at least one dose during 5-year period after diagnosis (renal cell carcinoma stage III)

Drug/incidence year (n)	2004 (181)	2005 (196)	2006 (190)	2007 (199)	2008 (229)	2009 (207)	2010 (244)	2011 (234)	2012 (214)	2013 (238)	2014 (233)	2015 (249)	2016 (264)	2017 (229)
Sunitinib	6.6%	10.7%	14.2%	21.1%	14.8%	14.5%	13.5%	12.4%	19.6%	16.4%	14.2%	8.0%	14.4%	7.9%
Sorafenib	1.7%	7.7%	10.0%	12.6%	7.9%	5.8%	9.0%	9.4%	5.1%	4.6%	3.0%	2.0%	0.4%	
Pazopanib			1.6%	1.5%	3.1%	6.8%	7.8%	17.9%	14.5%	12.6%	11.6%	12.4%	12.5%	11.8%
Axitinib						0.5%	2.0%	3.0%	8.9%	9.7%	6.4%	3.6%	2.3%	
Everolimus		1.5%	4.7%	3.0%	8.3%	7.7%	8.6%	12.8%	10.3%	8.8%	4.7%	2.4%	1.5%	0.4%
Temsirolimus		0.5%	3.2%	1.5%	3.5%	4.3%	5.3%	1.3%	1.4%	2.1%	2.6%	1.2%	0.8%	0.4%
Nivolumab									5.6%	8.8%	9.0%	8.4%	11.4%	9.6%

* Number in yellow indicates the first calendar year of reimbursement. For example, sunitinib was first reimbursed in 2007. The columns in this table indicate the incidence year. For example, for incidence year 2009, 14.5% of patients received reimbursed sunitinib during the 5 years after diagnosis. Source: BCR-IMA.

Remark: IMA data were only available up to the second trimester of 2019. Five-year follow-up data are thus not complete for the last years in this table.



Table 190 – Proportion of patients who received at least one dose during 5-year period after diagnosis (renal cell carcinoma stage IV)

Drug/incidence year (n)	2004 (164)	2005 (187)	2006 (185)	2007 (174)	2008 (217)	2009 (193)	2010 (181)	2011 (162)	2012 (180)	2013 (220)	2014 (221)	2015 (209)	2016 (192)	2017 (200)
Sunitinib	7.3%	13.4%	19.5%	54.0%	55.8%	50.8%	55.8%	43.8%	30.0%	31.8%	39.4%	38.3%	35.9%	23.0%
Sorafenib	5.5%	9.6%	15.7%	25.3%	29.5%	24.9%	19.3%	20.4%	17.8%	9.5%	9.5%	6.2%	2.1%	0.5%
Pazopanib				1.1%	4.6%	5.2%	8.8%	29.6%	38.3%	37.3%	32.1%	34.0%	31.8%	37.5%
Axitinib						1.0%	2.2%	6.2%	12.8%	26.8%	22.6%	16.7%	9.4%	3.5%
Everolimus		4.8%	1.6%	4.0%	11.5%	24.4%	29.8%	34.0%	22.8%	20.5%	14.9%	10.5%	3.6%	2.5%
Temsirolimus	1.2%		2.2%	4.6%	12.4%	21.8%	22.7%	16.0%	11.1%	7.7%	7.2%	6.2%	5.2%	2.0%
Nivolumab									3.3%	4.1%	14.5%	21.1%	32.3%	34.5%

* Number in yellow indicates the first calendar year of reimbursement. For example, sunitinib was first reimbursed in 2007. The columns in this table indicate the incidence year. For example, for incidence year 2009, 50.8% of patients received reimbursed sunitinib during the 5 years after diagnosis. Source: BCR-IMA.

Remark: IMA data were only available up to the second trimester of 2019. Five-year follow-up data are thus not complete for the last years in this table.



Appendix 12.2. Reimbursement criteria for selected drugs

Table 191 – Targeted therapy in renal cell carcinoma: reimbursement criteria in Belgium

Drug	Trade name	Date reimbursement	start	Indication NI	Indication Fr
Sunitinib	Sutent	1/4/2007		<p>De specialiteit komt in aanmerking voor vergoeding indien ze gebruikt wordt voor de behandeling van een gevorderd en/of gemetastaseerd niercelcarcinoom (stadium IV):</p> <ul style="list-style-type: none"> - bij een rechthebbende die voor deze kanker nog geen antineoplastische behandeling heeft gekregen voor zover deze patiënt een gunstige prognose vertoont volgens de IMDC classificatie; bij een patiënt met intermediaire of ongunstige prognose volgens de IMDC classificatie bij wie een eerste- en/of tweedelijsbehandeling met een immuun checkpoint inhibitor en/of cabozanitinib niet aangewezen, toepasbaar of terugbetaalbaar is bij wie ten minste twee eerdere therapieën, gebaseerd op interferon-alfa of interleukine-2, een immuun checkpoint inhibitor en/of een VEGF-gerichte therapie, anders dan sunitinib, faalden bij wie het een verlenging van eerder terugbetaalde sunitinib voor deze indicatie betreft 	<p>La spécialité entre en ligne de compte pour un remboursement si elle est administrée pour le traitement d'un cancer du rein avancé et ou métastasé (stade IV) :</p> <ul style="list-style-type: none"> chez un bénéficiaire qui n'a pas encore reçu de traitement antinéoplasique pour autant que ce patient ait un pronostic favorable selon la classification IMDC ; chez un patient dont le pronostic est intermédiaire ou défavorable selon la classification IMDC et pour lequel un traitement de première et/ou de deuxième ligne avec un inhibiteur du point de contrôle immunitaire et/ou le cabozanitinib n'est pas indiqué, approprié ou remboursable chez un bénéficiaire chez qui au moins deux traitements par interféron-alpha ou interleukine-2, un inhibiteur du point de contrôle immunitaire et/ou un traitement ciblé VEGF, autre que le sunitinib, ont échoué chez un bénéficiaire pour qui il s'agit d'une prolongation d'un traitement par sunitinib déjà remboursé pour cette indication
Pazopanib	Votrient	1/3/2011		<p>De specialiteit komt in aanmerking voor vergoeding ofwel indien ze gebruikt wordt voor de eerstelijsbehandeling van een gevorderd en/of gemetastaseerd niercelcarcinoom (stadium IV).</p> <ul style="list-style-type: none"> bij een rechthebbende die voor deze kanker nog geen antineoplastische behandeling heeft gekregen voor zover deze patiënt een gunstige prognose vertoont volgens de IMDC classificatie; bij een patiënt met intermediaire of ongunstige prognose volgens de IMDC classificatie bij wie een eerste- en/of tweedelijsbehandeling met een 	<p>La spécialité entre en ligne de compte pour un remboursement si elle est administrée pour le traitement de première ligne d'un carcinome rénal avancé et/ou métastasé (Stade IV).</p> <ul style="list-style-type: none"> chez un bénéficiaire qui n'a pas encore reçu de traitement antinéoplasique pour autant que ce patient ait un pronostic favorable selon la classification IMDC; chez un bénéficiaire dont le pronostic est intermédiaire ou défavorable selon la classification IMDC et pour lequel un traitement de première et/ou de deuxième ligne avec un inhibiteur du point de



Drug	Trade name	Date start reimbursement	Indication NI	Indication Fr
			<p>immuun checkpoint inhibitor en/of cabozantinib niet aangewezen, toepasbaar of terugbetaalbaar is</p> <ul style="list-style-type: none"> • bij wie ten minste twee eerdere therapieën, gebaseerd op interferon-alfa of interleukine-2, een immuun checkpoint inhibitor en/of een VEGF-gerichte therapie, anders dan pazopanib, faalden • bij wie het een verlenging van eerder terugbetaalde pazopanib voor deze indicatie betreft 	<p>contrôle immunitaire et/ou le cabozantinib n'est pas indiqué, approprié ou remboursable</p> <ul style="list-style-type: none"> • chez un bénéficiaire chez qui au moins deux traitements par interféron-alpha ou interleukine-2, un inhibiteur des points de contrôle immunitaires et/ou un traitement ciblé VEGF, autre que le pazopanib, ont échoué • chez un bénéficiaire chez qui il s'agit d'une prolongation du pazopanib précédemment remboursé pour cette indication
Everolimus	Afinitor	1/3/2010	<p>De specialiteit komt in aanmerking voor vergoeding indien ze gebruikt wordt voor de behandeling van een gevorderd niercelcarcinoom van het heldercellig type bij patiënten:</p> <ul style="list-style-type: none"> • bij wie een tweedelijsbehandeling met een immuun checkpoint inhibitor en/of een VEGF-gerichte therapie niet aangewezen, toepasbaar of terugbetaalbaar is • bij wie progressie werd vastgesteld na ten minste twee eerdere therapieën met een immuun checkpoint inhibitor en/of een VEGF-gerichte therapie • bij wie het een verlenging van eerder terugbetaalde everolimus voor deze indicatie betreft 	<p>La spécialité entre en ligne de compte pour un remboursement si elle est administrée pour le traitement d'un carcinome rénal avancé à cellules claires chez un patient :</p> <ul style="list-style-type: none"> • chez qui un traitement de deuxième ligne constitué des inhibiteurs du point de contrôle immunitaires et/ou d'un traitement dirigé contre le VEGF n'est pas indiqué, approprié ou remboursable • chez qui une progression de la maladie est constatée après au moins deux traitements précédents constitués d'un inhibiteur du point de contrôle immunitaires et/ou d'un traitement dirigé contre le VEGF • chez qui il s'agit d'une prolongation de l'everolimus précédemment remboursé pour cette indication
Sorafenib	Nexavar	1/4/2007	<p>De specialiteit komt in aanmerking voor vergoeding indien ze gebruikt wordt voor de behandeling van een gevorderd niercarcinoom (stadium IV), bij een rechthebbende :</p> <ul style="list-style-type: none"> • bij wie ten minste twee eerdere therapieën, gebaseerd op interferon-alfa of interleukine-2, een immuun checkpoint inhibitor en/of een VEGF-gerichte therapie, anders dan sorafenib, faalden of bij wie deze eerste- en/of tweedelijsbehandelingen niet aangewezen, toepasbaar of terugbetaalbaar zijn • bij wie het een verlenging van eerder terugbetaalde sorafenib voor deze indicatie betreft 	<p>La spécialité entre en ligne de compte pour un remboursement si elle est administrée pour le traitement d'un cancer du rein avancé (stade IV) chez un bénéficiaire :</p> <ul style="list-style-type: none"> • chez qui au moins deux traitements antérieurs à base d'interféron alpha ou l'interleukine-2, un inhibiteur du point de contrôle immunitaire et/ou un traitement ciblé VEGF, autre que sorafenib, ont échoué, ou chez qui ces traitements de première ou deuxième ligne ne sont pas indiqués, appropriés ou remboursables



Drug	Trade name	Date start reimbursement	Indication NI	Indication Fr
axitinib	Inlyta	1/10/2013	<p>De specialiteit komt in aanmerking voor vergoeding indien ze gebruikt wordt voor de behandeling van een gevorderd niercelcarcinoom (stadium IV), bij een rechthebbende:</p> <ul style="list-style-type: none">• bij wie ten minste twee eerdere therapieën met een immuun checkpoint inhibitor en/of een VEGF-gerichte therapie, anders dan axitinib, faalden• bij wie een tweedelijsbehandeling met een immuun checkpoint inhibitor en/of een VEGF-gerichte therapie, anders dan axitinib, niet aangewezen, toepasbaar of terugbetaalbaar is• bij wie het een verlenging van eerder terugbetaalde axitinib voor deze indicatie betreft	<ul style="list-style-type: none">• chez qui il s'agit d'une prolongation d'un traitement par sorafenib déjà remboursé pour cette indication <p>La spécialité entre en ligne de compte pour un remboursement si elle est administrée pour le traitement d'un cancer du rein avancé (stade IV) chez un bénéficiaire :</p> <ul style="list-style-type: none">• chez qui au moins deux traitements précédents, constitués d'un inhibiteur du point de contrôle immunitaire et/ou d'un traitement ciblé VEGF, autre que l'axitinib, ont échoué• chez qui un traitement de deuxième ligne, constitué d'un inhibiteur des points de contrôle immunitaires et/ou d'une thérapie ciblé VEGF, autre que le axitinib, n'est pas indiqué, approprié ou remboursable• chez qui il s'agit d'une prolongation de l'axitinib précédemment remboursé pour cette indication
temsirolimus	Torisel	1/12/2008	<p>eerstelijsbehandeling van patiënten met gevorderd niercelcarcinoom die ten minste drie van de zes hieronder vermelde prognostische risicofactoren hebben:</p> <ol style="list-style-type: none">1. minder dan 1 jaar tussen het tijdstip van de initiële diagnose niercel-carcinoom en het starten van de systemische behandeling;2. Karnofsky prestatieindex van 60 of 70;3. hemoglobine minder dan de laagste limiet van het normale;4. gecorrigeerd calcium > 10 mg/dl;5. lactaatdehydrogenase > 1,5 keer de bovenste limiet van het normale;6. meer dan één orgaan met metastasen. <p>EN voor zover bij deze patiënt een eerstelijsbehandeling met een immuun checkpoint inhibitor en/of met cabozantinib niet aangewezen, toepasbaar of terugbetaalbaar is.</p>	<p>traitement de première intention d'un carcinome rénal avancé chez les patients présentant au moins trois des six facteurs de risque pronostiques mentionnés ci-dessous:</p> <ol style="list-style-type: none">1. moins d'un an entre le diagnostic initial de carcinome rénal et le début du traitement systémique;2. indice de Karnofsky égal à 60 ou à 70 ;3. hémoglobine au-dessous de la limite inférieure à la normale ;4. calcémie corrigée > 10 mg/dl;5. lactate déshydrogénase > 1,5 fois la limite supérieure à la normale ;6. plus d'un organe métastaté. <p>ET pour autant que pour ce patient, un traitement de première ligne avec un inhibiteur des points de contrôle immunitaire et/ou avec le cabozantinib ne soit pas indiqué, approprié ou remboursable.</p>



Table 192 – Immunotherapy in renal cell carcinoma: reimbursement criteria

Drug	Trade name	Date start reimbursement	Indication NI	Indication Fr	EMA
Nivolumab Opdivo		01/02/2019	eerstelijnsbehandeling in combinatie met ipilimumab van gevorderd niercelcarcinoom met intermediair/ongunstig risicoprofiel bij volwassenen (ter info: ipilimumab wordt niet vergoed in deze indicatie)	traitement en association à l'ipilimumab, en première ligne des patients adultes atteints d'un carcinome à cellules rénales avancé de pronostic intermédiaire/défavorable (pour information: l'ipilimumab n'est pas remboursé dans cette indication)	
		01/01/2017	behandeling van gevorderd niercelcarcinoom na eerdere behandeling bij volwassenen (monotherapie)	traitement des patients adultes atteints d'un carcinome à cellules rénales avancé après un traitement antérieur (monothérapie)	
		01/07/2017	behandeling van lokaal gevorderd inoperabel of gemetastaseerd urotheelcarcinoom bij volwassenen na falen van eerdere platina-bevattende therapie (monotherapie)	traitement des patients adultes atteints d'un carcinome urothélial localement avancé non résécable ou métastatique après échec d'une chimiothérapie antérieure à base de sels de platine (monothérapie)	



Appendix 12.3. medical literature: Search for evidence

Appendix 12.3.1. Search medical literature (systematic reviews)

The search for systematic reviews in MEDLINE, PreMedline and the Cochrane library of systematic reviews (inception to search date) specifically developed for this research question, yielded 283 records (Figure 558), one additional SR was added. After de-duplication, 141 of the 284 remaining reviews (2020-2017) were screened based on title and abstract, of which 83 were excluded. In total 58 full text articles were assessed for eligibility. Based on full text evaluation, 54 reviews were excluded (Figure 559).

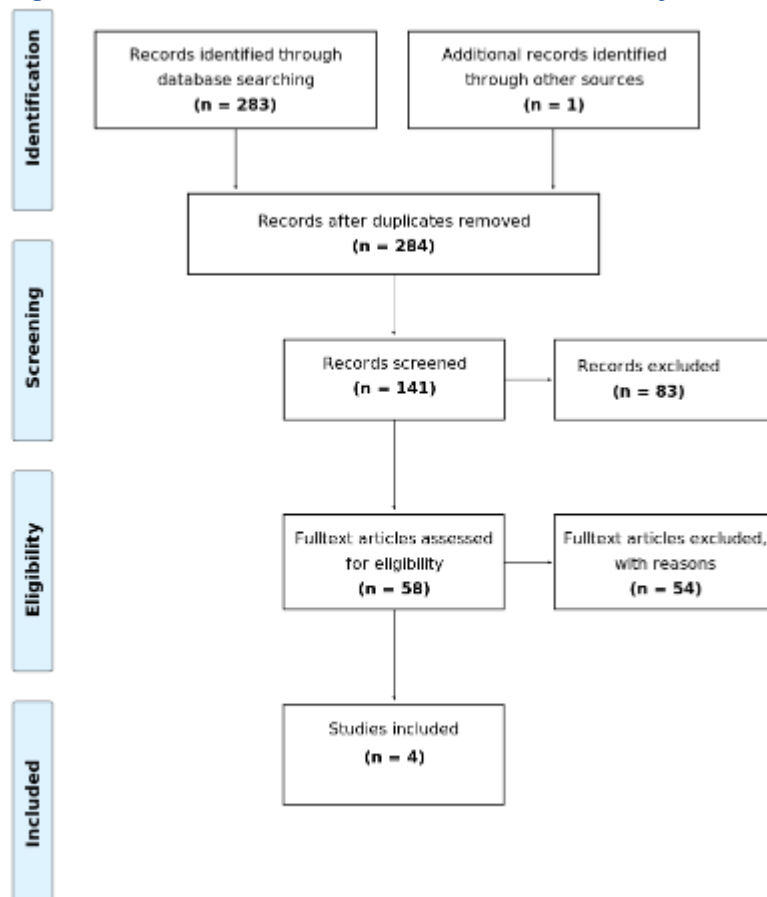
**Figure 366 – Renal cancer – Selection of SRs - Study flow**

**Table 193 – Renal cell carcinoma: excluded reviews and reason for exclusion**

Year	Publication	Reason for exclusion
1	2020 Yekeduz, E. Arzu Yasar, H. Utkan, G. Urun, Y. A systematic review: Role of systemic therapy on treatment and prevention of brain metastasis in renal cell carcinoma. J Oncol Pharm Pract 2020; 26(4):972-981	Wrong outcome
2	2020 Monteiro, F. S. M. Soares, A. Debiasi, M. et al. First-line Treatment of Metastatic Renal Cell Carcinoma in the Immuno-oncology Era: Systematic Review and Network Meta-analysis Clin Genitourin Cancer 2020;4:04	wrong comparison (for overall survival)
3	2020 Manz, K. M. Fenchel, K. Eilers, A. et al. Efficacy and Safety of Approved First-Line Tyrosine Kinase Inhibitor Treatments in Metastatic Renal Cell Carcinoma: A Network Meta-Analysis Adv Ther 2020;37(2):730-744	wrong outcome (PFS)
4	2020 Liu, X. L. Xue, H. Y. Chu, Q. et al. Comparative efficacy and safety of sunitinib vs sorafenib in renal cell carcinoma: A systematic review and meta-analysis Medicine (Baltimore) 2020;99(13):e19570	wrong comparison
5	2020 Chahoud, J. Msaouel, P. Campbell, M. T. et al. Nivolumab for the Treatment of Patients with Metastatic Non-Clear Cell Renal Cell Carcinoma (nccRCC): A Single-Institutional Experience and Literature Meta-Analysis. Oncologist 2020;25(3):252-258	wrong patient group
6	2020 Buti, S. Petrelli, F. Ghidini, A. et al. Immunotherapy-based combinations versus standard first-line treatment for metastatic clear cell renal cell carcinoma: a systematic review and meta-analysis. Clin Transl Oncol 2020;19:19	No critical appraisal
7	2020 Bersanelli, M. Brunelli, M. Gnetti, L. et al. Pazopanib as a possible option for the treatment of metastatic non-clear cell renal carcinoma patients: a systematic review Ther Adv Med Oncol 2020;12	wrong patient group
8	2020 Alam, M. U. Jazayeri, S. B. Gautam, S. et al. Combination Therapy for Metastatic Renal Cell Carcinoma: A Systematic Review and Network Meta-analysis. Am J Clin Oncol 2020;3:03	wrong comparisons, wrong outcomes
9	2019 Wang, J. Li, X. Wu, X. et al. Role of immune checkpoint inhibitor-based therapies for metastatic renal cell carcinoma in the first-line setting: A Bayesian network analysis. EBioMedicine 2019;47:78-88	Relevant results not reported (only network meta-analysis)
10	2019 Wang, H. T. Xia, M. A meta-analysis of efficacy and safety of sorafenib versus other targeted agents for metastatic renal cell carcinoma. Medicine (Baltimore) 2019;98(1):e13779	wrong comparison
11	2019 Vargas, C. Balmaceda, C. Rodriguez, F. et al. Economic evaluation of sunitinib versus pazopanib and best supportive care for the treatment of metastatic renal cell carcinoma in Chile: cost-effectiveness analysis and a mixed treatment comparison. Expert rev 2019;19(5):609-617	not a systematic review
12	2019 Tremblay, G. McElroy, H. J. Westley, T. et al. Indirect treatment comparisons including network meta-analysis: Lenvatinib plus everolimus for the second-line treatment of advanced/metastatic renal cell carcinoma. PLoS ONE 2019;14(3):e0212899	wrong comparisons
13	2019 Sneed, G. T. Lee, S. Brown, J. N. Hammond, J. M. The Role of Pazopanib in Non-Clear Cell Renal Cell Carcinoma: A Systematic Review. Clin Genitourin Cancer 2019;17(6):419-424	wrong patient group
14	2019 Schey, C. Meier, G. Pan, J. Metastatic Renal Cell Cancer: An Analysis of Reimbursement Decisions. Adv Ther 2019;36(6):1266-1278	Not a systematic review
15	2019 Roviello, G. Corona, S. P. Nesi, G. Mini, E. Results from a meta-analysis of immune checkpoint inhibitors in first-line renal cancer patients: does PD-L1 matter? Ther Adv Med Oncol 2019;11	Included



	Year	Publication	Reason for exclusion
16	2019	Riaz, I. B. Faridi, W. Husnain, M. et al. Adjuvant Therapy in High-Risk Renal Cell Cancer: A Systematic Review and Meta-analysis. <i>Mayo Clin Proc</i> 2019;94(8): 1524-1534	wrong patient group (adjuvant therapy not reimbursed in Belgium)
17	2019	Porta, C. Szczylik, C. Casciano, R. et al. Second-line cabozantinib versus nivolumab in advanced renal cell carcinoma: Systematic review and indirect treatment comparison. <i>Crit Rev Oncol Hematol</i> 2019;139:143-148	No additional information (wrong comparison)
18	2019	Peinemann, F. Unverzagt, S. Hadjinicolaou, A. V. Moldenhauer, I. Immunotherapy for metastatic renal cell carcinoma: A systematic review. <i>J Evid Based Med</i> 2019;12(4):253-262	No additional information
19	2019	Moran, M. Nickens, D. Adcock, K. et al. Sunitinib for Metastatic Renal Cell Carcinoma: A Systematic Review and Meta-Analysis of Real-World and Clinical Trials Data. <i>Target</i> 2019;14(4):405-416	No additional information
20	2019	Moran, M. Nickens, D. Adcock, K. et al. Augmenting the randomized controlled trial with real-world data to aid clinical decision making in metastatic renal cell carcinoma: a systematic review and meta-analysis. <i>Fut Oncol</i> 2019;15(34):3987-4001	No additional information
21	2019	Massari, F. Di Nunno, V. Mollica, V. et al. Adjuvant Tyrosine Kinase Inhibitors in Treatment of Renal Cell Carcinoma: A Meta-Analysis of Available Clinical Trials. <i>Clin Genitourin Cancer</i> 2019;17(2):e339-e344	wrong patient group (adjuvant therapy not reimbursed in Belgium)
22	2019	Karner, C. Kew, K. Wakefield, V. et al. Targeted therapies for previously treated advanced or metastatic renal cell carcinoma: systematic review and network meta-analysis. <i>BMJ Open</i> 2019;9(3):e024691	Included
23	2019	Huang, H. F. Fan, X. R. Ji, Z. G. The Effectiveness of Sorafenib over Other Targeted Agents in the Second-Line Treatment of Metastatic Renal Cell Carcinoma: a Meta-Analysis. <i>Pathol Oncol Res</i> 2019;25(4):1497-1503	No OS data
24	2019	Huang, H. F. Fan, X. R. Ji, Z. G. The Effectiveness of Sorafenib over Other Targeted Agents in the Second-Line Treatment of Metastatic Renal Cell Carcinoma: a Meta-Analysis. <i>Pathol Oncol Res</i> 2019;25(4):1497-1503	No OS data
25	2019	Hale, P. Hahn, A. W. Rathi, N. et al. Treatment of metastatic renal cell carcinoma in older patients: A network meta-analysis. <i>J Geriatr Oncol</i> 2019;10(1):149-154	No overall data
26	2019	Hahn, A. W. Klaassen, Z. Agarwal, N. et al. First-line Treatment of Metastatic Renal Cell Carcinoma: A Systematic Review and Network Meta-analysis. <i>Eur Urol Oncol</i> 2019;2(6):708-715	No additional information
27	2019	Deng, H. Liu, W. He, T. et al. Comparative Efficacy, Safety, and Costs of Sorafenib vs. Sunitinib as First-Line Therapy for Metastatic Renal Cell Carcinoma: A Systematic Review and Meta-Analysis. <i>Front</i> 2019;9:479	observational studies included
28	2019	Deng, H. Huang, Y. Hong, Z. et al. Pazopanib has equivalent anti-tumor effectiveness and lower Total costs than Sunitinib for treating metastatic or advanced renal cell carcinoma: a meta-analysis. <i>BMC Cancer</i> 2019;19(1):489	observational studies included
29	2019	Chung, D. Y. Kang, D. H. Kim, J. W. et al. Does an Alternative Sunitinib Dosing Schedule Really Improve Survival Outcomes over a Conventional Dosing Schedule in Patients with Metastatic Renal Cell Carcinoma? An Updated Systematic Review and Meta-Analysis. <i>Cancers (Basel)</i> 2019;11(12):21	wrong research question



Year	Publication	Reason for exclusion
30	2019 Chahoud, J. Msaouel, P. Campbell, M. T. et al. Nivolumab for the Treatment of Patients with Metastatic Non-Clear Cell Renal Cell Carcinoma (nccRCC): A Single-Institutional Experience and Literature Meta-Analysis. <i>Oncologist</i> 2019;9:09	No methodology for systematic review reported
31	2018 Wei, C. Wang, S. Ye, Z. Chen, Z. Efficacy of targeted therapy for advanced renal cell carcinoma: a systematic review and meta-analysis of randomized controlled trials. <i>Int Braz J Urol</i> 2019;44(2):219-237	results reported in an unclear fashion
32	2018 Wallis, C. J. D. Klaassen, Z. Bhindi, B. et al. First-line Systemic Therapy for Metastatic Renal Cell Carcinoma: A Systematic Review and Network Meta-analysis. <i>Eur Urol</i> 2018;74(3):309-321	No additional information
33	2018 Verma, V. Sprave, T. Haque, W. et al. A systematic review of the cost and cost-effectiveness studies of immune checkpoint inhibitors. <i>J Immunother Cancer</i> 2019;6(1):128	No critical appraisal of the clinical aspects
34	2018 Totzeck, M. Mincu, R. I. Mroczek, S. et al. Cardiovascular diseases in patients receiving small molecules with anti-vascular endothelial growth factor activity: A meta-analysis of approximately 29,000 cancer patients. <i>Eur J Prev Cardiol</i> 2018;25(5):482-494	wrong outcome
35	2018 Sun, M. Marconi, L. Eisen, T. et al. Adjuvant Vascular Endothelial Growth Factor-targeted Therapy in Renal Cell Carcinoma: A Systematic Review and Pooled Analysis. <i>Eur Urol</i> 2018;74(5):611-620	wrong patient group (adjuvant therapy not reimbursed in Belgium)
36	2018 Sonbol, M. B. Firwana, B. Hilal, T. et al. Adjuvant Antiangiogenic Agents in Post-nephrectomy Renal Cell Carcinoma: A Systematic Review and Meta-analysis. <i>Eur Urol Oncol</i> 2018;1(2):101-108	wrong patient group (adjuvant therapy not reimbursed in Belgium)
37	2018 Qin, F. Yu, H. Xu, C. R. et al. Safety of axitinib and sorafenib monotherapy for patients with renal cell carcinoma: a meta-analysis. <i>The Journal of Biomedical research</i> 2018;32(1):30-38	no critical appraisal, wrong outcomes
38	2018 Mendez-Vidal, M. J. Molina, A. Anido, U. et al. Pazopanib: Evidence review and clinical practice in the management of advanced renal cell carcinoma. <i>BMC Pharmacol Toxicol</i> 2018;19(1):77	not a systematic review
39	2018 Lyu, C. Li, W. Liu, S. et al. Systematic review on the efficacy and safety of immune checkpoint inhibition in renal cell carcinoma. <i>Fut Oncol</i> 2018;14(21):2207-2221	No additional information
40	2018 Kourie, H. R. Bakouny, Z. Eid, R. et al. The merit of tyrosine kinase inhibitors in the adjuvant setting of high-risk renal cell carcinoma: a meta-analysis. <i>Fut Oncol</i> 2018;14(9):829-835	wrong patient group (adjuvant therapy not reimbursed in Belgium)
41	2018 Karakiewicz, P. I. Zaffuto, E. Kapoor, A. et al. Kidney Cancer Research Network of Canada consensus statement on the role of adjuvant therapy after nephrectomy for high-risk, non-metastatic renal cell carcinoma: A comprehensive analysis of the literature and meta-analysis of randomized controlled trials. <i>Can Urol Assoc J</i> 2018;12(3):13-18	wrong patient group (adjuvant therapy not reimbursed in Belgium)
42	2018 Iacovelli, R. Ciccarese, C. Bria, E. et al. Immunotherapy versus standard of care in metastatic renal cell carcinoma. A systematic review and meta-analysis. <i>Cancer Treat Rev</i> 2018;70:112-117	No additional information
43	2018 Edwards, S. J. Wakefield, V. Cain, P. et al. Axitinib, cabozantinib, everolimus, nivolumab, sunitinib and best supportive care in previously treated renal cell carcinoma: a systematic review and economic evaluation. <i>Health Technol Assess</i> 2018;22(6):1-278	No additional information
44	2018 Climent, M. A. Munoz-Langa, J. Basterretxea-Badiola, L. Santander-Lobera, C. Systematic review and survival meta-analysis of real world evidence on first-line pazopanib for metastatic renal cell carcinoma. <i>Crit Rev Oncol Hematol</i> 2018;121:45-50	not a SR of RCTs



	Year	Publication	Reason for exclusion
45	2018	Castellano, D. Maroto, J. P. Espinosa, E. et al. Experience with Sunitinib in metastatic renal cell carcinoma (mRCC) patients: pooled analysis from 3 Spanish observational prospective studies. <i>Expert Opin Drug Saf</i> 2018;17(6):573-579	not a SR of RCTs
46	2018	Borowiack, E. Marzec, M. Nowotarska, A. et al. Chance of reimbursement for ADD-ON therapies in Poland and in the world - review of the reimbursement recommendations. <i>Przegl Epidemiol</i> 2018;72(1):99-109	Not a systematic review
47	2018	Bai, Y. Li, S. Jia, Z. et al. Adjuvant therapy for locally advanced renal cell carcinoma: A meta-analysis and systematic review. <i>Urol</i> 2018;36(2):79.e1-79.e10	wrong patient group (adjuvant therapy not reimbursed in Belgium)
48	2018	Abdel-Rahman, O. Surrogate end points for overall survival in trials of PD-(L)1 inhibitors for urinary cancers: a systematic review. <i>Immunotherapy</i> 2018;10(2):139-148	Not a systematic review
49	2017	Wen, T. Xiao, H. Luo, C. Efficacy of sequential therapies with sorafenib-sunitinib versus sunitinib-sorafenib in metastatic renal cell carcinoma: A systematic review and meta-analysis. <i>Oncotarget</i> 2017;8(12): 20441-20451	wrong comparison
50	2017	Unverzagt, S. Moldenhauer, I. Nothacker, M. et al. Immunotherapy for metastatic renal cell carcinoma. <i>Cochrane Database Syst Rev</i> 2017; CD011673	Included
51	2017	Rijnders, M. de Wit, R. Boormans, J. L. et al. Systematic Review of Immune Checkpoint Inhibition in Urological Cancers. <i>Eur Urol</i> 2017;72(3):411-423	No additional information
52	2017	Ornstein, M. C. Garcia, J. A. Toxicity of Checkpoint Inhibition in Advanced RCC: A Systematic Review. <i>Kidney Cancer</i> 2017;1(2):133-141	No additional information
53	2017	Khoja, L. Day, D. Wei-Wu Chen, T. et al. Tumour- and class-specific patterns of immune-related adverse events of immune checkpoint inhibitors: a systematic review. <i>Ann Oncol</i> 2017;28(10):2377-2385	wrong research question
54	2017	Fernandez-Pello, S. Hofmann, F. Tahbaz, R. et al. A Systematic Review and Meta-analysis Comparing the Effectiveness and Adverse Effects of Different Systemic Treatments for Non-clear Cell Renal Cell Carcinoma. <i>Eur Urol</i> 2017;71(3):426-436	wrong patient group
55	2017	El Rassy, E. Aoun, F. Sleilaty, G. et al. Network meta-analysis of second-line treatment in metastatic renal cell carcinoma: efficacy and safety. <i>Fut Oncol</i> 2017;13(29):2709-2717	no additional information
56	2017	Dos Santos, M. Brachet, P. E. Chevreau, C. Joly, F. Impact of targeted therapies in metastatic renal cell carcinoma on patient-reported outcomes: Methodology of clinical trials and clinical benefit. <i>Cancer Treat Rev</i> 2017;53:53-60	Searched only 1 database, no new information
57	2017	Crist, M. Hansen, E. Chablani, L. Guancial, E. Examining the bleeding incidences associated with targeted therapies used in metastatic renal cell carcinoma. <i>Crit Rev Oncol Hematol</i> 2017;120:151-162	wrong outcome
58	2008	C Coppin, L Le, F Porzsolt, T Wilt Targeted therapy for advanced renal cell carcinoma. <i>Cochrane Database Syst Rev</i> , 2008 Apr 16;(2):CD006017	Included



Appendix 12.3.2. Critical appraisal systematic reviews

	Unverzagt 2017 ²⁹¹		Coppin 2008 ²⁹²	
	Score	Rationale/comment	score	Rationale/comment
1. PICO	Y		Y	
2. A priori study design	N		N	
3. Inclusion study designs	Y		Y	
4. Comprehensive literature search	Y		Partial Y	No search of trial registries
5. Duplicate study selection	Y		Y	
6. Duplicate data extraction	Y		Y	
7. List of excluded studies and rationale	Y		Y	
8. Characteristics of included studies provided	Y		Y	
9. Assessment of risk of bias	Y		Y	
10. Sources of funding reported	Y		N	sources of funding of included studies not reported.
11. Appropriate methods to combine findings	Y		Y	
12. Assessment of impact RoB in included studies on results MA	Y		Y	
13. RoB assessment used in interpretation of results and in conclusions	Y		Y	
14. Explanation for and discussion of any observed heterogeneity	Y		Y	
15. Adequate investigation of publication bias and its impact on the results	Y		Y	
16. Potential sources of conflict of interest reported	Y		Y	



	Roviello 2019 ²⁹³		Karner 2019 ²⁹⁴	
	Score	Rationale/comment	score	Rationale/comment
1. PICO	Y		Y	
2. A priori study design	Y		Y	
3. Inclusion study designs	Y		Y	
4. Comprehensive literature search	Partial yes	No search of trial registries	Partial yes	No search of trial registries
5. Duplicate study selection	Y		Y	
6. Duplicate data extraction	Y		Y	
7. List of excluded studies and rationale	N		N	
8. Characteristics of included studies provided	Y		Y	
9. Assessment of risk of bias	Partial Y	No assessment of selective outcome reporting	Y	
10. Sources of funding reported	N	Funding of included studies not reported	Y	
11. Appropriate methods to combine findings	Y		Y	
12. Assessment of impact RoB in included studies on results MA	Y		Y	
13. RoB assessment used in interpretation of results and in conclusions	Y		Y	
14. Explanation for and discussion of any observed heterogeneity	N		Y	
15. Adequate investigation of publication bias and its impact on the results	Y	(number of trials too small)	N	
16. Potential sources of conflict of interest reported	Y		Y	



Appendix 12.3.3. Search strategy

Appendix 12.3.3.1. Cochrane library of systematic reviews

Date	24/06/2020 22:07:19	
Database	Cochrane@Wiley.com	
Search strategy		
#1	[mh "Kidney Neoplasms"]	1158
#2	((kidney\$ or renal) NEAR/3 (neoplasm* or cancer* or tumor* or carcinoma* or adenocarcinoma* or onco* or malign*)):ab,ti	3386
#3	#1 or #2	3653
#4	[mh ^"nivolumab"]	395
#5	Nivolumab:ab,ti	1566
#6	"bms 936558":ab,ti	121
#7	bms936558:ab,ti	36
#8	"mdx 1106":ab,ti	16
#9	mdx1106:ab,ti	22
#10	"ono 4538":ab,ti	61
#11	ono4538:ab,ti	0
#12	opdivo:ab,ti	85
#13	"cmab 819":ab,ti	0
#14	cmab819:ab,ti	0
#15	"946414-94-4":ab,ti	81
#16	31YO63LBSN:ab,ti	0
#17	#5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16	1587
#18	#4 or #17	1604
#19	[mh ^"Sunitinib"]	295
#20	sunitinib:ab,ti	1060
#21	sutent:ab,ti	107
#22	"su 011248":ab,ti	3
#23	su011248:ab,ti	30
#24	"su 11248":ab,ti	1
#25	su11248:ab,ti	21
#26	"341031-54-7":ab,ti	38
#27	"557795-19-4":ab,ti	14
#28	"pha 2909040ad":ab,ti	0
#29	pha2909040ad:ab,ti	0
#30	"su 010398":ab,ti	0



Date	24/06/2020 22:07:19	
#31	su010398:ab,ti	1
#32	"su 10398":ab,ti	0
#33	"su10398":ab,ti	0
#34	V99T50803M:ab,ti	0
#35	#20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34	1077
#36	#19 or #35	1085
#37	pazopanib:ab,ti	494
#38	votrient:ab,ti	30
#39	armala:ab,ti	0
#40	"gw 786034":ab,ti	1
#41	gw786034:ab,ti	40
#42	"gw 786034b":ab,ti	0
#43	gw786034b:ab,ti	15
#44	"gw 786034x":ab,ti	0
#45	gw786034x:ab,ti	0
#46	"sb 710468":ab,ti	2
#47	sb710468:ab,ti	0
#48	"sb 710468a":ab,ti	0
#49	sb710468a:ab,ti	0
#50	"444731-52-6":ab,ti	12
#51	"635702-64-6":ab,ti	18
#52	7RN5DR86CK:ab,ti	0
#53	GW786034:ab,ti	40
#54	#37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 or #53	499
#55	[mh ^"Everolimus"]	1491
#56	everolimus:ab,ti	3440
#57	afinitor:ab,ti	62
#58	affinitor:ab,ti	0
#59	certican:ab,ti	153
#60	votubia:ab,ti	2
#61	zortress:ab,ti	7
#62	"40-o-(2-hydroxyethyl)-rapamycin":ab,ti	1
#63	"rad 001":ab,ti	5
#64	rad001:ab,ti	186
#65	"rad 001a":ab,ti	0
#66	rad001a:ab,ti	1



Date	24/06/2020 22:07:19
#67	"sdz rad":ab,ti7
#68	"rad sdz":ab,ti0
#69	"159351-69-6":ab,ti88
#70	9HW64Q8G6G:ab,ti0
#71	#56 or #57 or #58 or #59 or #60 or #61 or #62 or #63 or #64 or #65 or #66 or #67 or #68 or #69 or #703498
#72	#55 or #713920
#73	[mh ^"sorafenib"]456
#74	sorafenib:ab,ti1645
#75	sorafenib:ab,ti4
#76	nexavar:ab,ti124
#77	"284461-73-0":ab,ti39
#78	9ZOQ3TZI87:ab,ti0
#79	"BAY-43-9006":ab,ti69
#80	"bay 439006":ab,ti0
#81	bay439006:ab,ti0
#82	"bay 545 9085":ab,ti0
#83	"bay 5459085":ab,ti0
#84	bay5459085:ab,ti0
#85	"bay 673472":ab,ti0
#86	bay673472:ab,ti0
#87	#74 or #75 or #76 or #77 or #78 or #79 or #80 or #81 or #82 or #83 or #84 or #85 or #861667
#88	#73 or #871696
#89	[mh ^"axitinib"]91
#90	axitinib:ab,ti270
#91	inlyta:ab,ti7
#92	"319460-85-0":ab,ti19
#93	C9LVQ0YUXG:ab,ti0
#94	"ag 013736":ab,ti46
#95	ag013736:ab,ti0
#96	"ag 13736":ab,ti2
#97	ag13736:ab,ti0
#98	#90 or #91 or #92 or #93 or #94 or #95 or #96 or #97278
#99	#89 or #98279
#100	temsirolimus:ab,ti228
#101	TORISEL:ab,ti28
#102	"162635-04-3":ab,ti12



Date	24/06/2020 22:07:19	
#103	"343261-52-9":ab,ti	0
#104	624KN6GM2T:ab,ti	0
#105	CCI-779:ab,ti	40
#106	cci779:ab,ti	0
#107	"cell cycle inhibitor 779":ab,ti	0
#108	"nsc 683864":ab,ti	1
#109	nsc683864:ab,ti	0
#110	#100 or #101 or #102 or #103 or #104 or #105 or #106 or #107 or #108 or #109	245
#111	#18 or #36 or #54 or #72 or #88 or #99 or #110	8409
#112	#3 and #111	1427
#113	(kinase* adj3 (inhibit* or antagonist? or target* or block* or against or anti or multi-targets or multi-target or multi-targeting or reduc*)):ab,ti	0
#114	(VEGF* NEAR/3 (inhibit* or antagonist? or target* or block* or against or anti or multi-targets or multi-target or multi-targeting or reduc*)):ab,ti	2262
#115	(RAF* NEAR/3 (inhibit* or antagonist? or target* or block* or against or anti or multi-targets or multi-target or multi-targeting or reduc*)):ab,ti	64
#116	(TOR* NEAR/3 (inhibit* or antagonist? or target* or block* or against or anti or multi-targets or multi-target or multi-targeting or reduc*)):ab,ti	1102
#117	(PDGF* NEAR/3 (inhibit* or antagonist? or target* or block* or against or anti or multi-targets or multi-target or multi-targeting or reduc*)):ab,ti	149
#118	(c-KIT* NEAR/3 (inhibit* or antagonist? or target* or block* or against or anti or multi-targets or multi-target or multi-targeting or reduc*)):ab,ti	34
#119	((PD-1 or PD1) NEAR/3 (inhibit* or antagonist? or target* or block* or against or anti or multi-targets or multi-target or multi-targeting or reduc*)):ab,ti	1254
#120	("immune checkpoint" NEAR/3 inhibitor*):ab,ti	529
#121	(antibod* NEAR/3 monoclonal):ab,ti	8824
#122	#113 OR #114 OR #115 OR #116 OR #117 OR #118 OR #119 OR #120 OR #121	13266
#123	#3 and #122	484
#124	((("new class" or "new classes" or innovative or target*) NEAR/3 (drug? or therapy or therapies or therapeutic* or treatment? or chemotherap*)):ab,ti	11940
#125	#3 and #124	298
#126	#112 or #123 or #125	1605
#127	#126 in Cochrane Reviews	5
#128	#127 with Cochrane Library publication date Between Jan 2010 and Dec 2020	4
Comments		



Appendix 12.3.3.2. Medline + PreMedline

Date	June 23, 2020	
Database	Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946 to June 23, 2020>	
Search strategy		
1	exp Kidney Neoplasms/	74228
2	((kidney? or renal) adj3 (neoplasm* or cancer* or tumor* or carcinoma* or adenocarcinoma* or onco* or malign* or adenoma?)).ab,ti,kf.	74807
3	nephroma.ab,ti,kf.	983
4	reninoma.ab,ti,kf.	68
5	2 or 3 or 4	75342
6	1 or 5	100343
7	nivolumab/	2385
8	Nivolumab.ab,ti,kf,rn.	5049
9	bms 936558.ab,ti,kf,rn.	24
10	bms936558.ab,ti,kf,rn.	0
11	mdx 1106.ab,ti,kf,rn.	6
12	mdx1106.ab,ti,kf,rn.	1
13	ono 4538.ab,ti,kf,rn.	16
14	ono4538.ab,ti,kf,rn.	0
15	opdivo.ab,ti,kf,rn.	65
16	cmab 819.ab,ti,kf,rn.	0
17	cmab819.ab,ti,kf,rn.	0
18	946414-94-4.ab,ti,kf,rn.	1
19	31YO63LBSN.ab,ti,kf,rn.	2386
20	8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19	5058
21	7 or 20	5058
22	Sunitinib/	3528
23	sunitinib.ab,ti,kf,rn.	6189
24	sutent.ab,ti,kf,rn.	155
25	"su 011248".ab,ti,kf,rn.	3
26	su011248.ab,ti,kf,rn.	10
27	su 11248.ab,ti,kf,rn.	20
28	su11248.ab,ti,kf,rn.	124
29	341031-54-7.ab,ti,kf,rn.	0
30	557795-19-4.ab,ti,kf,rn.	1
31	pha 2909040ad.ab,ti,kf,rn.	0
32	pha2909040ad.ab,ti,kf,rn.	0



Date	June 23, 2020	
33	"su 010398".ab,ti,kf,rn.	0
34	su010398.ab,ti,kf,rn.	0
35	"su 10398".ab,ti,kf,rn.	0
36	"su10398".ab,ti,kf,rn.	0
37	V99T50803M.ab,ti,kf,rn.	3529
38	23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37	6248
39	22 or 38	6248
40	pazopanib.ab,ti,kf,rn.	1778
41	votrient.ab,ti,kf,rn.	32
42	armala.ab,ti,kf,rn.	1
43	gw 786034.ab,ti,kf,rn.	4
44	gw786034.ab,ti,kf,rn.	22
45	gw 786034b.ab,ti,kf,rn.	0
46	gw786034b.ab,ti,kf,rn.	2
47	gw 786034x.ab,ti,kf,rn.	0
48	gw786034x.ab,ti,kf,rn.	0
49	sb 710468.ab,ti,kf,rn.	0
50	sb710468.ab,ti,kf,rn.	0
51	sb 710468a.ab,ti,kf,rn.	0
52	sb710468a.ab,ti,kf,rn.	0
53	444731-52-6.ab,ti,kf,rn.	1
54	635702-64-6.ab,ti,kf,rn.	0
55	7RN5DR86CK.ab,ti,kf,rn.	882
56	GW786034.ab,ti,kf,rn.	22
57	40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56	1784
58	Everolimus/	4682
59	everolimus.ab,ti,kf,rn.	7366
60	afinitor.ab,ti,kf,rn.	58
61	affinitor.ab,ti,kf,rn.	2
62	certican.ab,ti,kf,rn.	71
63	votubia.ab,ti,kf,rn.	3
64	zortress.ab,ti,kf,rn.	5
65	"40-o-(2-hydroxyethyl)-rapamycin".ab,ti,kf,rn.	27
66	"rad 001".ab,ti,kf,rn.	55
67	rad001.ab,ti,kf,rn.	506
68	rad 001a.ab,ti,kf,rn.	0



Date	June 23, 2020	
69	rad001a.ab,ti,kf,rn.	0
70	sdz rad.ab,ti,kf,rn.	67
71	rad sdz.ab,ti,kf,rn.	0
72	159351-69-6.ab,ti,kf,rn.	1
73	9HW64Q8G6G.ab,ti,kf,rn.	4683
74	59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73	7522
75	58 or 74	7522
76	sorafenib/	4772
77	sorafenib.ab,ti,kf,rn.	8841
78	sorafenib.ab,ti,kf,rn.	27
79	nexavar.ab,ti,kf,rn.	164
80	284461-73-0.ab,ti,kf,rn.	1
81	9ZOQ3TZI87.ab,ti,kf,rn.	4773
82	BAY-43-9006.ab,ti,kf,rn.	138
83	bay 439006.ab,ti,kf,rn.	0
84	bay439006.ab,ti,kf,rn.	0
85	bay 545 9085.ab,ti,kf,rn.	0
86	bay 5459085.ab,ti,kf,rn.	0
87	bay5459085.ab,ti,kf,rn.	0
88	bay 673472.ab,ti,kf,rn.	0
89	bay673472.ab,ti,kf,rn.	0
90	77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89	8886
91	76 or 90	8886
92	axitinib/	507
93	axitinib.ab,ti,kf,rn.	1005
94	inlyta.ab,ti,kf,rn.	15
95	319460-85-0.ab,ti,kf,rn.	1
96	C9LVQ0YUXG.ab,ti,kf,rn.	508
97	"ag 013736".ab,ti,kf,rn.	41
98	ag013736.ab,ti,kf,rn.	9
99	ag 13736.ab,ti,kf,rn.	1
100	ag13736.ab,ti,kf,rn.	1
101	93 or 94 or 95 or 96 or 97 or 98 or 99 or 100	1015
102	92 or 101	1015
103	temsirolimus.ab,ti,kf,rn.	1531
104	TORISEL.ab,ti,kf,rn.	22



Date	June 23, 2020	
105	162635-04-3.ab,ti,kf,rn.	1
106	343261-52-9.ab,ti,kf,rn.	0
107	624KN6GM2T.ab,ti,kf,rn.	837
108	CCI-779.ab,ti,kf,rn.	192
109	cci779.ab,ti,kf,rn.	4
110	cell cycle inhibitor 779.ab,ti,kf,rn.	7
111	nsc 683864.ab,ti,kf,rn.	7
112	nsc683864.ab,ti,kf,rn.	0
113	103 or 104 or 105 or 106 or 107 or 108 or 109 or 110 or 111 or 112	1601
114	21 or 39 or 57 or 75 or 91 or 102 or 113	26904
115	6 and 114	5527
116	exp Vascular Endothelial Growth Factors/ai [Antagonists & Inhibitors]	8313
117	exp Receptors, Vascular Endothelial Growth Factor/ai [Antagonists & Inhibitors]	2960
118	exp TOR Serine-Threonine Kinases/ai [Antagonists & Inhibitors]	4538
119	Proto-Oncogene Proteins c-kit/ai [Antagonists & Inhibitors]	278
120	exp Receptors, Platelet-Derived Growth Factor/ai [Antagonists & Inhibitors]	843
121	exp Receptors, Vascular Endothelial Growth Factor/ai [Antagonists & Inhibitors]	2960
122	Programmed Cell Death 1 Receptor/ai [Antagonists & Inhibitors]	2579
123	exp protein kinase inhibitors/	96082
124	exp immunosuppressive agents/	314734
125	exp Antibodies, Monoclonal/	235325
126	molecular targeted therapy/	27959
127	116 or 117 or 118 or 119 or 120 or 121 or 122 or 123 or 124 or 125 or 126	639018
128	(VEGF* adj3 (inhibit* or antagonist? or target* or block* or against or anti or multi-targets or multi-target or multi-targeting or reduc*)).ab,ti,kf.	20049
129	(PDGF* adj3 (inhibit* or antagonist? or target* or block* or against or anti or multi-targets or multi-target or multi-targeting or reduc*)).ab,ti,kf.	4280
130	(TOR* adj3 (inhibit* or antagonist? or target* or block* or against or anti or multi-targets or multi-target or multi-targeting or reduc*)).ab,ti,kf.	5236
131	(c-KIT* adj3 (inhibit* or antagonist? or target* or block* or against or anti or multi-targets or multi-target or multi-targeting or reduc*)).ab,ti,kf.	1174
132	((PD-1 or PD1) adj3 (inhibit* or antagonist? or target* or block* or against or anti or multi-targets or multi-target or multi-targeting or reduc*)).ab,ti,kf.	8411
133	(RAF* adj3 (inhibit* or antagonist? or target* or block* or against or anti or multi-targets or multi-target or multi-targeting or reduc*)).ab,ti,kf.	4117
134	(kinase* adj3 (inhibit* or antagonist? or target* or block* or against or anti or multi-targets or multi-target or multi-targeting or reduc*)).ab,ti,kf.	118182



Date	June 23, 2020	
135	("immune checkpoint" adj3 inhibitor?).ab,ti,kf.	7550
136	(antibod* adj3 monoclonal).ab,ti,kf.	196475
137	128 or 129 or 130 or 131 or 132 or 133 or 134 or 135 or 136	351462
138	127 or 137	825113
139	6 and 138	10696
140	((new class* or innovative or target*) adj3 (drug? or therapy or therapies or therapeutic* or treatment? or chemotherap*)),ab,ti,kf.	330433
141	6 and 140	5276
142	115 or 139 or 141	14302
143	((systematic review or systematic literature review or systematic scoping review or systematic narrative review or systematic qualitative review or systematic evidence review or systematic quantitative review or systematic meta-review or systematic critical review or systematic mixed studies review or systematic mapping review or systematic cochrane review or "systematic search and review" or systematic integrative review).ti. not comment.pt. not (protocol or protocols).ti. not medline.st.) or (Cochrane Database Syst Rev.ja. and review.pt.) or systematic review.pt.	159535
144	meta-analys*.ti.	109097
145	meta-analysis.pt.	116362
146	exp Technology Assessment, Biomedical/	11075
147	health technology assessment.ti,kf.	1925
148	HtA.ti,kf.	596
149	143 or 144 or 145 or 146 or 147 or 148	253258
150	142 and 149	302
151	limit 150 to yr="2010-current"	274
Comments		



Appendix 12.4. Economic literature

Appendix 12.4.1. Search economic literature (HTA reports)

The search strategy in CRD's HTA database identified 78 references (Table 194). In a first round, 27 references were selected based on a review of title, keywords and abstract. The 51 remaining references were excluded for the following reasons: intervention (42), design (3), or language (6). In a second round, the full text of the 27 selected references was reviewed. 20 references were excluded (design (18), update available (1)). Seven references were retained. These references are indicated in Table 27 with an asterisk (*). For one of these references, an updated report was identified later on.

Furthermore, in May 2020, the website of the National Institute for Health Research (NIHR) was searched for relevant reports. The following search terms were used: sunitinib (23 hits, 2 with a focus on renal cell carcinoma, both previously identified); pazopanib (1 hit, 1 with a focus on renal cell carcinoma, this report was previously identified). The search was not finished and continued in January 2021 for the remaining search terms: everolimus (8 hits, 2 with a focus on renal cell carcinoma, 2 not previously identified); sorafenib (17 hits, 1 with a focus on renal cell carcinoma, this report was previously identified); axitinib (10 hits, 1 with a focus on renal cell carcinoma, 1 not previously identified); temsirolimus (4 hits, 1 with a focus on renal cell carcinoma, this report was previously identified^b); nivolumab (30 hits, 2 with a focus on renal cell carcinoma, 2 not previously identified).

Finally, in May 2020, the website of the National Institute for Health and Care Excellence (NICE) was searched. The following search terms were used: sunitinib (25 hits, 2 relevant Technology Assessments (TAs), both previously identified); pazopanib (12 hits, 1 relevant TA, this report was previously identified); everolimus (34 hits, 3 relevant TAs, 2 not previously identified); sorafenib (20 hits, 1 relevant TA, this report was previously identified); axitinib (9 hits, 1 relevant TA, 1 not previously identified); temsirolimus (5 hits, 1 relevant TA, this report was previously identified); nivolumab (66 hits, 2 relevant TAs, 2 not previously identified).

An overview of the identified references is provided in Table 195.

^b The title of the identified project was initially "Bevacizumab, sorafenib, tosylate, sunitinib and temsirolimus for renal cell carcinoma: A systematic review and economic evaluation". However, the report is published with the following title (without mentioning temsirolimus): "Bevacizumab, sorafenib tosylate and sunitinib for renal cell carcinoma: a systematic review and economic evaluation."²⁹⁵ This report is already included in our overview.

**Table 194 – Search strategy and results for CRD: HTA**

Date			
Date covered	All		
Search Strategy	1	MeSH DESCRIPTOR Kidney Neoplasms EXPLODE ALL TREES	201
	2	MeSH DESCRIPTOR Carcinoma, Renal Cell EXPLODE ALL TREES	127
	3	* IN HTA	17351
	4	#1 OR #2	201
	5	#3 AND #4	78 references
Note	Renal Cell Carcinoma is indexed under Kidney Neoplasms. We preferred to opt for the widest search strategy and included the MeSH Kidney Neoplasms.		

Table 195 – Renal cell carcinoma – Identified HTA reports for the selected drugs

Selected reports	
Axitinib, everolimus, nivolumab & sunitinib	
<ul style="list-style-type: none"> Edwards SJ, Wakefield V, Cain P, Karner C, Kew K, Bacelar M, et al. Axitinib, cabozantinib, everolimus, nivolumab, sunitinib and best supportive care in previously treated renal cell carcinoma: a systematic review and economic evaluation. <i>Health Technol Assess</i> 2018;22(6).^{296 * α} 	
Axitinib	
<ul style="list-style-type: none"> NICE, TA333. February 2015. Axitinib for treating advanced renal cell carcinoma after failure of prior systemic treatment.^{297 β} <ul style="list-style-type: none"> Riemsma R, Al M, Corro Ramos I, Deshpande S, Worthy G, Noake C, Armstrong N, Severens JL, Kleijnen J. Axitinib for the treatment of advanced renal cell carcinoma after failure of prior systematic treatment: a Single Technology Appraisal. York: Kleijnen Systematic Reviews Ltd, 2012.^{298 α} 	
Everolimus	
<ul style="list-style-type: none"> NICE, TA498. January 2018. Lenvatinib with everolimus for previously treated advanced renal cell carcinoma.^{299 β} <ul style="list-style-type: none"> NICE, Single Technology Appraisal (8 December 2017). Lenvatinib with everolimus for previously treated advanced renal cell carcinoma [ID1029]. Committee Papers.^{300 α} NICE, TA432. February 2017. Everolimus for advanced renal cell carcinoma after previous treatment.^{301 β} <ul style="list-style-type: none"> NICE, CDF Rapid Reconsideration (8 March 2017). Everolimus for the second-line treatment of metastatic renal cell carcinoma (review of TA219) [1015]. Committee papers.^{302 α} 	
Nivolumab	
<ul style="list-style-type: none"> NICE, TA581. May 2019. Nivolumab with ipilimumab for untreated advanced renal cell carcinoma.^{303 β} 	



- NICE, Single technology appraisal (5 April 2019). Nivolumab with ipilimumab for untreated metastatic renal cell carcinoma [ID1182]. Committee papers.^{304 α}
- NICE, TA417. November 2016. Nivolumab for previously treated advanced renal cell carcinoma.^{305 β}
 - NICE, Single technology appraisal (21 October 2016). Nivolumab for treated or metastatic renal cell carcinoma [ID853]. Committee papers.^{306 α}

Pazopanib

- NICE, TA215. February 2011 (updated August 2013). Pazopanib for the first-line treatment of advanced renal cell carcinoma.^{307 * β α}
 - Kilonzo M, Hislop J, Elders A, Fraser C, Bissett D, McClinton S, Mowatt G, Vale L. Pazopanib for the first line treatment of patients with advanced and/or metastatic renal cell carcinoma: A Single Technology Appraisal. Aberdeen HTA Group, Institute of Applied Health Sciences, University of Aberdeen, 2010.^{308 *}

Sorafenib, sunitinib & temsirolimus

- NICE, TA178. August 2009. Bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced and/or metastatic renal cell carcinoma.^{309 * β}
 - Thompson Coon J, Hoyle M, Green C, Liu Z, Welch K. Bevacizumab, sorafenib tosylate and sunitinib for renal cell carcinoma: a systematic review and economic evaluation. Health Technol Assess 2010;14(2).^{295 * α}

Sunitinib

- NICE, TA169. March 2009. Sunitinib for the first-line treatment of advanced and/or metastatic renal cell carcinoma.^{310 * β}
 - It is mentioned that "the assessment report for this appraisal was prepared by Peninsula Technology Assessment Group, University of Exeter: Thompson Coon J, Hoyle M, Green C et al, Bevacizumab, sorafenib tosylate, sunitinib and temsirolimus for renal cell carcinoma, May 2008." However, searching for this reference, only the report published in 2010, and linked to TA178, could be identified.

Excluded reports**Everolimus**

- NICE, TA219. April 2011. Everolimus for the second-line treatment of advanced renal cell carcinoma.^{311 * β}
 - This guidance has been updated and replaced by NICE technology appraisal guidance 432.

Reports retrieved from search for systematic reviews

- Vargas, C. Balmaceda, C. Rodriguez, F. et al. Economic evaluation of sunitinib versus pazopanib and best supportive care for the treatment of metastatic renal cell carcinoma in Chile: cost-effectiveness analysis and a mixed treatment comparison. Expert rev 2019;19(5):609-617.³¹²
 - This article is a primary economic evaluation of sunitinib against metastatic renal cell carcinoma. It is however not performed in a European setting (Chile), and it does not contain a critical review of the clinical aspects related to sunitinib.
- Schey, C. Meier, G. Pan, J. Metastatic Renal Cell Cancer: An Analysis of Reimbursement Decisions. Adv Ther 2019;36(6):1266-1278.³¹³
 - This article is an economic review of several HTA reports on drug treatments against renal cell carcinoma. A primary economic evaluation was not performed.
- Verma, V. Sprave, T. Haque, W. et al. A systematic review of the cost and cost-effectiveness studies of immune checkpoint inhibitors. J Immunother Cancer 2018;6(1):128.³¹⁴
 - This article is a systematic review of published economic evaluations about immune checkpoint inhibitors against head/neck, lung, genitourinary, and melanoma malignancies. A primary economic evaluation was not performed.

* These references were identified in CRD's HTA database. α References identified on NIHR's website. β References identified on NICE's website.



Appendix 12.4.2. Results economic literature (HTA reports)

Appendix 12.4.2.1. Edwards (2018): axitinib, everolimus, nivolumab

- QoL:
 - “A systematic review was carried out in July 2016 to identify relevant published HRQoL evidence to populate the economic model.”²⁹⁶
 - “In the baseline analysis, the HSUVs [health state utility values] reported in TA333 are used for everolimus, axitinib, cabozantinib and BSC. These values were chosen because the methods used in TA333 to estimate HRQoL were clearly reported and were derived from EQ-5D data collected in the AXIS trial whose population reflects RCC patients encountered in UK clinical practice. Therefore, the values used in the model are 0.69 and 0.61 for PFS and PD, respectively.”²⁹⁶
 - “Patients receiving nivolumab are assumed to enjoy a superior quality of life before progression, as the CheckMate 025 trial EQ-5D results show that patients’ quality of life continues to improve throughout the trial period while on treatment. (...) The values used for nivolumab in the economic analysis are 0.73 and 0.65 for PFS and PD, respectively.”²⁹⁶
- Results:
 - “The review found that cabozantinib is probably the best treatment to delay tumour growth and prolong life, followed by nivolumab. All of the treatments delayed tumour growth compared with BSC; however, there are uncertainties, owing to the way in which studies have been conducted.”²⁹⁶
 - “These results mean that everolimus dominated axitinib as it accrued the same number of QALYs but incurred a lower cost, while nivolumab was dominated by cabozantinib, which accrued more QALYs at a slightly lower cost. The incremental analysis then simplifies to a comparison between cabozantinib, everolimus and BSC, resulting in an incremental cost-effectiveness ratio (ICER) of £45,000 per QALY for everolimus compared with BSC, and £126,000 per QALY for cabozantinib compared with everolimus.”²⁹⁶
 - “The economic analysis, using drug list prices, shows that everolimus may be more cost-effective than BSC [best-supportive care] with an incremental cost-effectiveness ratio (ICER) of £45,000 per quality-adjusted life-year (QALY), as it is likely to be considered an end-of-life treatment. Cabozantinib has an ICER of £126,000 per QALY compared with everolimus and is unlikely to be cost-effective. Nivolumab was dominated by cabozantinib (i.e. more costly and less effective) and axitinib was dominated by everolimus.”²⁹⁶



- Uncertainty and sensitivity:
 - “A systematic review was undertaken to compare the clinical effectiveness of treatments using mixed-treatment comparison (MTC). Randomised controlled trial (RCT) data were preferred but did not link all treatments in the network and so non-RCTs were sought to link in axitinib and sunitinib for the primary outcomes.”²⁹⁶
 - “The current evidence base to inform decisions between axitinib, cabozantinib, everolimus, nivolumab, BSC and sunitinib for previously treated RCC is limited by the number of studies providing comparative clinical effectiveness data, and by the quality of study reporting.”²⁹⁶
 - “The robustness of the results has therefore been thoroughly tested and the model was found to only be sensitive to a few key parameters: the relative OS of treatments and the RDI for each treatment. These results are not surprising as OS is an influential driver on the total QALYs by definition and the RDI has an impact on the treatment acquisition costs, which make up the majority of overall treatment costs.”²⁹⁶
 - “As a large aspect of the analysis relates to producing survival curves for PFS and OS that fit the trial data well and provide a plausible extrapolation beyond the trial period, the AG considered it important to assess a range of different models to find suitably fitting curves for each treatment group.”²⁹⁶
- Conclusions:
 - “Analyses of PFS and OS suggest that cabozantinib is likely to be the most effective treatment, closely followed by nivolumab, and with little difference between axitinib, everolimus and sunitinib. All treatments considered in this review appear to delay disease progression and prolong survival more than providing BSC.”²⁹⁶
 - “The economic analysis showed that the majority of current treatments for second-line RCC are very expensive and unlikely to be cost-effective at list price. The exception to this is everolimus, which may be cost-effective at the NICE threshold of £50,000 per QALY granted to treatments that qualify as an end-of-life treatment.”²⁹⁶
- (Confidential) price:
 - “The main limitation of the review is that the costs are based on the list prices of the drugs. There are patient access schemes (PASs) in place to provide these drugs on the NHS with a reduced price or pricing strategy. The details of these PASs are confidential and so could not be incorporated in the analysis. This limits the applicability of the results, which may not reflect current practice in the UK.”²⁹⁶
- Other remarks:
 - At the time of writing this article, the authors report that Cabozantinib was not yet available for use in the NHS in England.
 - Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.



Reference	Population, Intervention & comparator	Remarks on use of generic utility instrument (e.g. EQ-5D) to measure impact on QoL in economic evaluations	Most uncertain variables or important variables in sensitivity analysis																																										
Costs (list prices & remarks)	IC, IE and ICERs																																												
Axitinib, everolimus, nivolumab																																													
Edward (2018) ²⁹⁶	Second-line treatment of adults with advanced renal cell carcinoma (Previously treated advanced or metastatic renal cell carcinoma) Interventions compared: axitinib, cabozantinib, everolimus, nivolumab and best-supportive care* (BCS)																																												
List prices: axitinib (5 mg, twice daily): £3517 for a 5-mg 56-tablet pack cabozantinib (60 mg, once daily): £5143** everolimus (10 mg, once daily): £2673 for a 10-mg 30-tablet pack nivolumab (3 mg/kg, every 2 weeks): £439 for a 40-mg vial and £1097 for a 100-mg vial***	Results of the incremental analysis (based on list prices): <table><tr><th>Treatment</th><th>Total cost (£)</th><th>Total QALYs</th><th>ICER (£)</th></tr><tr><td>BSC</td><td>11 304</td><td>0.75</td><td>-</td></tr><tr><td>Everolimus</td><td>36 463</td><td>1.31</td><td>44 965</td></tr><tr><td>Axitinib</td><td>46 506</td><td>1.31</td><td>Dominated by everolimus</td></tr><tr><td>Cabozantinib</td><td>106 516</td><td>1.87</td><td>126 230</td></tr><tr><td>Nivolumab</td><td>106 761</td><td>1.60</td><td>Dominated by cabozantinib</td></tr></table> Conclusions: <ul style="list-style-type: none">- axitinib and nivolumab are dominated options- everolimus may be cost-effective at the NICE threshold of £50,000 per QALY granted to treatments that qualify as an end-of-life treatment- Compared with everolimus, cabozantinib is not a cost-effective option	Treatment	Total cost (£)	Total QALYs	ICER (£)	BSC	11 304	0.75	-	Everolimus	36 463	1.31	44 965	Axitinib	46 506	1.31	Dominated by everolimus	Cabozantinib	106 516	1.87	126 230	Nivolumab	106 761	1.60	Dominated by cabozantinib	EQ-5D QoL data were obtained from the literature: <ul style="list-style-type: none">- NICE TA333²⁹⁷- CheckMate 025 trial results³¹⁵ <table><tr><th>QoL</th><th>PFS</th><th>PD</th></tr><tr><td>Nivolumab</td><td>0.73</td><td>0.65</td></tr><tr><td>Everolimus</td><td>0.69</td><td>0.61</td></tr><tr><td>Axitinib</td><td>0.69</td><td>0.61</td></tr><tr><td>Cabozantinib</td><td>0.69</td><td>0.61</td></tr><tr><td>BSC</td><td>0.69</td><td>0.61</td></tr></table>	QoL	PFS	PD	Nivolumab	0.73	0.65	Everolimus	0.69	0.61	Axitinib	0.69	0.61	Cabozantinib	0.69	0.61	BSC	0.69	0.61	Key parameters: <ul style="list-style-type: none">- Relative treatments OS- Relative dose intensity
Treatment	Total cost (£)	Total QALYs	ICER (£)																																										
BSC	11 304	0.75	-																																										
Everolimus	36 463	1.31	44 965																																										
Axitinib	46 506	1.31	Dominated by everolimus																																										
Cabozantinib	106 516	1.87	126 230																																										
Nivolumab	106 761	1.60	Dominated by cabozantinib																																										
QoL	PFS	PD																																											
Nivolumab	0.73	0.65																																											
Everolimus	0.69	0.61																																											
Axitinib	0.69	0.61																																											
Cabozantinib	0.69	0.61																																											
BSC	0.69	0.61																																											

* BSC is defined as the standard care for people with RCC if the available drug therapies are contraindicated or not tolerated (e.g. social and palliative services, treatment for symptomatic relief). ** Information on dosage and tablets number is not provided. *** The administration cost for nivolumab was assumed to be £185.53. BSC: best-supportive care, ICER: incremental cost-effectiveness ratio, OS: overall survival, PD: progressed disease, PFS: progression-free survival, QoL: quality of life.



Appendix 12.4.2.2. NICE, TA333 (2015): axitinib

- QoL:
 - “The utility values used in the model were derived from the AXIS trial using the EQ-5D questionnaire. The mean utility value for the progression-free health state was 0.69, based on the average of the EQ-5D index value at each time point in the AXIS trial and weighted by the number of patients still on treatment at that time point. The utility value for the progressed disease health state was 0.61, based on the weighted average of the mean utility at the end of treatment.”²⁹⁷
 - “FKSI-15, FKSI-DRS and EQ-5D quality-of-life data were collected at day 1, every 4 weeks thereafter, at the end of trial treatment or withdrawal, and on day 28 of the follow-up period. (...) For EQ-5D, the overall between-treatment comparison for axitinib compared with sorafenib was not statistically significant (no p value given); however, quality of life was maintained while patients remained on treatment and declined when patients stopped trial medication.”²⁹⁷
- Results:
 - “All the incremental costs and QALYs gained in the company's submission are commercial in confidence.”²⁹⁷
 - “The economic evaluation was based on the 2 separate populations specified in the marketing authorisation for axitinib (the groups of people in whom treatment with sunitinib or cytokines has failed, also referred to as the prior-sunitinib and the prior-cytokine groups).”²⁹⁷
 - **Prior-cytokine group:** “For the prior-cytokine group, the Committee noted that the company's base-case ICER of approximately £55,300 per QALY gained (with the patient access scheme applied) compared with best supportive care was based on the overall survival for best supportive care of 24 months, but fell to £36,500 per QALY gained if 17.46 months for overall survival for best supportive care was used.”²⁹⁷
 - **Prior-sunitinib group:** “The Committee considered that the more plausible ICER for the prior-sunitinib group was likely to lie between the base-case estimate with a progression-free to overall survival gain relationship of 1 to 1.6 (approximately £33,500 per QALY gained) and the estimate assuming no survival gain with a survival relationship of 1 to 1 (approximately £52,900 per QALY gained) and concluded that the ICER would be likely to be towards the middle of this range.”²⁹⁷ [ICERs for the comparison axitinib versus BSC, with the patient access scheme applied]
- Uncertainty and sensitivity:
 - “Because there was no relevant comparator in the AXIS trial, the Committee concluded that its discussion of the efficacy of axitinib would need to be based on the results of the indirect and the simulated treatment comparisons performed by the company. It also concluded that it was reasonable to separate out the results for patients who had received only prior cytokines from people who had received prior tyrosine kinase inhibitors.”²⁹⁷
 - “The Committee concluded that the indirect comparison used to generate a best supportive care comparison for the **prior-cytokine group** based on the AXIS trial (axitinib compared with sorafenib) and the TARGET trial (sorafenib compared with placebo) and the VEG105192 trial (pazopanib compared with placebo) was adequately performed and the naïve comparison was the best option given the available evidence. It also concluded that there were serious limitations with the simulated treatment comparison performed for the **prior-sunitinib group** using evidence from the AXIS trial and the RECORD-1 trial (which compared everolimus with placebo), and with the indirect comparison using evidence from AXIS and the Swedish database (Renal Comparison; RENCOMP). The Committee also considered the naïve comparison performed to compare axitinib with sunitinib and the indirect



comparison performed to compare axitinib with pazopanib in the **prior-cytokine group**, and concluded that both the naive and indirect comparisons were subject to substantial uncertainty but that axitinib was likely to have clinical effectiveness comparable to pazopanib and sunitinib.”²⁹⁷

- Prior-cytokine group:
 - “The cost-effectiveness result for the prior-cytokine group was most sensitive to changes in the overall survival hazard ratio and the post-progression utilities for axitinib and best supportive care in the univariate deterministic sensitivity analysis.”²⁹⁷
 - “The results showed that the base-case ICER, when applying the patient access scheme, was most sensitive to the method of extrapolation of overall survival (£21,959 per QALY gained for the log-logistic method and £72,537 per QALY gained for the Gompertz method); whereas other scenarios resulted in ICERs close to the revised base case.”²⁹⁷
- Prior-sunitinib group
 - “The univariate sensitivity analysis performed for the prior-sunitinib group showed that the ICER was most sensitive to changes in the survival parameter values for the axitinib group. (...) The base-case ICER was also sensitive to changes in the progressed disease utility values for the axitinib and best supportive care groups and progression-free utility value for the axitinib group.”²⁹⁷
 - “The ICER was most sensitive to the use of the Weibull and Gompertz distributions to extrapolate overall survival using the RENCOMP method of comparison (£47,515 and £39,479 per QALY gained respectively, with the patient access scheme applied).”²⁹⁷
 - “The Committee concluded that the results from the simulated treatment comparison method used to derive a best supportive care comparison for axitinib in the prior-sunitinib group should be interpreted with caution because they lacked clinical plausibility.”²⁹⁷
- Conclusions:
 - “The Committee concluded that axitinib was shown to be a life-extending, end-of-life treatment for the **prior-sunitinib population**. Taking into account both the value of the ICERs and the uncertainty around the ICERs, the Committee concluded that axitinib could be considered a cost-effective use of NHS resources in the prior-sunitinib population under the supplementary criteria for appraising life-extending, 'end-of-life' treatments.”²⁹⁷
 - “For the **prior-cytokine group**, the Committee did not accept that axitinib was superior to sunitinib and pazopanib, and therefore did not accept that the end-of-life criteria had been met for this population, but it was aware that axitinib, sunitinib and pazopanib were used interchangeably in clinical practice. The Committee concluded that axitinib was comparable to the alternative treatments recommended by NICE that meet the end-of-life criteria (sunitinib for the first-line treatment of advanced and/or metastatic renal cell carcinoma and pazopanib for the first-line treatment of advanced renal cell carcinoma), and that there was now only a very small population included in the prior-cytokine group and more uncertainty could be accepted. It therefore concluded that an ICER compared with best supportive care above but close to the upper limit of the normal range, was acceptable, and axitinib could be considered a cost-effective use of NHS resources in the prior-cytokine population.”²⁹⁷



- (Confidential) price:
 - “The company manufacturing axitinib has agreed a patient access scheme with the Department of Health. The size of the discount is commercial in confidence.”²⁹⁷
- Other remarks:
 - “The Committee concluded that axitinib was shown to be a life-extending, end-of-life treatment for the prior-sunitinib population.”²⁹⁷

Reference Costs (list prices & remarks)	Population, Intervention & comparator IC, IE and ICERs	Remarks on use of generic utility instrument (e.g. EQ-5D) to measure impact on QoL in economic evaluations	Most uncertain variables or important variables in sensitivity analysis
Axitinib			
NICE, TA333 (2015) ²⁹⁷ Riemsma (2012) ²⁹⁸	Second-line treatment of adults with advanced renal cell carcinoma (patients with advanced renal cell carcinoma, after failure of prior treatment with sunitinib or a cytokine) Axitinib compared with best-supportive care (BSC)		
List price (confidential PAS): £3517 for a 5-mg 56-tablet pack (BNF November 2014)	Company's results (including PAS for axitinib): Prior-sunitinib group: - between £33 500 and £52 900 per QALY - Conclusion: axitinib meets EOL criteria and is cost-effective Prior-cytokine group: - between £36 500 and £55 300 per QALY - Conclusion: despite uncertainty, axitinib is considered cost-effective by the committee	EQ-5D data collected from the AXIS trial (not the underlying RCT) and applied per health state: PFS: 0.69 PD: 0.61 Before and after progression, utilities were assumed to be treatment independent	Impact on OS uncertain ICER sensitive to: - OS hazard ratio - PD utility - Extrapolation method for long-term effect on OS - Method used for indirect comparison

BNF: British national formulary, BSC: best-supportive care, ICER: incremental cost-effectiveness ratio, OS: overall survival, PAS: patient access scheme, PD: progressed disease, PFS: progression-free survival.



Appendix 12.4.2.3. NICE, TA498 (2018): everolimus (in combination with lenvatinib)

- QoL:
 - “(...) the company used utility values from the AXIS trial, which had compared axitinib with sorafenib for advanced renal cell carcinoma. The utility values from AXIS were 0.69 for the pre-progressed disease states and 0.61 for the progressed disease states.”²⁹⁹
 - “To estimate the impact of adverse events on health-related quality of life, the company deducted a decrement (an amount reflecting the effect of adverse events on health-related quality of life) from the baseline utility values from AXIS. (...) In response to the appraisal consultation document, the company revised its utility decrements to –0.097 for lenvatinib plus everolimus, –0.072 for axitinib, –0.084 for cabozantinib and –0.008 for nivolumab.”²⁹⁹
- Results: IC, IE not reported
 - “The committee noted that, in the ERG's deterministic base-case analysis, lenvatinib plus everolimus dominated cabozantinib and nivolumab, that is it was more effective and less costly. The incremental cost-effectiveness ratio for lenvatinib plus everolimus compared with axitinib was between £20,000 and £30,000 per quality-adjusted life year, which is the range normally accepted by NICE to represent cost-effective technologies.”²⁹⁹ [results including confidential discounts for all drugs]
- Uncertainty and sensitivity:
 - “Because there were no head-to-head trials comparing lenvatinib [plus everolimus] with axitinib, nivolumab or cabozantinib, the company compared the treatments indirectly using a network meta-analysis. It included the randomised controlled trials HOPE 205, CHECKMATE-025 and METEOR (lenvatinib plus everolimus, nivolumab and cabozantinib respectively, each compared with everolimus), and estimated overall and progression-free survival curves for each treatment using fractional polynomials.”²⁹⁹
 - “The data from HOPE 205 were relatively immature at the time of the analysis of progression-free survival (June 2014) because, across the lenvatinib plus everolimus and everolimus alone groups, disease had progressed in only 62% of patients.”²⁹⁹ [median follow-up of 32.0 months for lenvatinib plus everolimus].
 - “Both the company and the ERG assumed that the effect of lenvatinib plus everolimus continued beyond the trial follow-up, even after the disease progressed or people stopped treatment. (...) It [the committee] concluded that assuming the effect of lenvatinib plus everolimus continues for up to 20 years, based on a trial with a median follow-up of under 3 years for overall survival, was highly uncertain.”²⁹⁹
 - “The committee recalled that the utility values used in the model should have reflected the high rate of serious adverse events associated with lenvatinib plus everolimus. (...) the revised utility decrement for nivolumab also appeared too small given its immunotoxicity. The committee concluded that the utility values used in the model did not reflect quality of life appropriately.”²⁹⁹
 - “The committee appreciated that the uncertainty in the cost-effectiveness estimates came mainly from the limitations of HOPE 205, and from the modelling assumptions about the long-term performance of treatment and the impact of adverse events on health-related quality of life.”²⁹⁹



- Conclusions:
 - “The cost-effectiveness analyses for lenvatinib plus everolimus show it's more effective and less costly than cabozantinib and nivolumab. Compared with axitinib, the cost-effectiveness estimates are within what NICE normally considers acceptable. So, NICE is recommending lenvatinib plus everolimus as an option for use in the NHS in people with an ECOG performance status score of 0 or 1.”²⁹⁹
- (Confidential) price:
 - “The committee considered the cost-effectiveness results from the company's base case and the ERG's base case, including confidential discounts for all technologies.”²⁹⁹

Reference Costs (list prices & remarks)	Population, Intervention & comparator IC, IE and ICERs	Remarks on use of generic utility instrument (e.g. EQ- 5D) to measure impact on QoL in economic evaluations	Most uncertain variables or important variables in sensitivity analysis
Lenvatinib plus everolimus			
NICE, TA498 (2018) ²⁹⁹	Second-line treatment of adults with advanced renal cell carcinoma (patients with advanced renal cell carcinoma who have had only 1 previous vascular endothelial growth factor (VEGF)-targeted therapy)		
NICE, Committee Papers ID1029 (2017) ³⁰⁰	lenvatinib plus everolimus compared with axitinib, nivolumab and cabozantinib		
List prices (confidential PAS): Lenvatinib: £1437 per 30-capsule pack (4mg and 10mg). Everolimus: £2250 per 5 mg 30-tablet pack	Results of the ERG revised model (including PAS for all drugs): - Compared with cabozantinib and nivolumab: lenvatinib plus everolimus dominates - Compared with axitinib: between £20 000 and £30 000 per QALY Conclusion: lenvatinib plus everolimus is a cost-effective use of NHS resources in people with an ECOG performance status score of 0 or 1.	EQ-5D data collected from the AXIS trial (not the underlying RCT) and applied per health state for all drugs: PFS: 0.69 PD: 0.61 AE utility decrement: lenvatinib plus everolimus -0.097 axitinib -0.072 cabozantinib -0.084 nivolumab -0.008	Uncertain parameters: - Impact on OS - Utility decrement for adverse event - Long-term modelling of the treatment effect on OS (extrapolation method)

AE: adverse event, ERG: evidence review group, OS: overall survival, PAS: patient access scheme, PD: progressed disease, PFS: progression-free survival.



Appendix 12.4.2.4. NICE, TA432 (2017): Everolimus

- QoL:
 - “The committee noted that the utility estimates in the model were neither directly obtained nor mapped from the RECORD-1 trial.”³⁰¹
 - “CDF Reconsideration Model. 4-state Markov model: stable disease (no AEs); stable disease (with AEs); progressed disease and death. Utility values for states: 0.76; 0.71; 0.68 and 0 respectively. (...) In the model, the utilities used for health states for patients receiving second-line treatment for advanced renal cell carcinoma were obtained from the Assessment Group estimates from a previous NICE technology appraisal, ‘Bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced and/or metastatic renal cell carcinoma’ (NICE technology appraisal 178). These utility values were 0.76 for stable disease without adverse events, 0.71 for stable disease with adverse events and 0.68 for progressed disease.”³⁰²
- Results:
 - Including the previous PAS for everolimus:
 - “The committee considered the deterministic incremental cost-effectiveness ratio (ICER) of £49,300 per quality-adjusted life year (QALY) gained (derived by the manufacturer) and the mean probabilistic ICER of £51,700 per QALY gained (derived by the ERG).”
 - Including the revised PAS for everolimus:
 - “The resulting ICERs cannot be reported here because they are commercial in confidence. The committee concluded that the most plausible ICER for everolimus compared with best supportive care would be less than £30,000 per QALY gained.”³⁰¹
 - “The committee agreed that cost-minimisation analyses comparing everolimus and axitinib were suitable for its decision-making. In the cost-minimisation analyses, the cost of everolimus treatment was lower than the cost of axitinib treatment.”³⁰¹
- Uncertainty and sensitivity:
 - Everolimus compared with best supportive care:
 - “The committee discussed the results of the RECORD-1 placebo-controlled trial. (...) The committee acknowledged that the relative estimates of overall survival according to the intention-to-treat analyses were biased because 81% of people had crossed over to have everolimus in the trial. (...) The committee agreed that it was appropriate to adjust the intention-to-treat results (...) to control for the crossover using statistical modelling techniques. However, the committee agreed that any estimate of overall survival obtained using statistical modelling would be subject to uncertainty.”³⁰¹
 - “The committee therefore concluded that, although there was sufficient evidence that everolimus increased progression-free and overall survival compared with best supportive care, the exact magnitude of the overall survival gain was uncertain because it was based on modelled data as opposed to data directly seen in the trial, but accepted that it would be more than 3 months.”³⁰¹
 - “The committee noted that the key factor in determining the cost effectiveness was the estimate of overall survival.”³⁰¹



- “The committee agreed that, although the utility estimates were subject to some uncertainty, the utility assumptions in the economic model were acceptable.”³⁰¹
- Everolimus compared with axitinib
 - “The company presented evidence comparing everolimus and axitinib using matched indirect comparison of RECORD-1 subgroup of patients who had previously had sunitinib and data from the AXIS trial (comparing axitinib and sorafenib). (...) The company suggested that progression-free survival and overall survival for everolimus and axitinib can be considered the same. The ERG agreed that this assumption is plausible.”³⁰¹
- Conclusions:
 - “The committee concluded that everolimus compared with axitinib is a cost-effective use of NHS resources for advanced RCC.”³⁰¹
 - “The committee concluded that the most plausible ICER for everolimus compared with best supportive care would be less than £30,000 per QALY gained including the revised patient access scheme.”³⁰¹
 - “Taking into account the cost-effectiveness analyses, including the revised patient access scheme, the committee recommended everolimus as a cost-effective use of NHS resources within its marketing authorisation as an option for treating advanced renal cell carcinoma that has progressed during or after treatment with vascular endothelial growth factor targeted therapy, only if the company provides it with the discount agreed in the patient access scheme.”³⁰¹
- (Confidential) price:
 - “The manufacturer agreed a patient access scheme with the Department of Health in which the first treatment pack of everolimus is free to the NHS and following treatment packs cost £2,822 (that is, a 5% discount on the acquisition cost of everolimus). A revised patient access scheme was subsequently agreed, the details of which are confidential.”³⁰¹
- Other remarks:
 - “This appraisal was a Cancer Drugs Fund reconsideration of the NICE technology appraisal guidance on everolimus for the second-line treatment of advanced renal cell carcinoma [i.e. NICE technology appraisal guidance 219]. The company submission focused on cost-effectiveness analyses using a revised patient access scheme, which provides a simple discount to the list price of everolimus. The level of the discount is commercial in confidence.”³⁰¹
 - “The committee was aware that the most plausible ICER for this comparison [i.e. everolimus versus BSC] would be less than £30,000 per QALY gained and therefore that advice about life extending treatments for people with a short life expectancy was not needed for the economic analyses. (...) Overall, the committee considered the end-of-life criteria to be fulfilled but only when everolimus was compared with best supportive care.”³⁰¹



Reference	Costs (list prices & remarks)	Population, Intervention & comparator IC, IE and ICERs	Remarks on use of generic utility instrument (e.g. EQ-5D) to measure impact on QoL in economic evaluations	Most uncertain variables or important variables in sensitivity analysis
Everolimus				
NICE, TA432 (201) ³⁰¹		Second-line treatment of advanced renal cell carcinoma (patients with advanced renal cell carcinoma, whose disease has progressed on or after treatment with vascular endothelial growth factor (VEGF) targeted therapy)		
NICE, Committee Papers 1015 (2017) ³⁰²		Everolimus compared with best-supportive care (BSC) and axitinib		
	List prices (confidential revised PAS) £2673 for a 10-mg 30-tablet pack (BNF December 2016)	Results including the <u>previous PAS</u> for everolimus (compared with BSC): <ul style="list-style-type: none"> - Company: £49 300 per QALY gained - ERG: £51 700 per QALY gained - Conclusion: despite EOL criteria being fulfilled, everolimus is not cost-effective ERG results including <u>revised PAS</u> for everolimus: <ul style="list-style-type: none"> - compared with BSC (CUA): below £30 000 per QALY gained - compared with axitinib (CMA): everolimus is equally effective and less costly than axitinib - Conclusion: everolimus is a cost-effective use of NHS resources. 	Everolimus vs. BSC: utilities not collected in the underlying RCT (RECORD-1). Everolimus vs. axitinib: no underlying RCT Utilities obtained from NICE TA178: ³⁰⁹ <ul style="list-style-type: none"> - 0.76 stable disease without AE - 0.71 stable disease with AE - 0.68 progressed disease 	Uncertain parameters: <ul style="list-style-type: none"> - magnitude of the overall survival gain

AE: adverse event, BNF: British national formulary, BSC: best-supportive care, CMA: cost-minimisation analysis, CUA: cost-utility analysis, EOR: end-of-life, ERG: evidence review group, PAS: patient access scheme.



Appendix 12.4.2.5. NICE, TA581 (2019): nivolumab (in combination with ipilimumab)

- QoL:
 - “The company used a regression model to estimate quality of life using utility values from data on EQ-5D-3L (EuroQol 5 dimensions, 3 levels) collected in CheckMate 214.”³⁰³
 - “A regression model using utility values derived from the EQ-5D-3L data collected in CheckMate 214, with treatment arm, treatment status and progression status included as explanatory variables.”³⁰⁴ [EQ-5D data used are reported in the table below]
- Results:
 - “The cost-effectiveness results are commercial in confidence because they include the confidential treatment costs of therapies used as second treatment options and beyond, and cannot be reported here.”³⁰³
 - “The ERG’s estimated ICER was between £35,000 and £40,000 per QALY gained compared with sunitinib or pazopanib (...). It [the committee] concluded that nivolumab with ipilimumab did not meet the criteria to be recommended for routine commissioning in the NHS.”³⁰³
 - “The committee noted that the company proposed a commercial arrangement that would make nivolumab with ipilimumab available at a lower price while the combination was available in the Cancer Drugs Fund. It considered the estimates of cost effectiveness with this new pricing arrangement, noting that all the survival curves generated ICERs for nivolumab with ipilimumab compared with sunitinib in the range of £20,000 to £30,000 per QALY gained, with most estimates in the lower end of the range as preferred by the committee (see section 3.19). The committee was satisfied that the proposed pricing model compensates for the clinical uncertainty relating to survival while nivolumab with ipilimumab remains in the Cancer Drugs Fund.”³⁰³
- Uncertainty and sensitivity:
 - “Based on the strength of the survival benefit shown, CheckMate 214 was stopped early. The committee agreed that the benefit was substantial but was aware that trials stopped early for benefit can overestimate the benefit. It noted that the data were immature, with a median follow-up of 25.2 months, and only 32.9% of people randomised to nivolumab with ipilimumab having died at the time of analysis.”³⁰³
 - “To estimate parameters beyond the end of the trial, the company extrapolated survival outcomes (based on the August 2018 data cut) by fitting parametric curves to the observed data (a log-normal distribution for overall survival, cubic spline for progression-free survival, and gamma for time-to-stopping treatment). (...) In the absence of evidence on the long-term immunological effect, the committee could not determine which curve was more appropriate.”³⁰³
 - “The committee noted that, given the immaturity of the data, there was substantial clinical uncertainty about the long-term effectiveness of nivolumab with ipilimumab.”³⁰³
 - “The committee agreed that, if survival curves are re-fitted to more mature data, this would help predict the long-term benefit of nivolumab with ipilimumab with higher precision.”³⁰³



- Conclusions:
 - “Nivolumab with ipilimumab has the potential to be cost effective, but more evidence is needed to address the clinical uncertainties. (...) The committee concluded that (...) the data remained too immature to establish the long-term effect of treatment.”³⁰³
 - “Having concluded that nivolumab with ipilimumab does not qualify for routine commissioning, the committee then considered if it could recommend nivolumab with ipilimumab as part of a managed access agreement. (...) The committee agreed that nivolumab with ipilimumab had plausible potential to be cost effective either at a lower price, or by lessening the clinical uncertainty about overall survival by collecting longer-term data.”³⁰³
- (Confidential) price:
 - “The company has commercial arrangements for nivolumab with ipilimumab. This makes nivolumab with ipilimumab available to the NHS with a discount. The size of the discount is commercial in confidence.”³⁰³
- Other remarks:
 - “Nivolumab with ipilimumab is recommended for use within the Cancer Drugs Fund for people who have untreated advanced renal cell carcinoma, while the manufacturer of nivolumab and ipilimumab collects further data.”³⁰³



Reference Costs (list prices & remarks)	Population, Intervention & comparator IC, IE and ICERs	Remarks on use of generic utility instrument (e.g. EQ-5D) to measure impact on QoL in economic evaluations	Most uncertain variables or important variables in sensitivity analysis																					
Nivolumab (in combination with ipilimumab)																								
NICE, TA581 (2019) ³⁰³	First-line treatment of adults with intermediate- or poor-risk advanced renal cell carcinoma																							
NICE, Committee Papers ID1182 (2019) ³⁰⁴	Nivolumab plus ipilimumab compared with pazopanib and with sunitinib																							
List prices (confidential PAS): Nivolumab: £439 per 40-mg vial, £1097 per 100-mg vial (BNF November 2018). Ipilimumab: £3 750 per 50-mg vial, £15 000 per 200-mg vial (BNF November 2018).	ERG results: Without the managed access agreement for nivolumab with ipilimumab: <ul style="list-style-type: none">between £35 000 and £40 000 per QALY gainedconclusion: without managed access agreement, nivolumab with ipilimumab does not qualify for routine commissioning With the managed access agreement* for nivolumab with ipilimumab: <ul style="list-style-type: none">between £20 000 to £30 000 per QALY gained, with most estimates in the lower end of the rangeconclusion: Nivolumab with ipilimumab is recommended for use within the Cancer Drugs Fund, via a managed access arrangement, while further evidence is collected to address clinical uncertainty	EQ-5D data collected from the underlying CheckMate 214 RCT. <table><tr><th>Utility</th><th>Nivolumab + ipilimumab</th><th>Sunitinib</th></tr><tr><td colspan="3">On treatment</td></tr><tr><td>PFS</td><td>0.793</td><td>0.754</td></tr><tr><td>PPS</td><td>0.794</td><td>0.763</td></tr><tr><td colspan="3">Off treatment</td></tr><tr><td>PFS</td><td>0.749</td><td>0.707</td></tr><tr><td>PPS</td><td>0.702</td><td>0.707</td></tr></table>	Utility	Nivolumab + ipilimumab	Sunitinib	On treatment			PFS	0.793	0.754	PPS	0.794	0.763	Off treatment			PFS	0.749	0.707	PPS	0.702	0.707	Main uncertainties: <ul style="list-style-type: none">Impact on long-term OSExtrapolation method for long-term OS
Utility	Nivolumab + ipilimumab	Sunitinib																						
On treatment																								
PFS	0.793	0.754																						
PPS	0.794	0.763																						
Off treatment																								
PFS	0.749	0.707																						
PPS	0.702	0.707																						

* The managed access agreement includes a patient access scheme and a commercial access agreement for nivolumab. There is a simple discount patient access scheme for ipilimumab. BNF: British national formulary, ERG: evidence review group, OS: overall survival, PAS: patient access scheme, PFS: progression-free survival, PPS: post-progression survival.



Appendix 12.4.2.6. NICE, TA417 (2016): nivolumab

- QoL:
 - “The committee was aware that CheckMate 025 collected health-related quality-of-life data using EQ-5D. (...) In its original submission, the company took utility values for its model from CheckMate 025 for nivolumab and everolimus (...). The revised base cases from both the company and the ERG took utility values for axitinib and best supportive care from the everolimus group in CheckMate 025.”³⁰⁵
 - Detail on the utility values used in the model were not found in this TA³⁰⁵ or in the underlying committee papers.³⁰⁶
- Results:
 - “The committee used the results including the patient access scheme for nivolumab for decision-making, but this document does not present precise results because the discount is confidential.”³⁰⁵
 - “When the confidential discounts for nivolumab and axitinib were included, the company’s revised base-case ICERs and the majority of the evidence review group’s (ERG’s) revised base-case ICERs were below £50,000 per QALY gained for nivolumab compared with any comparator.”³⁰⁵
- Uncertainty and sensitivity:
 - Nivolumab compared with everolimus:
 - “The committee considered the survival data from CheckMate 025 to be immature because, at the time of the interim analysis that led to the study stopping (July 2015), 398 out of 821 (48%) patients had died and median follow-up was only about 18 months.”³⁰⁵
 - “The committee concluded that the most robust results came from the larger CheckMate 025 trial, which showed that nivolumab extended life by a median of 5.4 months compared with everolimus, but also concluded that there was uncertainty about the extent of the survival benefit when measured over the long term.”³⁰⁵
 - “Because the trial data were immature (see section 4.5), the committee was concerned that a large proportion of the benefit attributed to nivolumab for extending life was based on extrapolation rather than on trial data.”³⁰⁵
 - Nivolumab compared with axitinib and BSC
 - “The committee understood that, because there were no head-to-head trials comparing nivolumab with axitinib or best supportive care, the company had done a network meta-analysis to compare the treatments indirectly. (...) It noted advice from the evidence review group (ERG) that the results were likely to be biased because of differences between trials: number of previous treatments (...), choice of previous treatments (...), prognosis of patients at baseline (...), subsequent treatments (...). The committee concluded that the company’s network meta-analysis could potentially have been biased in favour of nivolumab.”³⁰⁵



- Conclusions:
 - “Most of the incremental cost-effectiveness ratios (ICERs) for nivolumab compared with any comparator were below £50,000 per quality-adjusted life year (QALY) gained. The committee acknowledged that scenarios assuming a greater long-term survival benefit reduced the ICERs. It concluded that, when applying the maximum weighting to the QALY that is possible under the end-of-life criteria, the ICER for nivolumab fell within the range of a cost-effective treatment.”³⁰⁵
- (Confidential) price:
 - “In response to consultation, the company proposed a new simple discount patient access scheme for nivolumab. The level of discount is commercial in confidence.”³⁰⁵
 - “All analyses included the patient access schemes for nivolumab and axitinib.”³⁰⁵
- Other remarks:
 - “Although data on mean life expectancy were not available, on the balance of the evidence the committee concluded that average life expectancy was less than 24 months for people with advanced renal cell carcinoma and that the life-expectancy criterion was met. (...) The committee discussed whether nivolumab extended life by at least 3 months (...) The committee observed that CheckMate 025 had shown a median increase in survival of 5.4 months compared with everolimus. The committee had assumed axitinib was similarly effective to everolimus and so accepted that the extension to life for people having axitinib would also be greater than 3 months. The committee assumed that any extension to life would be even longer for nivolumab compared with best supportive care. The committee therefore agreed that nivolumab met the end-of-life criteria.”³⁰⁵



Reference Costs (list prices & remarks)	Population, Intervention & comparator IC, IE and ICERs	Remarks on use of generic utility instrument (e.g. EQ- 5D) to measure impact on QoL in economic evaluations	Most uncertain variables or important variables in sensitivity analysis															
Nivolumab																		
NICE, TA417 (2016) ³⁰⁵ NICE, Committee Papers ID853 (2016) ³⁰⁶	Second-line treatment of adults with advanced renal cell carcinoma (previously treated advanced renal cell carcinoma in adults) Nivolumab compared with axitinib, with everolimus and with best-supportive care (BSC)																	
List price (confidential PAS): £439 per 40-mg vial or £1097 per 100-mg vial.	Results (including PAS for nivolumab and axitinib): <table><tr><td></td><td>nivolumab</td><td>axitinib</td><td>everolimus</td><td>BSC</td></tr><tr><td>Total QALYs</td><td>2.30</td><td>1.69</td><td>1.69</td><td>1.00</td></tr><tr><td>Incremental QALYs</td><td>-</td><td>0.61</td><td>0.61</td><td>1.30</td></tr></table> Most of the base-case ICERs from the company and ERG were below £50 000 per QALY gained Remark: nivolumab meets the end-of-life (EOL) criteria Conclusion: under the EOL criteria, nivolumab is cost-effective		nivolumab	axitinib	everolimus	BSC	Total QALYs	2.30	1.69	1.69	1.00	Incremental QALYs	-	0.61	0.61	1.30	EQ-5D data collected from the underlying CheckMate 025 RCT for nivolumab and everolimus. Utility values for axitinib and best supportive care taken from the everolimus group in CheckMate 025	Uncertain parameters: - Long-term survival benefit of nivolumab - The choice of distribution for modelling time-to-stopping treatment
	nivolumab	axitinib	everolimus	BSC														
Total QALYs	2.30	1.69	1.69	1.00														
Incremental QALYs	-	0.61	0.61	1.30														

BSC: best supportive care, ICER: incremental cost-effectiveness ratio, PAS: patient access scheme, QALY: quality-adjusted life-year.



Appendix 12.4.2.7. NICE, TA215 (2011, updated August 2013): pazopanib

- QoL:
 - “Health related quality of life measures were derived from the pivotal trial VEG105192 using the EQ-5D questionnaire administered at weeks 8, 16, 24 and 48 of follow-up.”³⁰⁸
 - “For the model, a utility value of 0.70 was assumed for patients who had no disease progression and no adverse events, based on the mean EQ-5D utility value among patients without adverse events in the VEG105192 trial. Disease progression was assumed to be associated with a decrement in utility of 15% (that is, a post-progression utility value of 0.59). These values were used for all the interventions in the model. Utility decrements for adverse events were also obtained from the VEG105192 trial.”³⁰⁷
- Results:
 - “The Committee agreed that the base-case ICERs for pazopanib (including a 12.5% discount on the list price) compared with best supportive care, interferon- α and sunitinib of £33,000, £38,900 and £1790 per QALY gained (based on incremental costs of £32,200, £27,900, £122 and incremental QALYs of 0.979, 0.717 and 0.068 respectively) were reasonable estimates.”³⁰⁷
- Uncertainty and sensitivity:
 - “The Committee concluded that there was sufficient evidence that pazopanib increased progression-free and overall survival compared with placebo, although there was uncertainty about the precise magnitude of the overall survival gain.”³⁰⁷
 - “No head-to-head trials analysing the efficacy of pazopanib compared with other active treatment options were available. Therefore, the manufacturer undertook a search for trials of comparator interventions and carried out an indirect comparison to estimate the relative effect of pazopanib versus the comparators (sunitinib, interferon- α and best supportive care).”³⁰⁷
 - “There was uncertainty surrounding the estimates reported by the indirect comparison, relating to the data used to derive the hazard ratios used to estimate relative effectiveness and hence cost-effectiveness. (...) Only a few studies informed the indirect comparison and there is uncertainty surrounding the estimates generated by it.”³⁰⁸
 - “The Committee noted the results of the indirect comparison that suggested pazopanib was associated with considerably improved overall survival compared with either interferon- α or best supportive care, and was comparable with sunitinib, although the confidence intervals around the hazard ratios were wide.”³⁰⁷
 - “The Committee acknowledged that the estimates of overall survival for pazopanib versus placebo according to the intention-to treat analysis (22.9 versus 23.5 months; HR 1.01, 95% CI 0.72 to 1.42) had been confounded by crossover and that 51% of patients who had received placebo crossed over to receive pazopanib after disease progression. (...) The Committee (...) agreed that it was appropriate to adjust the results to control for the crossover using statistical modelling techniques. (...) The Committee acknowledged that the ICERs were highly sensitive to the method used for adjusting for crossover for overall survival data from the VEG105192 trial, with ICERs ranging from £21,600 to £72,300 per QALY gained for pazopanib versus interferon- α , and from £1790 to £5330 per QALY gained for pazopanib versus sunitinib.”³⁰⁷
 - “The main drivers of the cost-effectiveness results were the drug costs and the hazard ratios.”³⁰⁸



- Conclusions:
 - “The Committee was aware of exploratory net benefit analyses carried out by the ERG which indicated that pazopanib would be considered cost effective at willingness to pay thresholds between £35,000 and £50,000 per QALY gained. The Committee considered that the magnitude of additional weight that would need to be assigned to the original QALY benefits in this patient group was within the range considered acceptable for an end of life treatment.”³⁰⁷
- (Confidential) price:
 - “Pazopanib is recommended (...) if the manufacturer provides pazopanib with a 12.5% discount on the list price as agreed in the patient access scheme.”³⁰⁷
- Other remarks:
 - “In summary, the Committee was satisfied that pazopanib met the criteria for being a life-extending, end-of-life treatment, and that the evidence presented for this consideration was sufficiently robust.”³⁰⁷

Reference Costs (list prices & remarks)	Population, Intervention & comparator IC, IE and ICERs	Remarks on use of generic utility instrument (e.g. EQ- 5D) to measure impact on QoL in economic evaluations	Most uncertain variables or important variables in sensitivity analysis																
Pazopanib																			
NICE, TA215 (2011, updated August 2013) ³⁰⁷ Kilonzo (2010) ³⁰⁸	First-line treatment of advanced renal cell carcinoma Pazopanib compared with best-supportive care (BSC), interferon-α and sunitinib																		
Pazopanib list price: £1121 for a 400-mg 30- tablets pack (Nov 2010) PAS: 12.5% discount from the list price Daily cost (list price): £74.73 Daily cost (with PAS): £65.39	Base-case results (including PAS* for pazopanib): <table border="1"> <tr> <td>Pazopanib compared with:</td><td>BSC</td><td>Interferon-α</td><td>Sunitinib</td></tr> <tr> <td>ICosts</td><td>£32 200</td><td>£27 900</td><td>£122</td></tr> <tr> <td>IQALYs</td><td>0.979</td><td>0.717</td><td>0.068</td></tr> <tr> <td>ICER</td><td>£33 000</td><td>£38 900</td><td>£1790</td></tr> </table> Remark: pazopanib meets the end-of-life criteria Conclusion: with EOL criteria, pazopanib is cost-effective	Pazopanib compared with:	BSC	Interferon-α	Sunitinib	ICosts	£32 200	£27 900	£122	IQALYs	0.979	0.717	0.068	ICER	£33 000	£38 900	£1790	EQ-5D data collected from the VEG105192 trial comparing pazopanib with placebo (no underlying RCT): - Progression-free without adverse event: 0.70 - Post-progression: 0.59	ICER sensitive to: - Method of adjusting for cross-over Uncertain parameters: - Gain in overall survival
Pazopanib compared with:	BSC	Interferon-α	Sunitinib																
ICosts	£32 200	£27 900	£122																
IQALYs	0.979	0.717	0.068																
ICER	£33 000	£38 900	£1790																

* The Patient Access Scheme consists of a 12.5% discount on the list price of pazopanib. BSC: best-supportive care, ICER: incremental cost-effectiveness ratio, ICosts: incremental costs, IQALYs: incremental QALYs, PAS: patient access scheme, QALY: quality-adjusted life-year.



Appendix 12.4.2.8. NICE, TA178 (2009): sorafenib, sunitinib & temsirolimus

- QoL:
 - “The health-state utilities used in the Assessment Group model were derived from trial data in the manufacturer submissions and UK EQ-5D tariffs.”³⁰⁹
 - **First-line treatment** for people suitable for immunotherapy with three of six factors indicating poor prognosis (temsirolimus):

“People with a poor prognosis who can receive first-line treatments were assumed to have a utility of 0.60 when in the PFS state and 0.45 when in the PD state; these assumptions came from the Wyeth submission [*i.e. the temsirolimus trial*].”³⁰⁹
 - **Second-line treatment** for people in whom immunotherapy has failed or who are unsuitable for immunotherapy (sorafenib):

“People who were receiving second-line treatments were assumed to have a utility of 0.76 when in the PFS state and 0.68 when in the PD state; these assumptions came from the Pfizer submission [*i.e. the single-arm phase II sunitinib trial*].”³⁰⁹
- Results:
 - A. People who are suitable for immunotherapy**
 - First-line treatment for people suitable for immunotherapy with three of six factors indicating poor prognosis:

Temsirolimus versus IFN- α : “These resulted in a base-case ICER of **£102,000 per QALY gained** and subgroup ICERs ranging from £63,100 ('non-clear-cell carcinoma and indeterminate histologies') to £121,300 (clear cell carcinoma) per QALY gained. However, The Committee noted the recently published price of £620 for a vial of temsirolimus and was aware that these ICER estimates were derived using an underestimate of the price of a vial of temsirolimus of £515. Therefore it concluded that the ICERs were **underestimates** and would all increase if the recently published price of temsirolimus was incorporated into the cost-effectiveness analyses.”³⁰⁹
 - Second-line treatment for people in whom immunotherapy has failed:

“The Committee, noting instructions from the Department of Health that all of the cost-effectiveness estimates should include the first pack of sorafenib as free to the NHS and the new increased price of sorafenib, accepted that the most plausible ICER for **sorafenib compared with best supportive care** for people in whom immunotherapy had failed was **£65,900 per QALY gained**.”³⁰⁹
 - B. People who are unsuitable for immunotherapy**
 - Second-line treatment for people unsuitable for immunotherapy:

“The resulting estimates of cost effectiveness [*for sorafenib compared with best-supportive care*] were broadly similar with a revised manufacturer base-case ICER for the whole trial population of **£72,500 per QALY gained** and a DSU revised Assessment Group base-case ICER of **£74,900 per QALY gained**.”³⁰⁹
- Uncertainty and sensitivity:
 - First-line treatment for people suitable for immunotherapy with three of six factors indicating poor prognosis:



"The deterministic sensitivity analyses demonstrated that estimates of treatment effectiveness, cost of acquisition and administration of temsirolimus, and health-state utility input parameters were the key drivers affecting the ICERs. The ICER was particularly sensitive to variations in estimates of the hazard ratio for overall survival (...)."309

- Second-line treatments for people in whom immunotherapy has failed (A.b.) or who are unsuitable for immunotherapy (B.b.):

"For progression-free survival, the trial data were used directly for both the sorafenib and placebo arms. However, because of a short follow-up period, the data for overall survival were **immature** and were extrapolated over time by using an exponential function."309

"The DSU also highlighted that the follow-up of the participants randomised to receive sorafenib was much longer than that of the participants randomised to receive best supportive care. This was because participants were allowed to **crossover** from best supportive care to sorafenib treatment after the study was terminated early on ethical grounds."309

"The deterministic sensitivity analyses demonstrated that estimates of treatment effectiveness and cost of sorafenib (dose intensity assumption) were the key drivers affecting the ICERs. The health-state utility parameters affected the ICER marginally."309

- "It [the Committee] noted that in relation to first-line treatment for people who are unsuitable for immunotherapy and second-line treatment for people who are unsuitable for immunotherapy its recommendations are based on the view that there is limited or no evidence of clinical effectiveness for any patient group."309

- Conclusions:

- A. People who are suitable for immunotherapy**

- First-line treatment for people suitable for immunotherapy with three of six factors indicating poor prognosis:

"Therefore the Committee concluded that **temsirolimus** [compared with *IFN-α*] as a first-line treatment for people with advanced RCC and a poor prognosis would **not** be a **cost-effective** use of NHS resources."309

- Second-line treatment for people in whom immunotherapy has failed:

"Therefore the Committee concluded that **sorafenib** as a second-line treatment for people with advanced RCC in whom immunotherapy has failed would **not** be a **cost-effective** use of NHS resources."309

"However, in the absence of further robust data, the Committee concluded that **sunitinib** could **not** be considered a **clinically effective** second line treatment for people with advanced and/or metastatic RCC in whom immunotherapy had failed. (...) The cost effectiveness of sunitinib as a second-line treatment compared with best supportive care was not evaluated in the Assessment Group model because the data came from two single-arm trials and were considered inadequate by the Assessment Group."309

- B. People who are unsuitable for immunotherapy**

- First-line treatment for people unsuitable for immunotherapy with three of six factors indicating poor prognosis:



"The Committee concluded that **temsirolimus** had **not** been shown to be a **clinically effective** first-line treatment for people with advanced RCC and a poor prognosis and who were unsuitable for immunotherapy."³⁰⁹

"The Committee concluded that, in the absence of evidence, **sorafenib** had **not** been shown to be a **clinically effective** first-line treatment for people with advanced RCC and a poor prognosis and who were unsuitable for immunotherapy."³⁰⁹

- Second-line treatment for people in whom non-immunotherapy first-line treatment has failed and who are unsuitable for immunotherapy:

"The Committee (...) concluded that **sorafenib** as second-line treatment for people in whom non-immunotherapy first-line treatment has failed and who are unsuitable for immunotherapy with advanced RCC would **not** be a **cost-effective** use of NHS resources."³⁰⁹

- Second-line treatment for people in whom sunitinib has failed and who are unsuitable for immunotherapy:

"In the absence of robust data, the Committee could **not** reach any conclusions on whether **sorafenib** could be considered a **clinically effective** second-line treatment for people with advanced RCC who had received sunitinib as a first-line treatment."³⁰⁹

C. General conclusion

- "It [the Committee] noted that in relation to first-line treatment for people who are unsuitable for immunotherapy and second-line treatment for people who are unsuitable for immunotherapy its recommendations are based on the view that there is limited or no evidence of clinical effectiveness for any patient group. For the other patient populations the Committee's conclusions are based on the view that the treatments are not cost effective for any patient group."³⁰⁹
- (Confidential) price:
 - "The manufacturer of sorafenib (Bayer) has agreed a patient access scheme with the Department of Health for advanced RCC."³⁰⁹
 - "The revised cost-effectiveness estimates also incorporated a patient access scheme in which the first pack of sorafenib is free to the NHS."
- Other remarks:

A. People who are suitable for immunotherapy

- First-line treatment for people suitable for immunotherapy with three of six factors indicating poor prognosis:

"In summary, the Committee was satisfied that **temsirolimus** met the criteria for being a life extending, end-of-life treatment for the whole trial population."³⁰⁹
- Second-line treatment for people in whom immunotherapy has failed:

"Therefore the Committee was satisfied that **sorafenib** meets the criteria for being a life-extending, end-of-life treatment and that the trial evidence presented for this consideration was robust."³⁰⁹

B. People who are unsuitable for immunotherapy

- Second-line treatment for people in whom non-immunotherapy first-line treatment has failed and who are unsuitable for immunotherapy:



“The Committee agreed that the criterion for the robustness of evidence for this subgroup was not convincing therefore the Committee did not discuss whether **sorafenib** for the second-line treatment of people with advanced RCC who are unsuitable for immunotherapy fulfilled the criteria for consideration as a life extending, end-of-life treatment.”³⁰⁹

Reference Costs (list prices & remarks)	Population, Intervention & comparator IC, IE and ICERs	Remarks on use of generic utility instrument (e.g. EQ- 5D) to measure impact on QoL in economic evaluations	Most uncertain variables or important variables in sensitivity analysis																									
Sorafenib, sunitinib & temsirolimus																												
NICE, TA178 (2009) ³⁰⁹ Thomson Coon (2010) ²⁹⁵	<p>A. Advanced and/or metastatic renal cell carcinoma who are <u>suitable</u> for immunotherapy</p> <p>a. First-line treatment of adults with 3 of 6 factors indicating poor prognosis: temsirolimus compared with IFN-α</p> <p>b. Second-line treatment of adults in whom immunotherapy has failed: sorafenib compared with BSC, sunitinib compared with BSC</p> <p>B. Advanced and/or metastatic renal cell carcinoma who are <u>not suitable</u> for immunotherapy</p> <p>a. First-line treatment for adults with three of six factors indicating poor prognosis: temsirolimus compared with BSC, sorafenib compared with BSC</p> <p>b. Second-line treatment of adults in whom non-immunotherapy first-line treatment has failed: sorafenib compared with BSC</p> <p>c. Second-line treatment of adults in whom sunitinib has failed: sorafenib compared with BSC</p> <p>Sorafenib, sunitinib and temsirolimus compared with IFN-α and best-supportive care (BSC)</p>																											
<p>List prices (PAS** for sorafenib):</p> <p>Sorafenib: £2980.47 for a 200-mg 112-tablets pack</p> <p>Sunitinib: £3363 for a 50-mg 30-tablets pack</p> <p>Temsirolimus: £620 for a 30-mg vial</p>	<p>Decision-making ICERs (with PAS for sorafenib):</p> <table> <tr> <th></th><th>Indication</th><th>Intervention</th><th>ICER (per QALY gained)</th></tr> <tr> <td rowspan="2">Immunotherapy suitable</td><td>First-line (A.a.)</td><td>temsirolimus</td><td>£102 000</td></tr> <tr> <td>Second-line (A.b.)</td><td>sorafenib</td><td>£65 900</td></tr> <tr> <td rowspan="5">Immunotherapy unsuitable</td><td rowspan="2">First-line (B.a.)</td><td>sunitinib</td><td>No evidence*</td></tr> <tr> <td>temsirolimus</td><td>No evidence*</td></tr> <tr> <td rowspan="2">Second-line (B.b.)</td><td>sorafenib</td><td>No evidence*</td></tr> <tr> <td>sorafenib</td><td>£72 500 to £74 900</td></tr> <tr> <td>Second-line after sunitinib (B.c)</td><td>sorafenib</td><td>No evidence*</td></tr> </table>		Indication	Intervention	ICER (per QALY gained)	Immunotherapy suitable	First-line (A.a.)	temsirolimus	£102 000	Second-line (A.b.)	sorafenib	£65 900	Immunotherapy unsuitable	First-line (B.a.)	sunitinib	No evidence*	temsirolimus	No evidence*	Second-line (B.b.)	sorafenib	No evidence*	sorafenib	£72 500 to £74 900	Second-line after sunitinib (B.c)	sorafenib	No evidence*	<p>First-line treatment: EQ-5D data collected from the underlying temsirolimus trial</p> <ul style="list-style-type: none"> - PFS state: 0.60 - PD state: 0.45 <p>Second-line treatment: EQ-5D data collected from the single-arm phase II sunitinib trial (not the underlying trial):</p> <ul style="list-style-type: none"> - PFS state: 0.76 - PD state: 0.68 	<p>Key parameters:</p> <ul style="list-style-type: none"> - Estimates for OS - Drug costs
	Indication	Intervention	ICER (per QALY gained)																									
Immunotherapy suitable	First-line (A.a.)	temsirolimus	£102 000																									
	Second-line (A.b.)	sorafenib	£65 900																									
Immunotherapy unsuitable	First-line (B.a.)	sunitinib	No evidence*																									
		temsirolimus	No evidence*																									
	Second-line (B.b.)	sorafenib	No evidence*																									
		sorafenib	£72 500 to £74 900																									
	Second-line after sunitinib (B.c)	sorafenib	No evidence*																									



Remark: temserolimus (first-line A.a.) and sorafenib (second-line A.b.) meet the EOL criteria when administered to people suitable for immunotherapy.

Conclusions:

- Immunotherapy suitable: despite meeting the EOL criteria, temserolimus and sorafenib are not cost-effective
- Immunotherapy unsuitable: sorafenib is not cost-effective

** For those interventions, the Assessment Group did not undertake a cost-effectiveness analysis because there was no (or too weak) evidence to demonstrated clinical efficacy.*

*** In this PAS, the first pack of sorafenib is free to the NHS. EOL: end-of-life, ICER: incremental cost-effectiveness ratio, OS: overall survival, PAS: patient access scheme, PFS: progression-free survival, PD: progressed disease, QALY: quality-adjusted life-year.*



Appendix 12.4.2.9. NICE, TA169 (2009): sunitinib

- QoL:
 - “The health-state utilities used in the Assessment Group model were derived from trial data in the manufacturer submission and UK EQ-5D tariffs. Participants were assumed to be similar at baseline in terms of health-state value. Therefore treatment-specific health-state values were not applied. People who receive first-line treatments were assumed to have a utility of 0.78 when in the PFS state and 0.70 when in the PD state; these assumptions came from the manufacturer (Pfizer) submission.”³¹⁰
- Results:
 - “The Committee noted the DSU [*Decision Support Unit*] and Assessment Group analyses based on the Committee's preferred assumptions. (...) The Committee noted the DSU's resulting cost-effectiveness estimate of **£49,300 per QALY gained**. The Committee noted the DSU's comments that this was likely to be an underestimate and also noted the cost-effectiveness estimate of **£54,400 per QALY gained** from the same preferred Committee assumptions in the Assessment Group model.”³¹⁰
 - “The Committee was aware that there was a paucity of data on quality of life and acknowledged consultation responses that the difference of 0.08 between the utility assigned to a progression-free health state and a progressed disease health state was too small. (...) Therefore the Committee agreed that an increased utility difference between the two health states was plausible (...). Taking this into account (...), the Committee was persuaded that the ICER for sunitinib 'no post-study treatment group' could be **less than £50,000 per QALY gained**.”³¹⁰
- Uncertainty and sensitivity:
 - “Three interim analyses were scheduled and after the second analysis the study was unblinded and participants in the IFN- α group with progressive disease were allowed to cross over into the sunitinib group. This is at variance with the study protocol which stated that all treatment would be stopped when there was evidence of disease progression. (...) There were 25 participants in the IFN- α arm who, during the course of the study, crossed over to receive sunitinib treatment after disease progression.”³¹⁰
 - “Median overall survival had not been reached in either treatment arm at the time of the interim data analyses.”³¹⁰
 - “In particular, the Assessment Group highlighted a paucity of data surrounding accurate health-state utility values and best supportive care costs.”³¹⁰
- Conclusions:
 - “The Committee concluded that sunitinib as a first-line treatment for advanced and/or metastatic RCC could be recommended as a cost-effective use of NHS resources, if a patient has an ECOG performance status of 0 or 1 and there are no further treatment options recommended by NICE after first-line sunitinib treatment.”³¹⁰
- (Confidential) price:
 - “The manufacturer of sunitinib (Pfizer) has agreed a patient access scheme with the Department of Health, in which the first treatment cycle of sunitinib is free to the NHS.”³¹⁰
- Other remarks:



- “In summary, the Committee was satisfied that sunitinib currently meets the criteria for being a life-extending end-of-life treatment, and that the evidence presented for this consideration was sufficiently robust.”³¹⁰

Reference Costs (list prices & remarks)	Population, Intervention & comparator IC, IE and ICERs	Remarks on use of generic utility instrument (e.g. EQ- 5D) to measure impact on QoL in economic evaluations	Most uncertain variables or important variables in sensitivity analysis
Sunitinib			
NICE, TA169 (2009) ³¹⁰	First-line treatment of advanced and/or metastatic renal cell carcinoma for people who are suitable for immunotherapy Sunitinib compared with IFN-α		
Sunitinib: List price: £3363 for a 50- mg 30-capsules pack PAS: the first treatment cycle is free to the NHS	Decision-making ICERs (including PAS): - DSU: £49 300 per QALY gained - ERG: £54 400 per QALY gained - Committee most plausible ICER: below £50 000 per QALY gained Remark: sunitinib (first-line) meets the EOL criteria Conclusion: sunitinib is a cost-effective use of NHS resources.	EQ-5D data collected from the underlying sunitinib trial (first- line): - PFS: 0.78 - PD: 0.70	Uncertain parameters: - QoL estimates - Magnitude of OS

EOL: end-of-life, ICER: incremental cost-effectiveness ratio, OS: overall survival, PAS: patient access scheme, PD: progressed disease, PFS: progression-free survival, QoL: quality of life.



APPENDIX 13. OVERVIEW FINDINGS MEDICAL LITERATURE

Cancer type	Observational data	drug	OS medical literature	QoL	comments
Breast cancer	No noticeable improvement in observed survival is observed over the three incidence periods	pertuzemab HER(+)	1st line PTP vs PT: HR 0.68 (95%CI 0.56-0.83) 2nd line Per-Tras-Cap vs Cap HR 0.66 (95%CI 0.39-1.22) Per-Tras-Cap vs Lap-Cap HR 0.74 (95%CI 0.46 – 1.77) Per-Tras-Cap vs Tras-Cap HR 0.76 (95%CI 0.50-1.07)	no data in SR	highest uptake 16.7% in 2015
		trastuzumab emtansine HER(+)	T-DM1 vs Cap HR 0.68 (95%CI 0.39-1.10) T-DM1 vs Lap-Cap HR 0.76 (95%CI 0.51-1.07) T-DM1 vs Tras-Cap HR 0.78 (95%CI 0.44-1.19) T-DM1 vs Per-Tras-Cap	no data in SR	highest uptake 7.1% in 2014
		palbociclib abemaciclib ribociclib HR(+)/HER(-)	overall: HR 0.76 (95%CI 0.67-0.87) First-line therapy HR 0.74 (95%CI 0.60-0.90) Subsequent-line therapy: HR 0.78 (95%CI 0.66-0.92)	no data in SR	palbociclib: highest uptake 18.4% in 2017 abemaciclib: reimbursed since 2019 ribociclib: reimbursed since 2018
CML	An improvement in overall survival and relative survival over the years was seen.	imatinib	imatinib vs IFN- α (response data only: huge effect)	HRQoL better for patients treated with imatinib than those with IFN- α + Ara-C as first-line therapy	Uptake of 79.1% already in 2004 maximum uptake 88.6% in 2009, then decreased to between 58-67%



Cancer type	Observational data	drug	OS medical literature	QoL	comments
		nilotinib	1st line Imatinib vs 300mg nilotinib HR 0.80 (95%CI 0.43-1.50) Imatinib vs 400mg nilotinib HR 0.44 (95%CI 0.21-0.93)	no data in SR	maximum uptake 45% in 2012
		dasatinib	1st line Imatinib vs dasatinib HR 1.01 (95%CI 0.58-1.73)	no data in SR	maximum uptake 47% in 2015
		bosutinib	1st line nilotinib, dasatinib, bosutinib or ponatinib 1 year: RR 0.82 (95%CI 0.45-1.51) 2 years: RR 0.62 (95%CI 0.20-1.94) 3 years: RR 0.73 (95%CI 0.46-1.17)	no data in SR	maximum 5.6% in 2014
		ponatinib	1st line nilotinib, dasatinib, bosutinib or ponatinib 1 year: RR 0.82 (95%CI 0.45-1.51) 2 years: RR 0.62 (95%CI 0.20-1.94) 3 years: RR 0.73 (95%CI 0.46-1.17)	no data in SR	maximum uptake 5% in 2015
Colorectal cancer	Observed survival and relative survival did not	bevacizumab	First line HR 0.85 (95%CI 0.78-0.94) second line	no data in SR	Maximum uptake 47.7% in 2012



Cancer type	Observational data	drug	OS medical literature	QoL	comments
	change substantially over time		HR 0.79 (95%CI 0.70-0.88)		
		panitumumab	First line Oxaliplatin-based chemotherapy + anti-EGFR therapy HR 0.89 (95%CI 0.78-1.02) Irinotecan-based chemotherapy + anti-EGFR therapy HR 0.89 (95%CI 0.80-0.98) Second line HR 0.93 (95%CI 0.82-1.05) Third line HR 0.79 (95%CI 0.50-1.24)	2 studies showed neutral or equivocal results	maximum uptake 12.4% in 2010
		cetuximab	First line Oxaliplatin-based chemotherapy + anti-EGFR therapy HR 0.89 (95%CI 0.78-1.02) Irinotecan-based chemotherapy + anti-EGFR therapy HR 0.89 (95%CI 0.80-0.98) Second line HR 0.93 (95%CI 0.82-1.05) Third line HR 0.79 (95%CI 0.50-1.24)	2 studies showed neutral or equivocal results	maximum uptake 7.1% in 2005
		aflibercept	Second line HR 0.82 (95%CI 0.71-0.94)	no data in SR	maximum uptake 2.1% in 2013
		regorafenib	refractory metastatic colorectal cancer	"Trials showed a similar deterioration in quality of	maximum uptake 2.8% in 2014



Cancer type	Observational data	drug	OS medical literature	QoL	comments
			HR 0.67 (95%CI 0.48-0.93)	life in both the regorafenib and comparator groups."	Tthe CORRECT and the CONCUR trials investigating the use of regorafenib in the third-line setting were positive studies, but survival benefit was limited to 1.4 and 2.5 months, respectively."
Head & Neck	Observed overall survival and relative survival of stage IV head and neck cancer did not change significantly over time	cetuximab	anti-EGFR + radiotherapy vs radiotherapy alone HR 0.76 (95%CI 0.61-0.94) anti-EGFR + radiotherapy vs chemoradiotherapy HR not reported (95%CI 0.87-2.05) recurrent or metastatic HR 0.86 (95%CI 0.78-0.95)	no data in SR	maximum uptake 29% in 2011
Melanoma	For stage IV patients, we do not observe a clear positive trend in the observed survival over the years. For the patients with stage NA tumour, survival has not substantially changed between 2004 and 2013 whereas it has improved for patients diagnosed in the incidence period 2014-2017	Nivolumab	Anti-PD1 monoclonal antibodies vs chemo HR 0.42 (95%CI 0.37-0.48)	no data in SR	change in population characteristics maximum uptake 37.5% in 2015
		Pembrolizumab	Anti-PD1 monoclonal antibodies vs chemo HR 0.42 (95%CI 0.37-0.48)	From KEYNOTE-002 trial: participants treated with pembrolizumab consistently reported less deterioration in individual function and symptoms scales when compared to	maximum uptake 26.7% in 2017



Cancer type	Observational data	drug	OS medical literature	QoL	comments
				those treated with chemotherapy. Fewer patients in the pembrolizumab group reported decrements of more than 10 points in the global health status QoL score compared to the chemotherapy group	
		Ipilimumab	Ipilimumab vc chemo HR 0.72 (95%CI 0.59-0.88)	Quality-adjusted survival was not significantly different between the groups during the first year of study (0.50 months favouring the ipilimumab/dacarbazine) but after extended follow-up, this difference gradually increased to 1.5 months, 2.36 months and 3.28 months at 2,3 and 4 years respectively	maximum uptake 33.3% in 2013
		Vemurafenib	BRAF inh vs chemotherapy HR 0.40 (95%CI 0.28-0.57)	no data in SR	maximum uptake 21.4% in 2013
		Dabrafenib	BRAF inh vs chemotherapy HR 0.40 (95%CI 0.28-0.57)	Single agent dabrafenib was found superior to dacarbazine chemotherapy in improving quality of life	maximum uptake 23.1% in 2015
		Trametinib	BRAF + MEK inh vs BRAF inh HR 0.70 (95%CI 0.59-0.82)	no data in SR	maximum uptake 20.0% in 2017
Mesothelioma	No clear improvement in observed survival and relative survival is noticeable	Pemetrexed	median survival 13.2 months for pemetrexed + cisplatin versus 9.3 months for cisplatin alone (p=0.02)	"Patients treated with pemetrexed plus cisplatin demonstrated greater	maximum uptake 69.6% in 2015



Cancer type	Observational data	drug	OS medical literature	QoL	comments
	over the three incidence periods.			improvement in global QoL (p=0.0012)."	
Multiple myeloma	Observed survival has remained stable between 2004 and 2013 while it tends to be higher in the last incidence period 2014-2017	Lenalidomide	1st line RD vs MP HR 0.63 (95%CI 0.40-0.99) continuous RD vs MP HR 0.69 (95%CI 0.47-1.03) RD vs TMP HR 0.77 (95%CI 0.51-1.16)	QoL was reported in 4 of the 25 studies included in the SR 1) disease symptoms were substantially lower in patients receiving RD compared to TMP and side effects of treatment were lower in patients receiving RDc compared to TMP 2) for other studies, comparing the effect on QoL for the different treatment arms was not possible based on the reports in the NMA.	maximum uptake 48.9% in 2017
		Bortezomib	1st line VRDc vs RD HR 0.79 (95%CI 0.42-1.48) VRDc vs RDc HR 0.71 (95%CI 0.44-1.15)	for other studies, comparing the effect on QoL for the different treatment arms was not possible based on the reports in the NMA.	maximum uptake 67.3% in 2014
		Pomalidomide	recurrent disease HR 0.74 (95%CI 0.56-0.97)	"Better results were reached with pomalidomide, statistically and clinically significant differences were found in most scales of the PRO instruments."	maximum uptake 13.2% in 2014 median OS 12.7 months (95%CI 10.4-15.5 months) in the Pomalidomide group versus 8.1 months (95%CI 6.9-10.8 months) in the control group



Cancer type	Observational data	drug	OS medical literature	QoL	comments
		Daratumumab	Kaplan-Meier rate of overall survival at 12 months was 92.1% (95%CI 88.2-94.7%) in the daratumumab group and 86.8% (95%CI 82.2% -90.3%)	no data in SR	maximum uptake 10.6% in 2016
CLL & SLL	Overall survival and relative survival slightly improved over the years	Rituximab	HR 0.65 (95%CI 0.54-0.78) Maintenance HR:0.86, 95%CI:0.58–1.28	no data in SR	Maximum uptake 28.4% in 2010
		Ibrutinib	HR 0.289 (95% CI, 0.071-1.175)	no data in SR	Maximum uptake 7.1% in 2014
		Obinutuzumab	G-Clb vs R-Clb HR 0.70 (95%CI 0.47-1.02) C-Clb vs Clb HR 0.47 (95%CI 0.29-0.76)	no data in SR	Maximum uptake 5.7% in 2016
DLBCL	Overall survival and relative survival slightly increased between 2004-2008 and 2009-2013; no further improvement was seen for the period 2014-2017	Rituximab	1 st line OR 0.91 (95%CI 0.78-1.07) salvage therapy HR = 0.66, (95% CI: 0.27-1.29)	no data in SR	Maximum uptake 82.7% in 2017.
Mantle cell lymphoma	Overall survival and relative survival have not clearly improved over the years, with the best observed survival probability in the middle of the three incidence periods	Rituximab	HR 0.65 (95%CI 0.54-0.78)	no data in SR	Maximum uptake 80.9% in 2015
		Ibrutinib	HR 0.74 (95%CI 0.54-1.02)	no data in SR	Maximum uptake 26.8% in 2014



Cancer type	Observational data	drug	OS medical literature	QoL	comments
NSCLC	For patients with stage IV NSCLC, observed survival seems relative stable during the incidence period 2004-2013 (Error! Reference source not found. B&C). Compared to earlier incidence years, observed survival of patients diagnosed in 2014-2017 seems to have improved	Erlotinib	1st line EGFR M+ Erlotinib vs chemotherapy HR 0.95 [0.75, 1.22] Erlotinib + chemotherapy vs Chemotherapy + placebo HR 0.48 [0.27, 0.85] 2nd line EGFR inhibitor vs chemotherapy HR 1.02 (95%CI 0.95-1.09) erlotinib vs placebo HR 0.70 (95%CI 0.58-0.85) Median OS 6.7 months in the erlotinib group; 4.7 months in the placebo group	TORCH study: "Improvement in terms of global QoL and physical functioning was particularly evident in the small numbers of EGFR M+ participants (n = 36/39 available for analysis) for erlotinib compared to cytotoxic chemotherapy." <u>OPTIMAL study</u> : "in favour of erlotinib" <u>Ensure study</u> : time to deterioration in QoL was 8.2 months for erlotinib compared to 2.8 months for chemotherapy (HR 0.64, 95% CI 0.44 to 0.93; P = 0.0168)	Maximum uptake 23.8% in 2009
		Gefitinib	2nd line All patients HR 1.02 (95%CI 0.91-1.15) EGFR mutation + patients HR 0.83 (95%CI 0.41-1.66)	no data in SR	Maximum uptake 3.6% in 2011
		Afatinib	1st line Afatinib vs pemetrexed + cisplatin HR 0.91 [0.66, 1.25] Afatinib vs gemcitabine + cisplatin HR 0.95 [0.68, 1.33]	no data in SR	Maximum uptake 1.2% in 2017
		Crizotinib	HR 0.83 (0.69, 1.00)	no data in SR	Maximum uptake 1.3% in 2014



Cancer type	Observational data	drug	OS medical literature	QoL	comments
		Nivolumab Pembrolizumab	Immunotherapy + chemotherapy vs chemotherapy HR 0.77 (95%CI 0.66-0.89) Immunotherapy monotherapy vs chemotherapy HR 0.75 (95%CI 0.67-0.83)	no data in SR	N: Maximum uptake 19.3% in 2016 P: Maximum uptake 21% in 2017
Ovarian cancer	No clear improvement in observed survival is perceptible over the three incidence periods	Bevacizumab	Newly diagnosed HR = 0.94, 95%CI 0.84-1.05 Recurrent HR = 0.93; 95%CI 0.77-1.12 FIGO stage IV (GOG-028 trial) HR 0.72 (95%CI 0.53-0.97) FIGO stage IV or FIGO stage IIIC and > 1cm residual disease after cytoreductive surgery (ICON-7 trial) HR 0.78 (95%CI 0.63-0.97)	"Pooled estimate shows that bevacizumab is associated with an early (at 18 weeks) worse QoL. This negative effect on QoL disappears in the long run (54-60 weeks)" "Bevacizumab increases the proportion of patients achieving a 15% improvement in patient-reported abdominal/gastrointestinal symptoms (measured with EORTC QLQ-OV28) during chemotherapy in patients with recurrent platinum-resistant epithelial ovarian, primary peritoneal, or fallopian-tube cancer. This treatment effect extends until 30 weeks."	maximum uptake 50.3% in 2017
Prostate cancer	Observed survival and relative survival slightly improved over time	Enzalutamide	Enzalutamide vs placebo/best supportive care:	"The authors found a significant HRQoL benefit for the enzalutamide group compared to the	maximum uptake 19.2% in 2014



Cancer type	Observational data	drug	OS medical literature	QoL	comments
			HR 0.77 (95%CI 0.77-0.88) Enzalutamide vs weekly docetaxel + prednisone HR 0.87 (95%CI 0.66-1.13)	placebo group, observed for the total FACT-P score as well as subdomains of the FACT-P questionnaire."	
Renal cell carcinoma	For stage IV RCC, an improvement (with overlapping confidence intervals) of observed and relative survival is seen for patients diagnosed between 2014 and 2017.	Sunitinib	1 st line Median OS 26.4 months with sunitinib versus 21.8 months with interferon- α (HR 0.82; 95%CI 0.669-0.999) p= 0.049	"Summarizing these results, the treatment options may lead to similar QoL"	Maximum uptake 55.8% in 2008 and 2010
		Sorafenib	2 nd line Median OS was 17.8 months for sorafenib versus 15.2 months for placebo (HR 0.88, p=0.15) (with censoring of placebo patients at the time of cross-over HR 0.78 95%CI 0.62-0.97; however patients who crossed-over were different from patients who did not)	"The authors documented symptomatic improvement of sorafenib over placebo on formal QoL assessment with validated QoL measures."	Maximum uptake 29.5% in 2008
		Pazopanib	1 st line "Interim over-all survival did not cross the prespecified difference threshold and final results are awaited" OS: 22.9 vs 20.5 months HR 0.91 (95%CI 0.71-1.16)	"This benefit (of PFS) did not translate into any improvement of formal quality of life measurement"	Maximum uptake 38.3% in 2012
		Axitinib	Axitinib vs everolimus: HR 1.14 (95%CI 0.95 – 1.37)	no data in SR	Maximum uptake 26.8% in 2013



Cancer type	Observational data	drug	OS medical literature	QoL	comments
		Everolimus	2nd line, vs placebo "overall survival was essentially the same in both arms"	no data in SR	Maximum uptake 34% in 2011
		Temsirolimus	Median OS was 10.9 months for temsirolimus versus 7.3 months for interferon- α . HR 0.73 (95%CI 0.58-0.92)	no data in SR	Maximum uptake 22.7% in 2010
		Nivolumab	1st line checkpoint-inhibitors vs subitinib HR 0.65 (95%CI 0.54-0.79) Recurrent disease nivolumab vs everolimus RR 0.70 (95%CI 0.56-0.87)	"Clinically relevant differences in improvements were more frequently observed in patients treated with nivolumab."	Maximum uptake 34.5% in 2017

'Positive' results that were statistically significant are marked in green, inconclusive results in blue.



APPENDIX 14. DRUG PRICES

Monthly prices for pharmaceutical products in Belgium have been monitored and compared to UK prices at the time of NICE reports. Belgian prices were communicated by INAMI – RIZIV in October 2020. Packaging selection (price in green in the tables) was made to correspond to UK products to allow a direct comparison. To convert GBP to EUR, we have taken the following exchange rate: 1 EUR = 0.8579 GBP (14/03/2021).

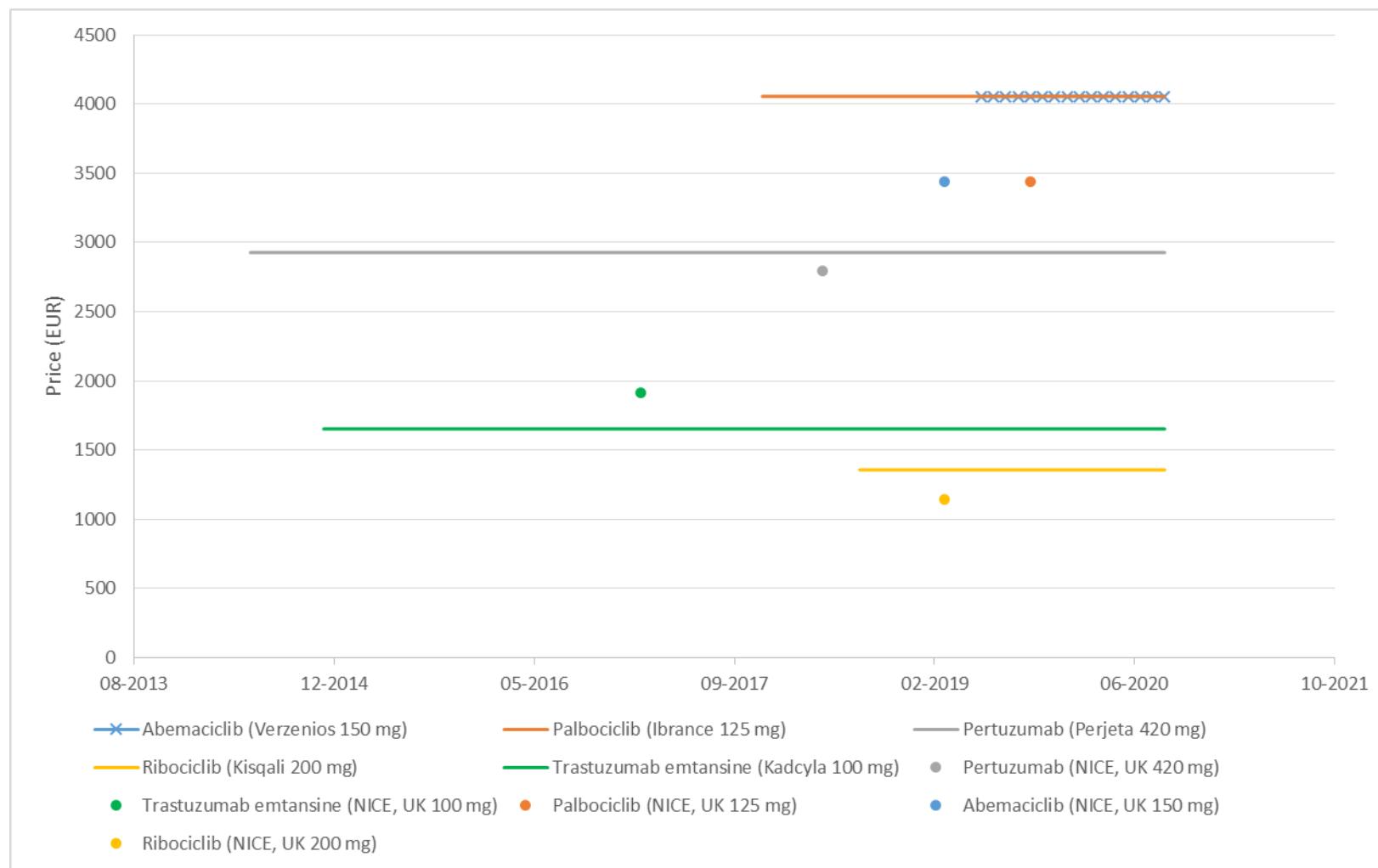
Abbreviations:

- S_COD: unique serial number of each speciality pack
- S_NAM: name of the speciality
- S_NAM_SPECIF: quantity of the speciality per unit
- F_ORGA: company
- ATC_COD: ATC5
- SRC_COD_T: code T : is the price confidential? (1=yes/0=no)
- SPB_PUBLIC: public price (in EUR)
- SRC_DEL_ID: delivery source : 1=public; 2=ambulatory (price per unit); 3=hospitalised (price per unit); 5= nursing home (price per unit)
- Extra information: quantity per package

[illegible]



Figure 368 – Drugs prices for breast cancer



Appendix 14.2. Chronic myeloid leukaemia (CML)

Figure 369 – Drugs prices for CML

S_COD	S_NAM	S_NAM_S PECIF	F_ORGA	ATC_COD	SRC_COD_ T	SPB_PUBLIC					Extra information
						SRC_DEL_ D : 1	SRC_DEL_ _ID : 2	SRC_DEL_ _ID : 3	SRC_DEL_ _ID : 4	SRC_DEL_ _ID : 5	
Imatinib (Glivec)											
407400	GLIVEC	100 mg	NOVARTIS PHARMA	L01XE01	0	943.86	7.6153	7.5561	855.41	7.8272	120 capsules, hard
552896	GLIVEC	400 mg	NOVARTIS PHARMA	L01XE01	0	924.18	29.825	29.588	837.4	30.6531	30 filmomhulde tabletten
1340317	IMATINIB EG	400 mg	EUROGENERICS	L01XE01	0	2205.18	23.7524	23.6734	2010.01	30.6361	90 filmomhulde tabletten
1342034	IMATINIB EG	100 mg	EUROGENERICS	L01XE01	0	943.34	7.6113	7.552	854.94	7.8229	120 filmomhulde tabletten
1342135	IMATINIB EG	400 mg	EUROGENERICS	L01XE01	0	923.67	23.7524	23.6734	836.94	30.6361	30 filmomhulde tabletten
1343650	IMATINIB KRKA	100 mg	KRKA D.D..(KRKA BELGIUM)	L01XE01	0	943.95	7.6162	7.5569	855.5	7.828	120 filmomhulde tabletten
1343852	IMATINIB KRKA	400 mg	KRKA D.D..(KRKA BELGIUM)	L01XE01	0	924.29	29.8287	29.5917	837.5	30.6566	30 filmomhulde tabletten
1349007	IMATINIB TEVA	100 mg	AREGA PHARMA	L01XE01	0	943.95	7.6162	7.5569	855.5	7.828	120 filmomhulde tabletten
1349108	IMATINIB TEVA	400 mg	AREGA PHARMA	L01XE01	0	924.29	29.8287	29.5917	837.5	30.6566	30 filmomhulde tabletten
1350421	IMATINIB SANDOZ	100 mg	SANDOZ	L01XE01	0	943.95	7.6162	7.5569	855.5	7.828	120 filmomhulde tabletten
1350522	IMATINIB SANDOZ	400 mg	SANDOZ	L01XE01	0	924.29	29.8287	29.5917	837.5	30.6566	30 filmomhulde tabletten
1353249	IMATINIB ACCORD	100 mg	ACCORD HEALTHCARE	L01XE01	0	943.95	7.6162	7.5569	855.5	7.828	120 filmomhulde tabletten
1353350	IMATINIB ACCORD	400 mg	ACCORD HEALTHCARE	L01XE01	0	924.29	29.8287	29.5917	837.5	30.6566	30 filmomhulde tabletten
1371437	GLIVEC	100 mg	PI-PHARMA	L01XE01	0	943.86	7.6153	7.5561	855.41	7.8272	120 capsules, hard
1412661	IMATINIB MYLAN	100 mg	MYLAN	L01XE01	0	943.34	7.6113	7.552	854.94	7.8229	120 filmomhulde tabletten
1412863	IMATINIB MYLAN	400 mg	MYLAN	L01XE01	0	2205.18	23.7524	23.6734	2010.01	24.451	90 filmomhulde tabletten
1490051	IMATINIB EG	100 mg	EUROGENERICS	L01XE01	0	943.34	7.6113	7.552	854.94	7.8229	120 filmomhulde tabletten
1490052	IMATINIB EG	400 mg	EUROGENERICS	L01XE01	0	923.67	23.7524	23.6734	836.94	30.6361	30 filmomhulde tabletten
1490053	IMATINIB EG	400 mg	EUROGENERICS	L01XE01	0	2205.18	23.7524	23.6734	2010.01	30.6361	90 filmomhulde tabletten
1490181	IMATINIB KRKA	100 mg	KRKA D.D..(KRKA BELGIUM)	L01XE01	0	943.34	7.6113	7.552	854.94	7.8229	120 dispergeerbare tabletten
1490182	IMATINIB KRKA	400 mg	KRKA D.D..(KRKA BELGIUM)	L01XE01	0	923.67	29.809	29.572	836.94	30.6361	30 dispergeerbare tabletten
TA426 (2016): "Imatinib was available at a cost of £1,604.00 for a 400-mg 30-tablet pack (excluding VAT; BNF edition 61) resulting in an annual cost of imatinib treatment of £39,033.00, assuming a treatment regimen of 400 mg twice daily. The cost of imatinib has increased to £1,836.48 for a 400-mg 30-tablet pack (excluding VAT; BNF online, accessed October 2016). The cost of imatinib treatment is now £44,718.00 per year assuming a treatment regimen of 400 mg twice daily. Costs may vary in different settings because of negotiated procurement discounts."											
Nilotinib (Tasigna)											
691730	TASIGNA	200 mg	NOVARTIS PHARMA	L01XE08	0		35.6715	35.608	3762.36		112 capsules, hard
928772	TASIGNA	150 mg	NOVARTIS PHARMA	L01XE08	0		24.8038	24.7404	2614.08		112 capsules, hard
1510638	TASIGNA	50 mg	NOVARTIS PHARMA	L01XE08	0		8.3061	8.2468	933.6		120 capsules, hard
TA426 (2016): "Nilotinib is available at a cost of £2,432.85 for a pack of 112 150-mg tablets (excluding VAT; BNF online, accessed October 2016). The cost of nilotinib treatment is £31,715.00 per year, assuming a treatment regimen of 300 mg twice daily. The company has agreed a patient access scheme with the Department of Health. This scheme provides a simple discount to the list price of nilotinib, with the discount applied at the point of purchase or invoice. The level of the discount is commercial in confidence."											



Figure 370 – Drugs prices for CML

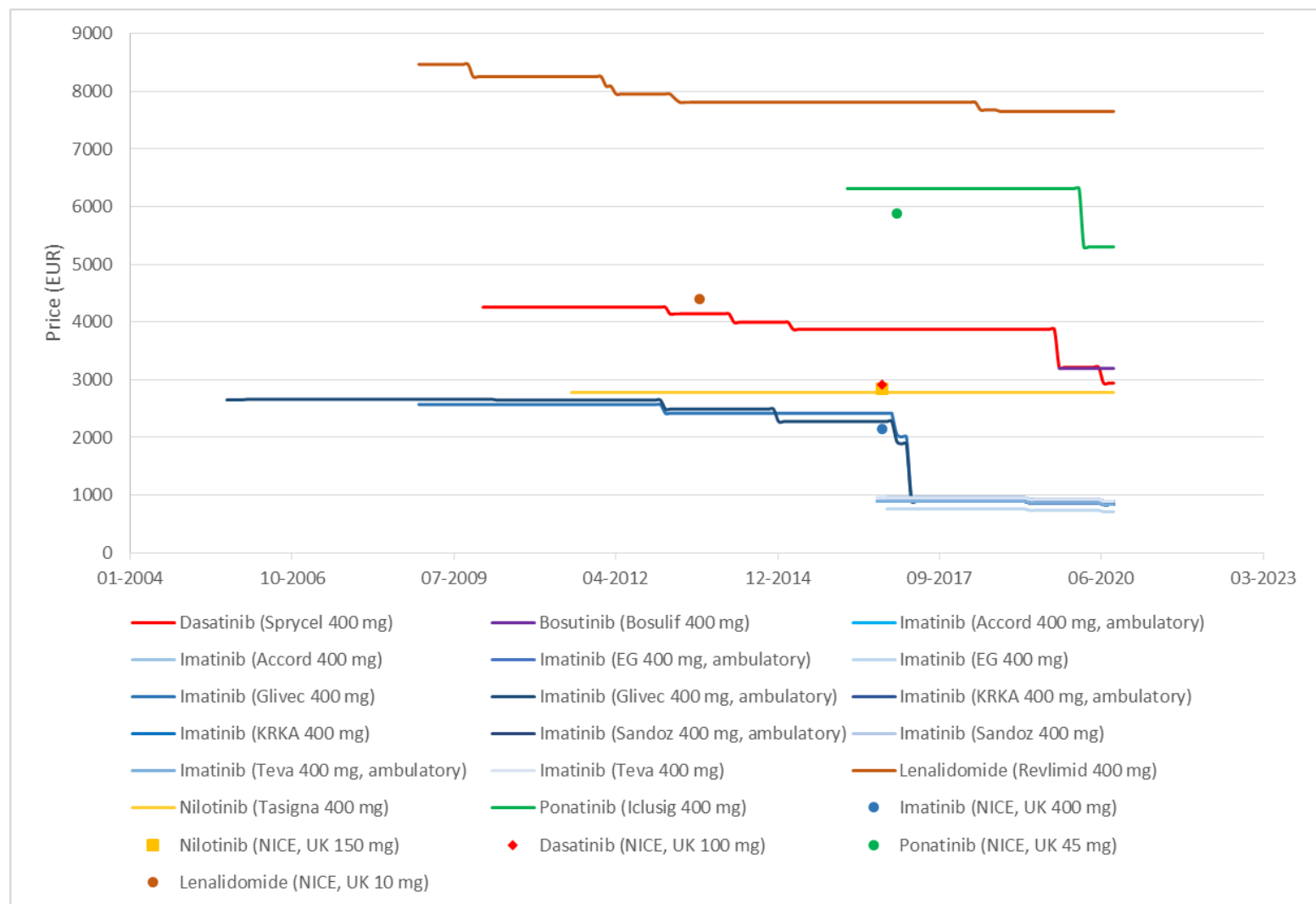
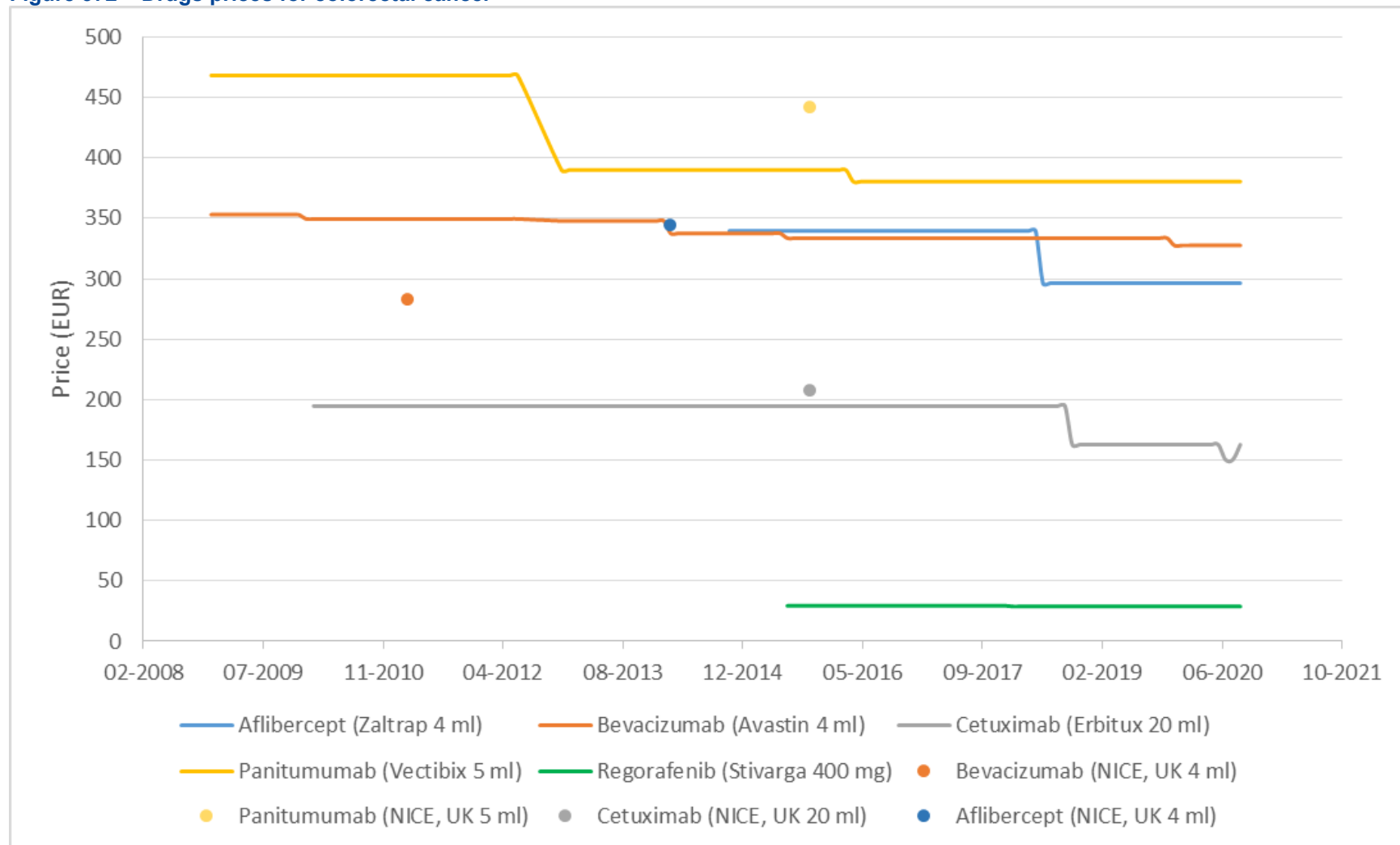




Figure 372 – Drugs prices for colorectal cancer





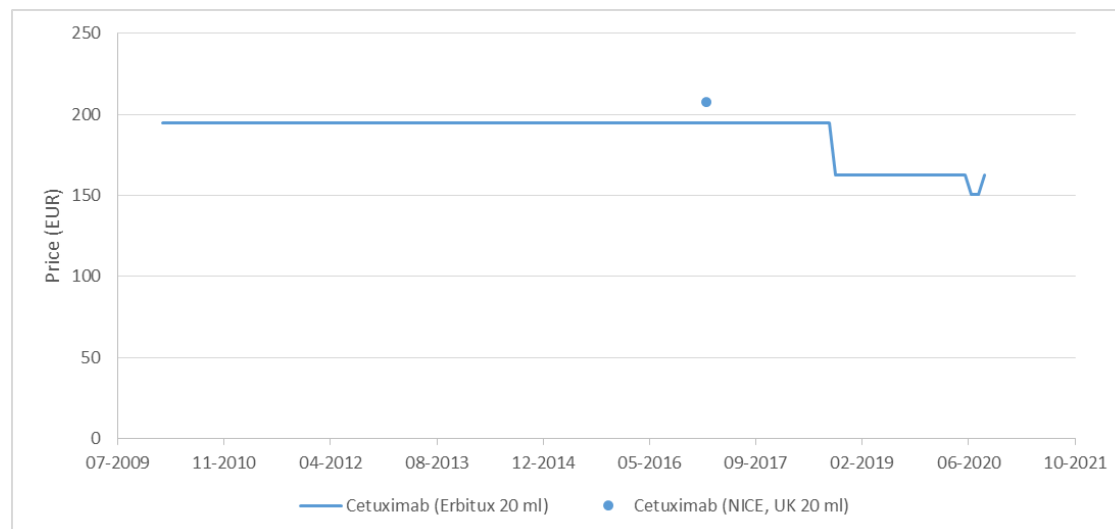
Appendix 14.4. Head and neck cancer

Figure 373 – Drugs prices for head and neck cancer

S_COD	S_NAM	S_NAM_S PECIF	F_ORGA	ATC_COD	SRC_COD_ T	SPB_PUBLIC SRC_DEL _ID : 2	SRC_DEL _ID : 3	SRC_DEL _ID : 4	Extra information
Cetuximab (Erbixux)									
804490	ERBITUX	5 mg/ml	MERCK	L01XC06	0	162.83	155.72	146.91	1 injectieflacon 20 ml oplossing voor intraveneuze infusie
804591	ERBITUX	5 mg/ml	MERCK	L01XC06	0	785.73	778.62	734.55	1 injectieflacon 100 ml oplossing voor intraveneuze infusie

TA473 (2017): "The list price of cetuximab is £178.10 for a 5mg/ml 20-ml vial and £890.50 for a 5 mg/ml 100-ml vial (excluding VAT; British national formulary [BNF] online, accessed February 2017). ... The pricing arrangement considered during guidance development was one in which the company (Merck) had agreed a patient access scheme with the Department of Health. ... This has now been replaced by a commercial access agreement between the company and NHS England, which incorporates this same simple discount applied at the point of purchase or invoice of all cetuximab but also includes additional and separate commercial arrangements. The financial terms of the agreement are commercial in confidence."

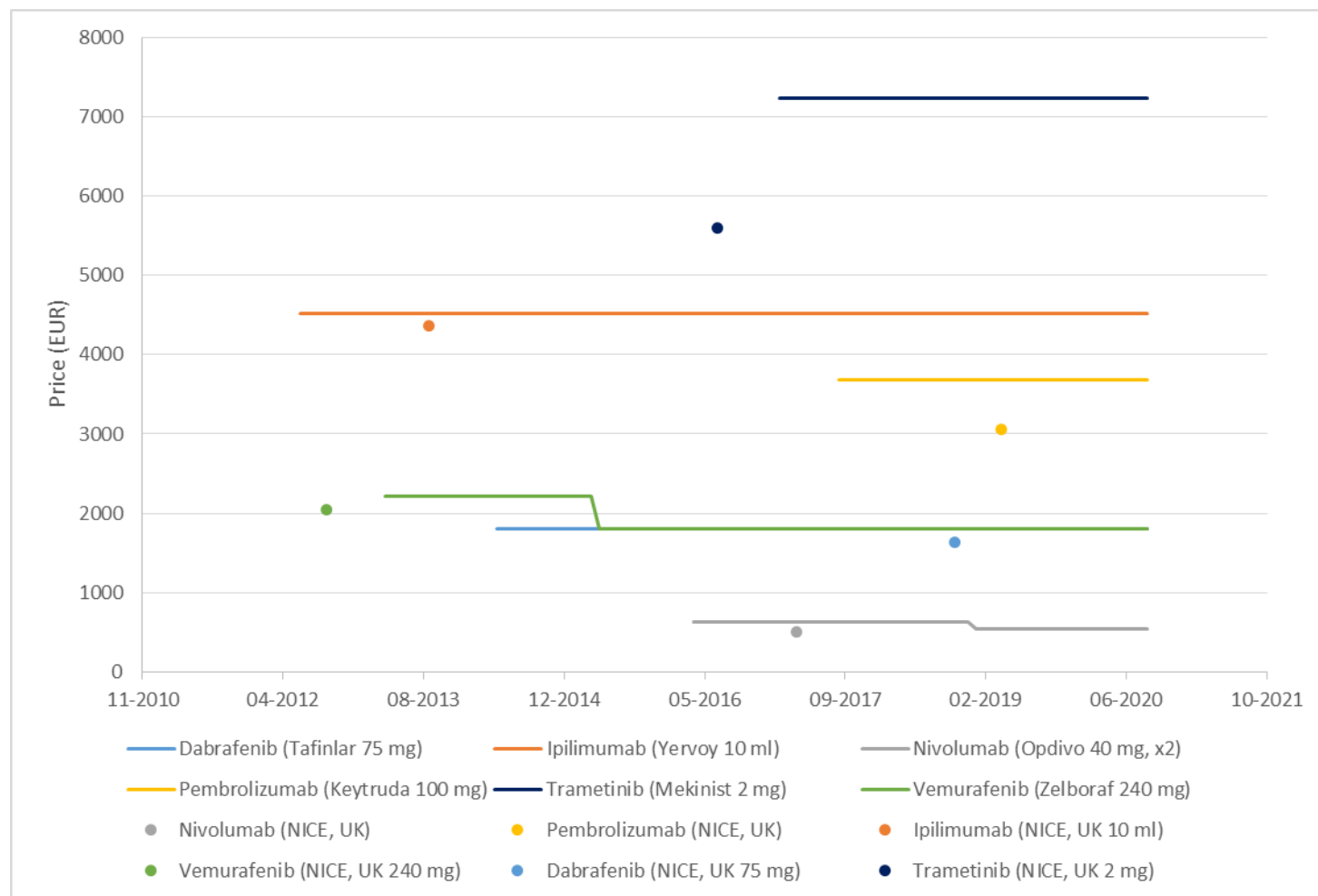
Figure 374 – Drugs prices for head and neck cancer



[illegible]



Figure 376 – Drugs prices for melanoma





Appendix 14.6. Mesothelioma

Figure 377 – Drugs prices for mesothelioma

S_COD	S_NAM	S_NAM_S PECIF	F_ORGA	ATC_COD	SRC_COD_ T	SPB_PUBLIC SRC_DEL _ID : 2	SRC_DEL _ID : 3	SRC_DEL _ID : 4	Extra information
Pemetrexed (Alimta)									
581390	ALIMTA	500 mg	ELI LILLY BENELUX	L01BA04	0	1269.27	1262.16	1190.72	1 injectieflacon 500 mg poeder voor concentraat voor infusie
1301921	ALIMTA	100 mg	ELI LILLY BENELUX	L01BA04	0	259.54	252.43	238.14	1 injectieflacon (glas) 100 mg poeder voor concentraat voor infusie
1439532	PEMETREXED FRESENIUS KABI	100 mg	FRESENIUS KABI	L01BA04	0	102.98	95.87	90.44	1 injectieflacon (glas) 100 mg poeder voor concentraat voor oplossing voor infusie
1439533	PEMETREXED FRESENIUS KABI	500 mg	FRESENIUS KABI	L01BA04	0	486.47	479.36	452.23	1 injectieflacon (glas) 500 mg poeder voor concentraat voor oplossing voor infusie
1541607	ALIMTA	500 mg	ABACUS MEDICINE	L01BA04	0	1269.27	1262.16	1190.72	1 injectieflacon 500 mg poeder voor concentraat voor oplossing voor infusie
TA135 (2008): "Pemetrexed costs £800 for a 500-mg vial (excluding VAT, 'British national formulary' [BNF]53rd edition). The cost per patient, assuming an average of five treatment cycles and a body surface area of 1.8m ² , is approximately £8000. Costs may vary in different settings because of negotiated procurement discounts."									

Figure 378 – Drugs prices for mesothelioma

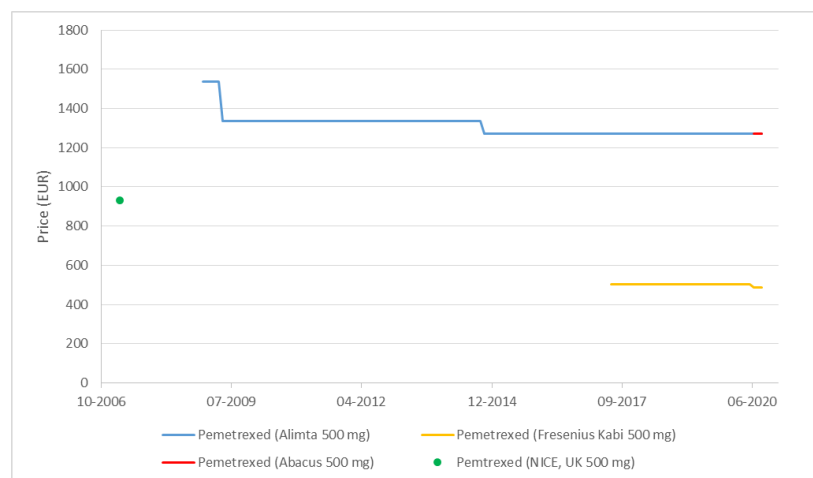




Figure 380 – Drugs prices for multiple myeloma

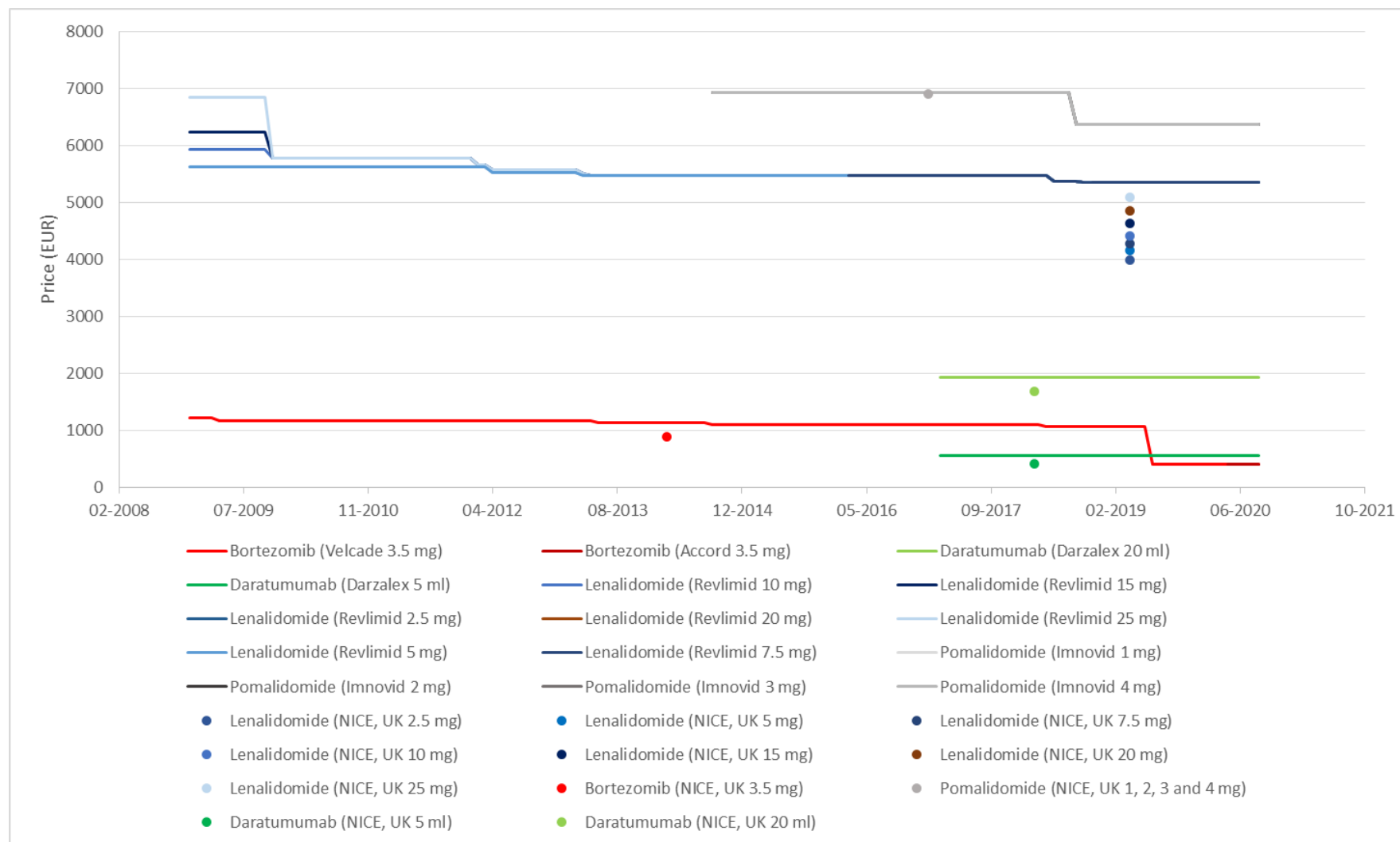


Figure 382 – Drugs prices for NHL

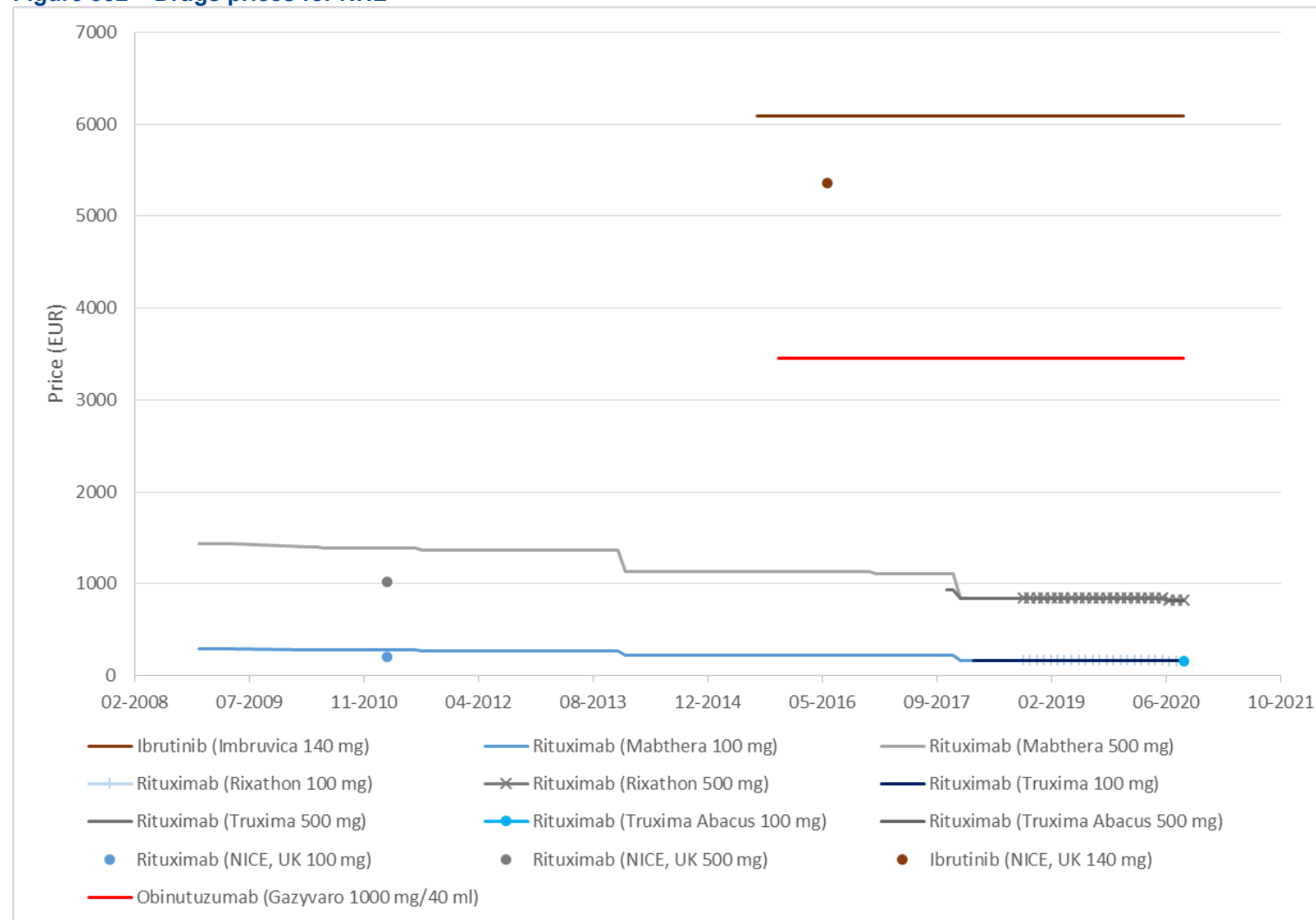




Figure 384 – Drugs prices for NSCLC

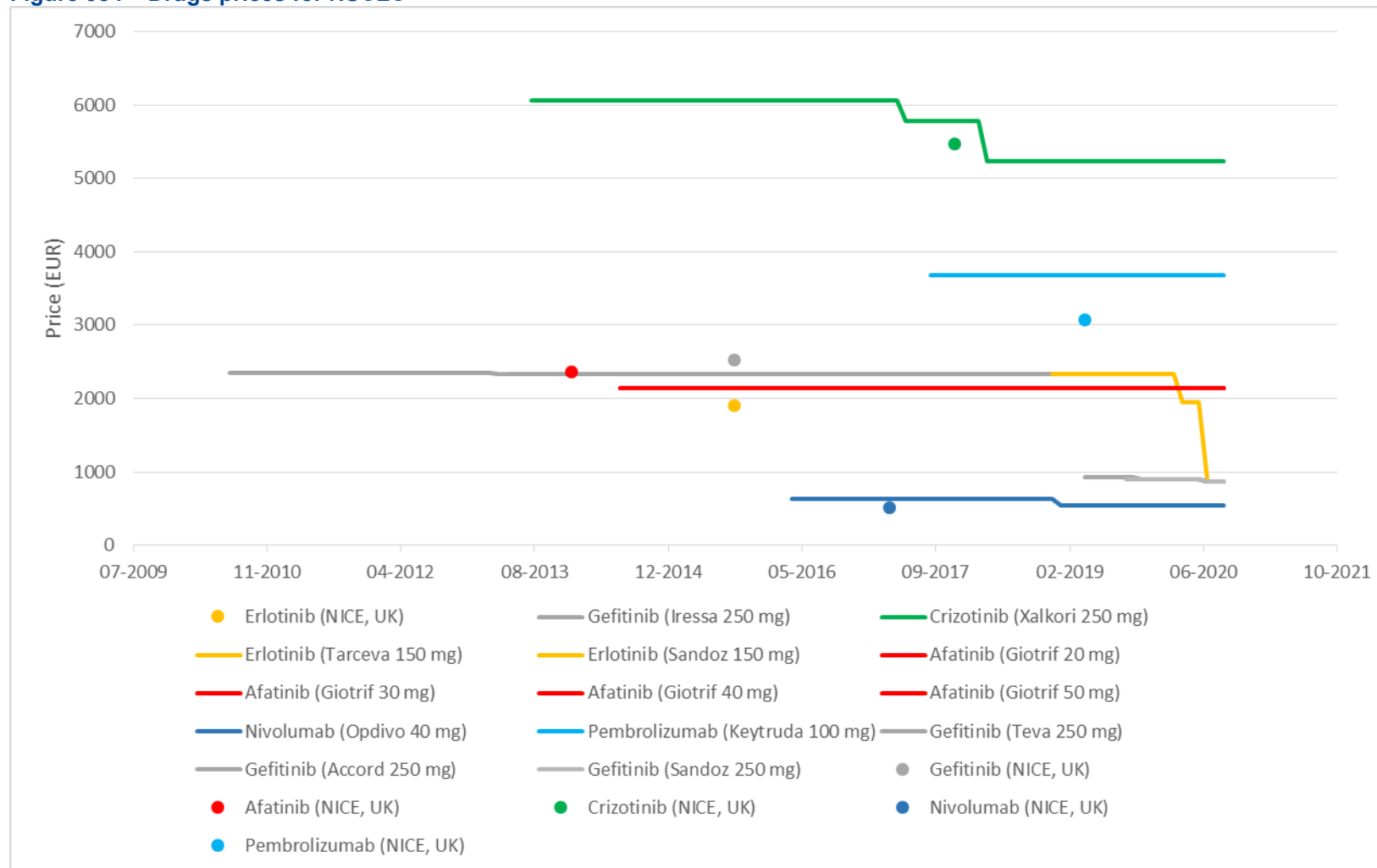
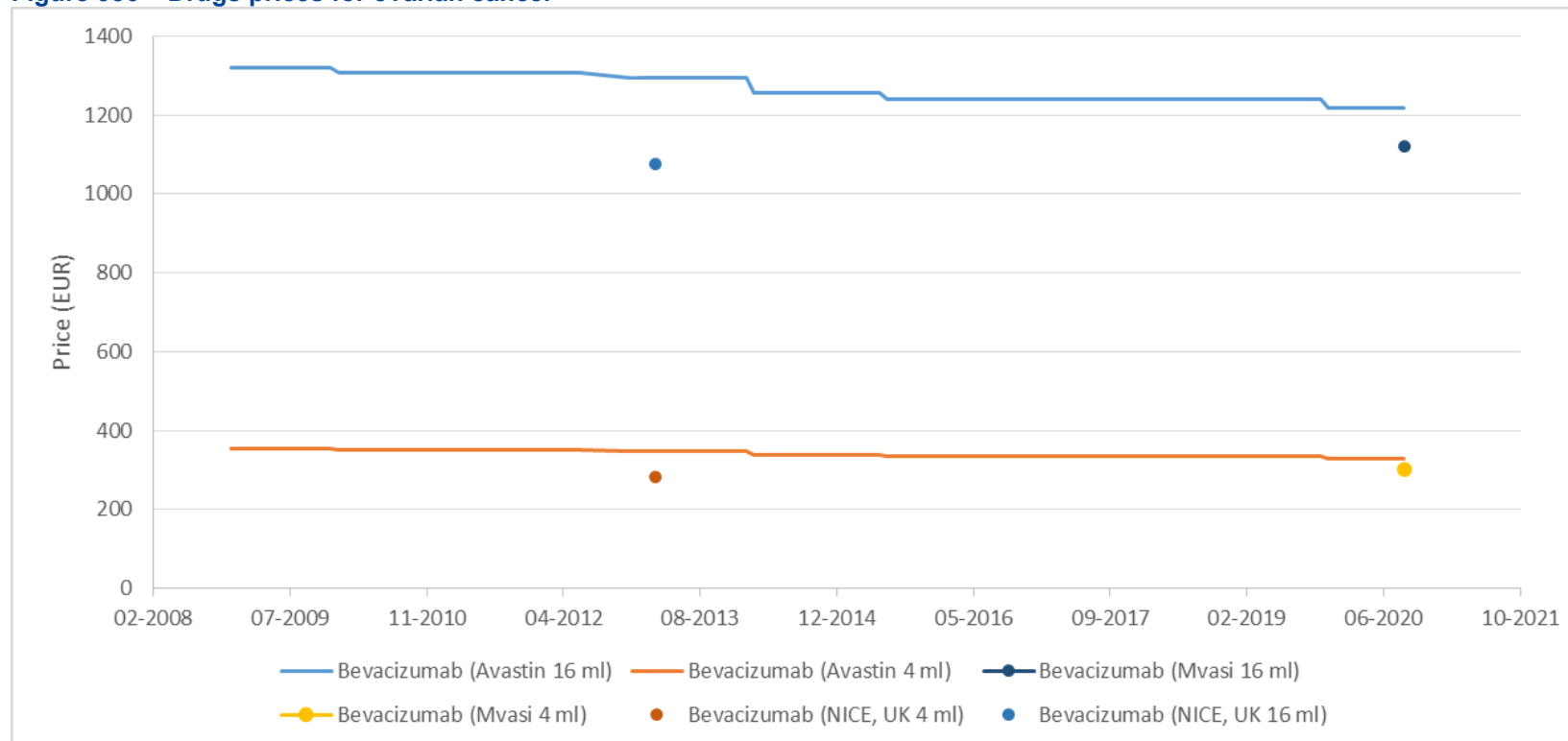




Figure 385 – Drugs prices for ovarian cancer

S_COD	S_NAM	S_NAM_S PECIF	F_ORGA	ATC_COD	SRC_COD_ T	SPB_PUBLIC			Extra information
						SRC_DEL _ID : 2	SRC_DEL _ID : 3	SRC_DEL _ID : 4	
Bevacizumab (Avastin)									
700420	AVASTIN	25 mg/ml	ROCHE	L01XC07	1	327.63	320.52	302.38	1 injectieflacon 4 ml concentraat voor oplossing voor infusie
700521	AVASTIN	25 mg/ml	ROCHE	L01XC07	1	1217.83	1210.72	1142.19	1 injectieflacon 16 ml concentraat voor oplossing voor infusie
1541520	MVASI	100 mg	AMGEN	L01XC07	0	301.99	294.88	278.19	1 injectieflacon 4 ml concentraat voor oplossing voor infusie
1541521	MVASI	400 mg	AMGEN	L01XC07	0	1120.97	1113.86	1050.81	1 injectieflacon 16 ml concentraat voor oplossing voor infusie
1541700	ZIRABEV	25 mg/ml	PFIZER	L01XC07	0	301.99	294.88	278.19	1 injectieflacon 4 ml concentraat voor oplossing voor infusie
1541706	ZIRABEV	25 mg/ml	PFIZER	L01XC07	0	1120.97	1113.86	1050.81	1 injectieflacon 16 ml concentraat voor oplossing voor infusie
TA285 (2013): "Beverizumab is available in 100 mg and 400 mg vials at net prices of £242.66 and £924.40 respectively (excluding VAT; 'British national formulary' edition 65)."									

TA285 (2013): "Bevacizumab is available in 100 mg and 400 mg vials at net prices of £242.66 and £924.40 respectively (excluding VAT; 'British national formulary' edition 65)."

**Figure 386 – Drugs prices for ovarian cancer**

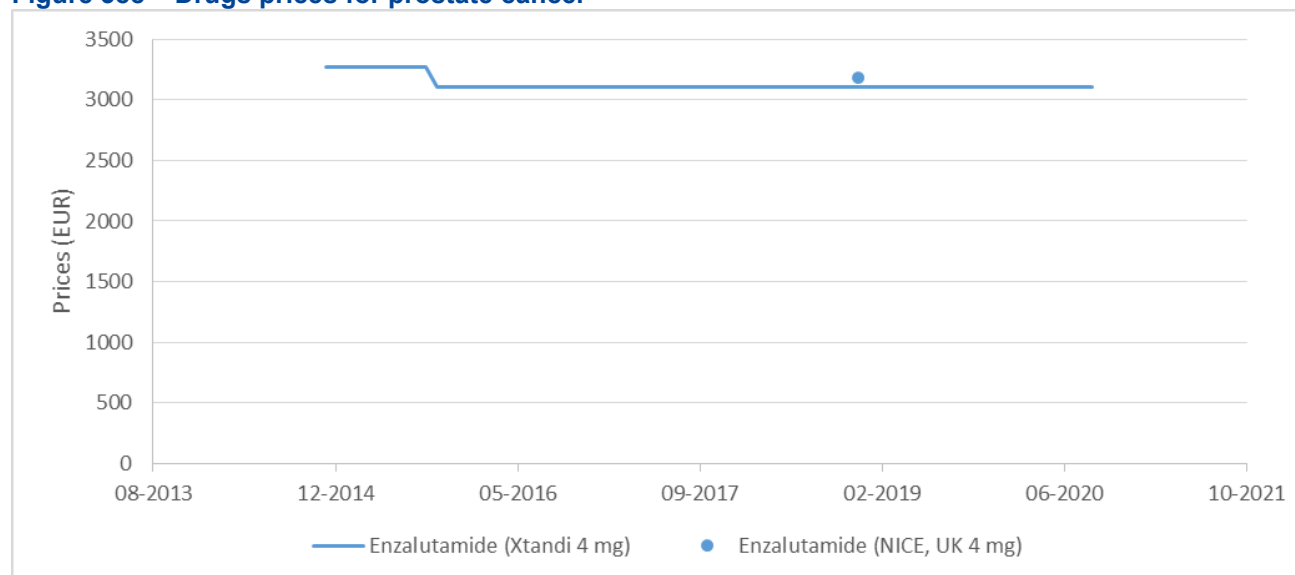


Appendix 14.11. Prostate cancer

Figure 387 – Drugs prices for prostate cancer

S_COD	S_NAM	S_NAM_S PECIF	F_ORGA	ATC_COD	SRC_COD_ T	SRC_DEL _ID : 2	SPB_PUBLIC SRC_DEL _ID : 3	SRC_DEL _ID : 4	Extra information
Enzalutamide (Xtandi)									
1196231	XTANDI	40 mg	ASTELLAS PHARMA	L02BB04	1	27.756	27.6925	2926	112 capsules, zacht
1510684	XTANDI	40 mg	ASTELLAS PHARMA	L02BB04	1	27.756	27.6925	2926	112 filmomhulde tabletten
TA580 (2019): "Enzalutamide is administered orally at a dose of 160 mg (4×40 mg soft capsules) daily. £2,734.67 per 112 capsules (excluding VAT; British national formulary online, accessed December 2018). The daily dose comprises 4 capsules and costs £97.67. The company has a commercial arrangement which would apply if the technology had been recommended."									
TA377 (2016): "The cost (list price) of enzalutamide is £2734.67 for a 112-capsule pack of 40 mg enzalutamide. The daily dose of enzalutamide is 160 mg and costs £97.67 per day. The company has agreed a patient access scheme with the Department of Health. This is a simple discount to the list price of enzalutamide. The level of the discount is commercial in confidence."									

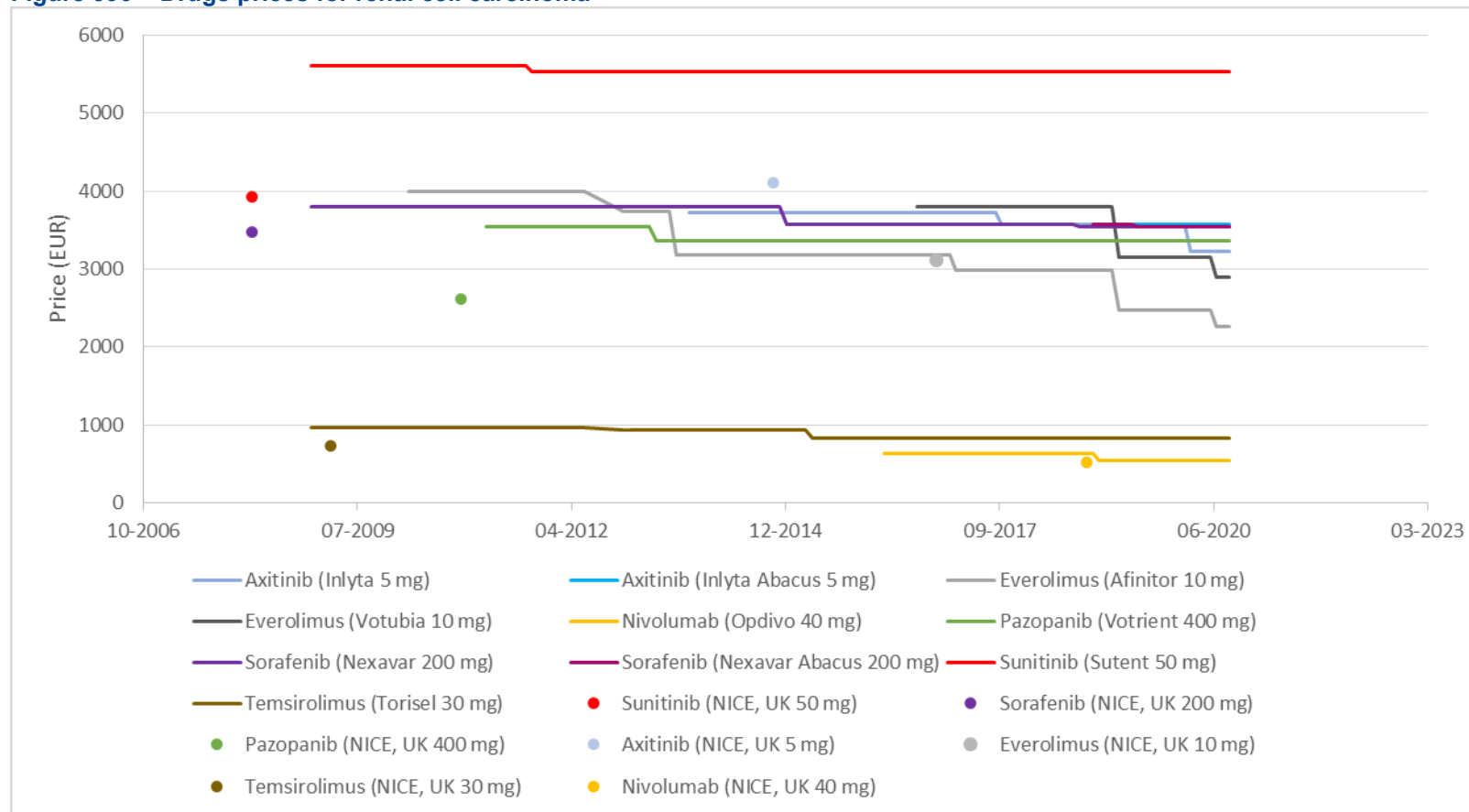
Figure 388 – Drugs prices for prostate cancer



[illegible]



Figure 390 – Drugs prices for renal cell carcinoma





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