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Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Centre

BENEFITS AND COSTS OF INNOVATIVE ONCOLOGY DRUGS IN BELGIUM (2004-2017)





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HEALTH TECHNOLOGY ASSESSMENT

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TABLE OF CONTENTS

LIST OF FIGURES **10**
LIST OF TABLES **11**
LIST OF ABBREVIATIONS **16**
■ **SCIENTIFIC REPORT** **22**
1 INTRODUCTION **22**
1.1 SETTING THE SCENE 22
1.1.1 Increasing expenditures for oncology drugs 22
1.1.2 The increasing cancer drug prices 23
1.1.3 Patient benefit, no longer a hard requirement for marketing authorisation 24
1.2 ARE THE EXTRA EXPENDITURES ASSOCIATED WITH PATIENT BENEFITS? 26
1.2.1 Cancer drugs as one of many contributors to cancer survival 26
1.2.2 Small and uncertain patient benefit of new cancer medicines 27
2 OBJECTIVES **28**
2.1 OPPORTUNITY COST OR DISPLACEMENT EFFECT 28
2.2 RESEARCH QUESTIONS 28
3 METHODOLOGY **29**
3.1 PART 1: DATABASES, STATISTICAL ANALYSES, AND PRESENTATION OF RESULTS 29
3.1.1 Belgian Cancer Registry (BCR) data selection and linkage with Intermutualistic Agency (IMA) data and vital status 29
3.1.1.1 Selection of the study population in the Belgian Cancer Registry database 29
3.1.1.2 Linkage with health insurance data 32
3.1.1.3 Vital status 32
3.1.2 Statistical analyses 33
3.1.2.1 Descriptive analyses 33

3.1.2.2 Survival analysis 33
3.1.2.3 Statistical software 34
3.1.3 Graphics and Tables 34
3.2 PART 2: SELECTION OF DRUGS 35
3.2.1 Selection criteria and process 35
3.2.2 Selected cancer types and drugs 37
3.3 PART 3: LITERATURE SEARCHES 37
3.3.1 Search medical literature 37
3.3.2 Search economic literature 38
3.4 PART 4: RIZIV REIMBURSEMENT CRITERIA 39
4 RESULTS PER CANCER TYPE 40
4.1 BREAST CANCER 40
4.1.1 Introduction 40
4.1.2 Observational data 42
4.1.2.1 Patient characteristics, survival and expenditures 42
4.1.2.2 Drug uptake for a selection of drugs during the first 5 years after diagnosis 47
4.1.3 Medical literature: efficacy 48
4.1.3.1 HER2(+) Breast cancer: neo-adjuvant and adjuvant setting (pertuzumab) 48
4.1.3.2 HER2(+) Breast cancer: metastatic disease or locally advanced disease – first line (pertuzumab) 49
4.1.3.3 HER2(+) Breast cancer: metastatic disease or locally advanced disease – second line (pertuzumab, trastuzumab emtansine) 49
4.1.3.4 HER2(-) Breast cancer: metastatic disease or locally advanced disease 50
4.1.3.5 Discussion 50
4.1.4 Economic literature: cost-effectiveness 51

4.1.5 Summary 57
4.2 CHRONIC MYELOID LEUKAEMIA 59
4.2.1 Introduction 59
4.2.2 Observational data 60
4.2.2.1 Patient characteristics, survival and expenditures 60
4.2.2.2 Drug uptake for a selection of drugs during the first 5 years after diagnosis 67
4.2.3 Medical literature: efficacy 67
4.2.3.1 First-line treatment 68
4.2.3.2 Second- and third-line treatment 70
4.2.3.3 Discussion 70
4.2.4 Economic literature: cost-effectiveness 71
4.2.5 Summary 76
4.3 COLORECTAL CANCER 78
4.3.1 Introduction 78
4.3.2 Observational data 79
4.3.2.1 Patient characteristics, survival and expenditures 79
4.3.2.2 Drug uptake for a selection of drugs during the first 5 years after diagnosis 84
4.3.3 Medical literature: efficacy 84
4.3.3.1 First-line treatment 85
4.3.3.2 Second-line (or later) treatment 86
4.3.3.3 Discussion 87
4.3.4 Economic literature: cost-effectiveness 87
4.3.5 Summary 91
4.4 HEAD AND NECK CANCER 93

4.4.1 Introduction 93
4.4.2 Observational data 94
4.4.2.1 Patient characteristics, survival and expenditures 94
4.4.2.2 Drug uptake for a selection of drugs during the first 5 years after diagnosis 100
4.4.3 Medical literature: efficacy 100
4.4.3.1 Discussion 102
4.4.4 Economic literature: cost-effectiveness 103
4.4.5 Summary 106
4.5 MELANOMA 107
4.5.1 Introduction 107
4.5.2 Observational data 108
4.5.2.1 Patient characteristics, survival and expenditures 108
4.5.2.2 Drug uptake for a selection of drugs during the first 5 years after diagnosis 119
4.5.3 Medical literature: efficacy 120
4.5.3.1 BRAF and MEK inhibitors melanoma 121
4.5.3.2 Immunotherapy in melanoma 122
4.5.3.3 Discussion 123
4.5.4 Economic literature: cost-effectiveness 124
4.5.5 Summary 129
4.6 MESOTHELIOMA 132
4.6.1 Introduction 132
4.6.2 Observational data 132
4.6.2.1 Patient characteristics, survival and expenditures 132
4.6.2.2 Drug uptake for a selection of drugs during the first 5 years after diagnosis 139

4.6.3 Medical literature: efficacy 139
4.6.3.1 Discussion 140
4.6.4 Economic literature: cost-effectiveness 141
4.6.5 Summary 142
4.7 MULTIPLE MYELOMA 143
4.7.1 Introduction 143
4.7.2 Observational data 145
4.7.2.1 Patient characteristics, survival and expenditures 145
4.7.2.2 Drug uptake for a selection of drugs during the first 5 years after diagnosis 150
4.7.3 Medical literature: efficacy 150
4.7.3.1 Multiple Myeloma: First-line treatment in adult patients ineligible for stem-cell transplantation 151
4.7.3.2 Multiple myeloma: first-line treatment in adult patients eligible for stem-cell transplant 152
4.7.3.3 Multiple myeloma: treatment of relapsed or refractory disease 152
4.7.3.4 Discussion 153
4.7.4 Economic literature: cost-effectiveness 154
4.7.5 Summary 158
4.8 NON-HODGKIN LYMPHOMA 160
4.8.1 Introduction 160
4.8.2 Observational data 161
4.8.2.1 Patient characteristics, survival and expenditures 161
4.8.2.2 Drug uptake for a selection of drugs during the first 5 years after diagnosis 175
4.8.3 Medical literature: efficacy 176
4.8.3.1 CLL/SLL 176

4.8.3.2 DLBCL ... 178
4.8.3.3 Mantle cell lymphoma ... 179
4.8.3.4 Discussion ... 181
4.8.4 Economic literature: cost-effectiveness ... 183
4.8.4.1 Chronic lymphocytic leukaemia ... 183
4.8.4.2 Mantel-cell lymphoma ... 188
4.8.5 Summary ... 190
4.8.5.1 CLL/SLL ... 190
4.8.5.2 DLBCL ... 191
4.8.5.3 Mantle cell lymphoma ... 192
4.9 NON-SMALL CELL LUNG CANCER ... 193
4.9.1 Introduction ... 193
4.9.2 Observational data ... 194
4.9.2.1 Patient characteristics, survival and expenditures ... 194
4.9.2.2 Drug uptake for a selection of drugs during the first 5 years after diagnosis ... 199
4.9.3 Medical literature: efficacy ... 199
4.9.3.1 Anti-EGFR therapy in NSCLC ... 200
4.9.3.2 ALK inhibitors for non-small cell lung cancer ... 203
4.9.3.3 Immunotherapy ... 203
4.9.3.4 Discussion ... 205
4.9.4 Economic literature: cost-effectiveness ... 205
4.9.5 Summary ... 209
4.10 OVARIAN CANCER ... 211
4.10.1 Introduction ... 211

4.10.2 Observational data 211
4.10.2.1 Patient characteristics, survival and expenditures 211
4.10.2.2 Drug uptake for a selection of drugs during the first 5 years after diagnosis 220
4.10.3 Medical literature: efficacy 220
4.10.3.1 Bevacizumab in ovarian cancer 221
4.10.3.2 Discussion 222
4.10.4 Economic literature: cost-effectiveness 222
4.10.5 Summary 226
4.11 PROSTATE CANCER 227
4.11.1 Introduction 227
4.11.2 Observational data 227
4.11.2.1 Patient characteristics, survival and expenditures 227
4.11.2.2 Drug uptake for a selection of drugs during the first 5 years after diagnosis 233
4.11.3 Medical literature: efficacy 233
4.11.3.1 Discussion 235
4.11.4 Economic literature: cost-effectiveness 235
4.11.5 Summary 238
4.12 RENAL CELL CARCINOMA (RCC) 239
4.12.1 Introduction 239
4.12.2 Observational data 241
4.12.2.1 Patient characteristics, survival and expenditures 241
4.12.2.2 Drug uptake for a selection of drugs during the first 5 years after diagnosis 247
4.12.3 Medical literature: efficacy 249
4.12.3.1 Targeted therapy – first line treatment 250

4.12.3.2 Targeted therapy – second line treatment *250*
4.12.3.3 Immunotherapy *251*
4.12.3.4 Discussion *252*
4.12.4 Economic literature: cost-effectiveness 253
4.12.5 Summary 259
5 USE OF ANTICANCER DRUGS AT THE END OF LIFE 261
6 SUMMARY 266
7 DISCUSSION 276
7.1 REAL-WORLD OBSERVATIONAL DATA 276
7.1.1 Data from the Belgian Cancer Registry (BCR) and Intermutualistic Agency (IMA) – strengths/limitations and nuance needed 276
7.1.2 Limitations inherent to the use of observational data – no good estimate of treatment effect 280
7.2 LIMITED BENEFITS IN OVERALL SURVIVAL 284
7.3 QOL AS AN IMPORTANT ENDPOINT 287
7.3.1 A patient-relevant endpoint in clinical trials 287
7.3.2 Measuring QoL with a generic utility instrument 287
7.3.3 Improvement needed in measuring and reporting QoL, and using the results in economic evaluations 288
7.3.4 An example to show (the importance of) transparent reporting of QoL data 292
7.4 THE USE OF PROGRESSION-FREE SURVIVAL AS A SURROGATE ENDPOINT 295
7.4.1 Is PFS a valid surrogate for OS? 295
7.4.2 Can PFS be considered as a surrogate for quality of life? 296
7.4.3 The problem of PFS in economic evaluations 297
7.4.4 Do we try hard enough? Searching for a solution that fits both goals 298
7.5 SUBSTANTIAL INCREASE IN GROSS EXPENDITURES, LIMITED BY REFUNDS AND TAXES 299

7.5.1 Managed entry agreement refunds 299
7.5.2 Taxes and clawback 300
7.6 MANAGED ENTRY AGREEMENT 301
7.6.1 Managed entry agreement – when the exception becomes the rule 301
7.6.2 Incentives to demonstrate survival or QoL benefits for the patients 302
7.6.2.1 Before marketing approval 302
7.6.2.2 After marketing approval 304
7.6.3 Confidential prices 307
7.6.3.1 A short-term advantage creating long-term problems and making the system intransparent 307
7.6.3.2 Confidential prices making economic evaluations and policy decisions intransparent 308
7.7 WHY WE MAINLY RELIED ON UK DOSSIERS FOR INFORMATION ON ECONOMIC EVALUATIONS IN THIS REPORT 309
7.8 THE IMPORTANCE OF THE (DISCOUNT FOR THE) COMPARATOR 311
7.9 DIFFERENT ARGUMENTS USED FROM DIFFERENT PERSPECTIVES 313
■ **REFERENCES 317**

LIST OF FIGURES

Figure 1 – Annual net expenditures of the NIHDI for reimbursable pharmaceutical specialties in public pharmacies and hospitals (2012 - 2019) 23

Figure 2 – The monthly treatment cost of new cancer drugs, by year of FDA approval 24

Figure 3 – Chronic myeloid leukaemia (2004-2017) (observed survival): Kaplan-Meier graph 2004-2009 vs 2011-2017 63

Figure 4 – Head and neck cancers (2004-2017), combined stage IV (observed survival): Kaplan-Meier graph 2004-2006 vs 2008-2017 96

Figure 5 – Melanoma (2004-2017), combined stage IV (observed survival): Kaplan-Meier graph 2004-2010 vs 2012-2017 112

Figure 6 – Melanoma (2004-2017), combined stage NA (observed survival): Kaplan-Meier graph 2004-2010 vs 2012-2017 113

Figure 7 – Epithelial Ovarian Cancer (2004-2017), combined stage IV (observed survival): Kaplan-Meier graph 2004-2011 vs 2013-2017 216

Figure 8 – Prostate cancer (2004-2017), combined stage IV (observed survival): Kaplan-Meier graph 2004-2010 vs 2012-2017 229

Figure 9 – Renal Cell Carcinoma (2004-2017), combined stage IV (observed survival): Kaplan-Meier graph 2004-2005 vs 2007-2017 243

Figure 10 – Average yearly cancer incidence for the three incidence periods (panel A: absolute numbers; panel B: crude incidence rate (per 100 000 persons) 278

Figure 11 – Comparison of propensity score analyses and RCT results from 3 empirical assessments 281

Figure 12 – Comparison of Hazard Ratios (HRs) From Randomized Clinical Trials and Analyses With Data From the National Cancer Database (NCDB) 283

Figure 13 – Magnitude of overall survival benefit at the time of EMA approval (of interventions where a significant improvement of survival was proven). 285

Figure 14 – The impact of incorrectly excluding (left box) or including (right box) a comparator on cost-effectiveness of an intervention 312

Figure 15 – Oncological drug expenditures per calendar year (2004-2018) 314

LIST OF TABLES

Table 1 – Annual net expenditures of the NIHDI for medicines (2012 – 2019) 23
Table 2 – Selection criteria for the included tumours based on ICD-O-3.2*/ICD-10** 31
Table 3 – List of selected drugs in 12 cancer types 37
Table 4 – Selected drugs for breast cancer 41
Table 5 – Female breast cancer (2004-2017), combined stage IV (observed survival): A) Patient characteristics; B) Kaplan-Meier graph per incidence period; C) Time trend with incidence year*; D) Median survival time* ** 43
Table 6 – Female breast cancer: drug expenditures 44
Table 7 – Proportion of patients who received at least one dose during 5-year period after diagnosis (breast cancer stage IV) 47
Table 8 – Drugs selected for CML 60
Table 9 – Chronic myeloid leukaemia (2004-2017) (observed survival): A) Patient characteristics; B) Kaplan-Meier graph per incidence period; C) Time trend with incidence year*; D) Median survival time* ** 61
Table 10 – Chronic myeloid leukaemia Flanders (2000-2017) (observed survival): A) Patient characteristics; B) Kaplan-Meier graph per incidence period; C) Time trend with incidence year*; D) Median survival time* ** 62
Table 11 – Chronic myeloid leukaemia: drug expenditures 64
Table 12 – CML: proportion of patients who received at least one dose during 5-year period after diagnosis 67
Table 13 – Selected drugs for colorectal cancer 78
Table 14 – Colorectal cancer (2004-2017), combined stage IV (observed survival): A) Patient characteristics; B) Kaplan-Meier graph per incidence period; C) Time trend with incidence year*; D) Median survival time* ** 80
Table 15 – Colorectal cancer: drug expenditures 81
Table 16 – Colorectal cancer stage IV: proportion of patients who received at least one dose during 5-year period after diagnosis 84
Table 17 – Selected drugs for head & neck cancer 93

Table 18 – Head and neck cancers (2004-2017), combined stage IV (observed survival): A) Patient characteristics; B) Kaplan-Meier graph per incidence period; C) Time trend with incidence year*; D) Median survival time* ** 95

Table 19 – Head and neck cancers: drug expenditures 97

Table 20 – Proportion of patients who received at least one dose during 5-year period after diagnosis (stage IV H&N cancer) 100

Table 21 – Drugs selected for Melanoma 108

Table 22 – Melanoma (2004-2017), combined stage IV (observed survival): A) Patient characteristics; B) Kaplan-Meier graph per incidence period; C) Time trend with incidence year*; D) Median survival time* ** 110

Table 23 – Melanoma (2004-2017), combined stage NA (observed survival): A) Patient characteristics; B) Kaplan-Meier graph per incidence period; C) Time trend with incidence year*; D) Median survival time* ** 111

Table 24 – Melanoma stage IV: drug expenditures 114

Table 25 – Melanoma stage NA: drug expenditures 117

Table 26 – Proportion of patients who received at least one dose during 5-year period after diagnosis (stage IV Melanoma) 119

Table 27 – Proportion of patients who received at least one dose during 5-year period after diagnosis (stage NA Melanoma) 120

Table 28 – Selected drugs for Mesothelioma 132

Table 29 – Mesothelioma (2004-2017), combined stage III/IV/X (observed survival): A) Patient characteristics; B) Kaplan-Meier graph per incidence period; C) Time trend with incidence year*; D) Median survival time* ** 134

Table 30 – Mesothelioma Flanders (2000-2017), combined stage III/IV/X (observed survival): A) Patient characteristics; B) Kaplan-Meier graph per incidence period; C) Time trend with incidence year*; D) Median survival time* ** 135

Table 31 – Mesothelioma cancer: drug expenditures 136

Table 32 – Mesothelioma stage III-IV-X: proportion of patients who received at least one dose during 5-year period after diagnosis 139

Table 33 – selected drugs for multiple myeloma 144

Table 34 – Multiple myeloma (2004-2017) (observed survival): A) Patient characteristics; B) Kaplan-Meier graph per incidence period; C) Time trend with incidence year*; D) Median survival time* ** 146

Table 35 – Multiple myeloma: drug expenditures 147

Table 36 – Proportion of patients diagnosed with multiple myeloma who received at least one dose during 5-year period after diagnosis 150

Table 37 – Selected drugs non-Hodgkin lymphoma 160

Table 38 – B-cell chronic lymphocytic leukaemia (CLL) and small lymphocytic lymphoma (SLL) (2004-2017) (observed survival): A) Patient characteristics; B) Kaplan-Meier graph per incidence period; C) Time trend with incidence year*; D) Median survival time* ** 163

Table 39 – B-cell chronic lymphocytic leukaemia (CLL) and small lymphocytic lymphoma (SLL): drug expenditures 164

Table 40 – Diffuse large B-cell lymphoma (DLBCL) (2004-2017) (observed survival): A) Patient characteristics; B) Kaplan-Meier graph per incidence period; C) Time trend with incidence year*; D) Median survival time* ** 167

Table 41 – Diffuse large B-cell lymphoma (DLBCL): drug expenditures 168

Table 42 – Mantle cell lymphoma (2004-2017) (observed survival): A) Patient characteristics; B) Kaplan-Meier graph per incidence period; C) Time trend with incidence year*; D) Median survival time* ** 171

Table 43 – Mantle cell lymphoma: drug expenditures 172

Table 44 – CLL/SLL: uptake of selected drugs 175

Table 45 – DLBCL: uptake of selected drugs 175

Table 46 – Mantle cell lymphoma: uptake of selected drugs 176

Table 47 – Drugs selected for NSCLC 194

Table 48 – Non-small-cell lung carcinoma (2004-2017), combined stage IV (observed survival): A) Patient characteristics; B) Kaplan-Meier graph per incidence period; C) Time trend with incidence year*; D) Median survival time* ** 195

Table 49 – Non-small-cell lung carcinoma: drug expenditures 196

Table 50 – Proportion of patients who received at least one dose during 5-year period after diagnosis (stage IV NSCLC) 199

Table 51 – Selected drugs ovarian cancer 211

Table 52 – Epithelial Ovarian Cancer (2004-2017), combined stage IV (observed survival): A) Patient characteristics; B) Kaplan-Meier graph per incidence period; C) Time trend with incidence year*; D) Median survival time* ** 213

Table 53 – Epithelial Ovarian Cancer (2004-2017), combined stage IV – no debulking (observed survival): A) Patient characteristics; B) Kaplan-Meier graph per incidence period; C) Time trend with incidence year*; D) Median survival time* ** 214

Table 54 – Epithelial Ovarian Cancer (2004-2017), combined stage IV – debulking (observed survival): A) Patient characteristics; B) Kaplan-Meier graph per incidence period; C) Time trend with incidence year*; D) Median survival time* ** 215

Table 55 – epithelial ovarian cancer: drug expenditures 217

Table 56 – Epithelial ovarian cancer stage IV: uptake of selected drugs 220

Table 57 – Selected drugs for prostate cancer 227

Table 58 – Prostate cancer (2004-2017), combined stage IV (observed survival): A) Patient characteristics; B) Kaplan-Meier graph per incidence period; C) Time trend with incidence year*; D) Median survival time* ** 228

Table 59 – Prostate cancer: drug expenditures 230

Table 60 – Prostate cancer stage IV: uptake of selected drugs 233

Table 61 – Selected drugs for renal cancer 240

Table 62 – Renal Cell Carcinoma (2004-2017), combined stage IV (observed survival): A) Patient characteristics; B) Kaplan-Meier graph per incidence period; C) Time trend with incidence year*; D) Median survival time* ** 242

Table 63 – Renal Cell Carcinoma: drug expenditures 244

Table 64 – Renal cell carcinoma stage III: uptake of selected drugs 248

Table 65 – Renal cell carcinoma stage IV: uptake of selected drugs 248

Table 66 – Proportion of patients with stage IV (/non-stageable) cancer who received systemic therapy within 7 days, 14 days and 30 days of death 262

Table 67 – Proportion of patients with stage IV (/non-stageable) cancer who received systemic therapy within 7 days of death, time trend 263

Table 68 – Proportion of patients with stage IV (/non-stageable) cancer who received systemic therapy within 14 days of death, time trend 264

Table 69 – Proportion of patients with stage IV (/non-stageable) cancer who received systemic therapy within 30 days of death, time trend 265

Table 70 – Overview of observational results for 12 cancer indications (2004-2017, information per incidence year): simplified figures of Time trend (1- to 5-year observed survival probability (%) – 1st column), Median survival time (2nd column), Oncology drug expenditures for the first two years after incidence (3rd column), Mean drug expenditures per patient for the first two years after incidence (4th column)..... 271

Table 71 – Overview of QoL findings in the 12 included cancer indications 290

Table 72 – Mean (±SE) EQ-5D utility index scores (left panel) and mean (±SE) changes from baseline in the EQ-5D utility index scores (right panel) for the nivolumab and DTIC arms of CheckMate 066..... 293

Table 73 – Evolution of gross expenditures for medicines and net costs for the NIHDI (2014 – 2019) (in € 000) 299

Table 74 – Overview of turnover figures, compensations and net expenditures in the context of MEAs (2010-2019) (in € 000) 300

LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
5-FU	5-Fluorouracil
ADT	Androgen deprivation therapy
AE	Adverse event
ALK	Anaplastic lymphoma kinase
AML	Acute myeloid leukemia
ASCT	Autologous stem cell transplantation
ATC	Anatomical Therapeutic Chemical
AWMSG	All Wales Medicines Strategy Group
BC	Breast cancer
BCR	Belgian Cancer Registry (Stichting Kankerregister – Fondation Registre du Cancer)
BRAF	B - Rapidly Accelerated Fibrosarcoma (oncogene)
BSC	Best supportive care
BTK	Bruton's tyrosine kinase
CCyR	Complete cytogenic response
CDF	Cancer Drug Fund
CDK	Cyclin-dependent kinase
CEA	Cost-effectiveness analysis
CER	Comparative effectiveness research
CHOP	Cyclophosphamide, vincristine, doxorubicin and prednisone
CI	Confidence interval
CLL	Chronic lymphocytic leukemia
CM/MC	Christelijke Mutualiteit – Mutualité Chrétienne
CMF	Cyclophosphamide-methotrexate-fluorouracil
CML	Chronic myeloid leukaemia
COPD	Chronic obstructive pulmonary disease
CRC	Colorectal cancer

CRD	Centre for Reviews and Dissemination
CRM (CTG/CRM)	Commission for the Reimbursement of Medicines, Belgium (Commissie Tegemoetkoming Geneesmiddelen/Commission de Remboursement des Médicaments)
CRPC	Castration-resistant prostate cancer
CS	Cancer specific survival
CTLA4	Cytotoxic T lymphocyte antigen 4
CUA	Cost-utility analysis
DFS	Disease-free-survival
DLBCL	Diffuse large b-cell lymphoma
EGFR	Epidermal growth factor receptor
EFS	Event-free survival
EMA	European Medicines Agency
EOC	Epithelial ovarian cancer
EOL	End of life
EORTC-QLQC30	European Organisation for Research and Treatment of Cancer - quality of life questionnaire core 30
EPAR	European public assessment report
EQ-5D	EuroQol five dimensions questionnaire
ER	Estrogen receptors
ERG	Evidence review group
EUnetHTA	European network for Health Technology Assessments
FACT-G	Functional assessment of cancer therapy – general
FC	Fludarabine and cyclophosphamide
FDA	Food and Drug Administration, US
FPS (FOD/SPF)	Federal Public Service (Federale Overheidsdienst/Service public fédéral)
FOLFIRI	5-FU and irinotecan
FOLFOX	5-FU and oxaliplatin
H&N	Head and neck

HNC	Head and neck cancer
HER2	Human epidermal growth factor receptor 2
HPV	Human papilloma virus
HR	Hormone receptors
HRQoL	Health-related quality of life
HSUV	Health state utility value
HTA	Health technology assessment
HUI	Health utility index
HuMAb	Monoclonal antibody
IC	Incremental costs
ICER	Incremental cost-effectiveness ratio
IE	Incremental effects
IFN-α	Interferon-alpha
IMA (IMA/AIM)	Intermutualistic Agency (InterMutualistisch Agentschap/Agence InterMutualiste)
IMDC	International Metastatic RCC Database Consortium
KCE	Belgian Healthcare Knowledge Centre (Federaal Kenniscentrum voor de Gezondheidszorg/Centre Fédéral d'Expertise en Soins de Santé)
KM	Kaplan-Meier
KRAS	Kirsten rat sarcoma viral oncogene
LABC	Locally advanced breast cancer
LA SCCHN	Locally advanced squamous-cell carcinoma of the head and neck
LUSS	Ligue des Usagers des Services de Santé
MEA	Managed entry agreement
MEK	MAPK/ERK kinase
MeSH	Medical Subject Headings
MDS	Myelodysplastic syndrome
MGUS	Monoclonal gammopathy of undetermined significance
MLOZ	Mutualités Libres/Onafhankelijke Ziekenfondsen

MM	Multiple myeloma
MMR	Major molecular response
MORSE	Monitoring of reimbursement significant expenses
MP	Melphalan and prednisone
m-TOR	Mammalian target of rapamycin
NA	Not applicable
NHL	Non-Hodgkin lymphoma
NHS	National Health Service, UK
NICE	National Institute for Health and Care Excellence, UK
NIHDI (RIZIV/INAMI)	National Institute for Health and Disability Insurance, Belgium (Rijksinstituut voor Ziekte- en Invaliditeitsverzekering / Institut national d'assurance maladie-invalidité)
NIHR	National Institute for Health Research, UK
NMA	Network meta-analysis
NSAI	Non-steroidal aromatase inhibitor
NSCLC	Non-small cell lung cancer
OECD	Organisation for Economic Cooperation and Development
OR	Odds ratio
ORR	Objective response rate
OS	Overall survival / observed survival
PARP	Poly (ADP-ribose) polymerase
PAS	Patient access scheme
pCR	Pathological complete response rates
PD	Progressive disease
PD-1	Programmed cell death protein 1
PD-L1	Programmed cell death protein 1 ligand
PDGF	Platelet-derived growth factor
PFS	Progression-free survival
PI	Proteasome inhibitor

PI3K	Phosphoinositide 3 kinase
PS	Performance status
QALY	Quality-adjusted life year
QD	One a day (quaque die)
QoL	Quality of life
RAS WT	Rat sarcoma wild type
RCC	Renal cell carcinoma
RCT	Randomised controlled trial
Rd/RD	Lenalidomide with low-dose dexamethasone – lenalidomide with high-dose dexamethasone
REA	Relative effectiveness assessment
RECIST	Response Evaluation Criteria in Solid Tumors
RFC	rituximab plus fludarabine and cyclophosphamide
RR	Relative risk
R/R MCL	Relapsed or refractory mantel cell lymphoma
RTK	Receptor tyrosine kinase
SAE	Serious adverse event
SCC	Squamous cell carcinoma
SCCHN	Squamous-cell carcinoma of the head and neck
SCLC	Small cell lung cancer
SEER	Surveillance, Epidemiology and End Results database
SF-6D	Short form-6 dimension
SocMut/MutSoc	Socialistische Mutualiteit/Mutualité Socialiste
SLL	Small lymphocytic lymphoma
SOC	Standard of care
SR	Systematic review
TA	Technology assessment
T-DM1	Trastuzumab emtansine
TKI	Tyrosine kinase inhibitor

TMP	Thalidomide-melphalan-prednisone
TT	Targeted therapy
UK	United Kingdom
US	United States
VAS	Visual analogue scale
VEGF	Vascular endothelial growth factor
VMP	Bortezomib, melphalan and prednisone
VPP	Vlaams Patiëntenplatform
VRd/VRD	Bortezomib - lenalidomide- (low dose) dexamethasone – bortezomib - lenalidomide- (high dose) dexamethasone
WHO	World Health Organisation

SCIENTIFIC REPORT

1 INTRODUCTION

1.1 Setting the scene

1.1.1 Increasing expenditures for oncology drugs

Innovative medicinal products for the treatment of patients with cancer aim to improve patient survival and/or quality of life, in comparison with standard of care. Payers see a sharp increase in expenditures for these drugs. The Monitoring Of Reimbursement Significant Expenses (MORSE) report, published in November 2020, provides further insights in these expenditures for Belgium. The global net expenditures[a] of the National Institute for Health and Disability Insurance (NIHDI – RIZIV/INAMI) for drugs increased in 2017-2019 with about 6% yearly. In 2019 expenditures exceeded €5.2[b] billion (Table 1). The evolution is different between public pharmacies and hospitals. Expenditures are relatively stable in public pharmacies at about €2.6-2.7 billion. In contrast, there is a sharp increase in hospital expenditures (Figure 1). As mentioned in the MORSE report, the last three years, there is an increase of 17% (2017), 13.2% (2018) and 14.4% (2019) (Table 1). In 2019, hospital drug expenditures count for about half (49.4%) of total drug expenditures.[1]

The expenditures per Anatomical Therapeutic Chemical (ATC) class at the 3rd level (ATC3) show that the L01X class (other antineoplastic agents) represents the largest part of these hospital expenditures, about €1 billion in 2019.[1] L01X includes therapies such as monoclonal antibodies and immunotherapy (but not chemotherapy and protein kinase inhibitors (L01E)[c]). L01X drugs expenditure increased sharply from about €140 million in 2007 to €403 million in 2016, €806 million in 2018 and already €1 billion in 2019.[2]

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[a] The net expenditures equal the gross expenditures minus the patient co-payments.

[b] We notice that these expenditures do not take into account the refunds related to the managed entry agreements (MEAs, art.81/111) and other annual charges borne by the pharmaceutical industry. We come back to these refunds in the discussion of this report.

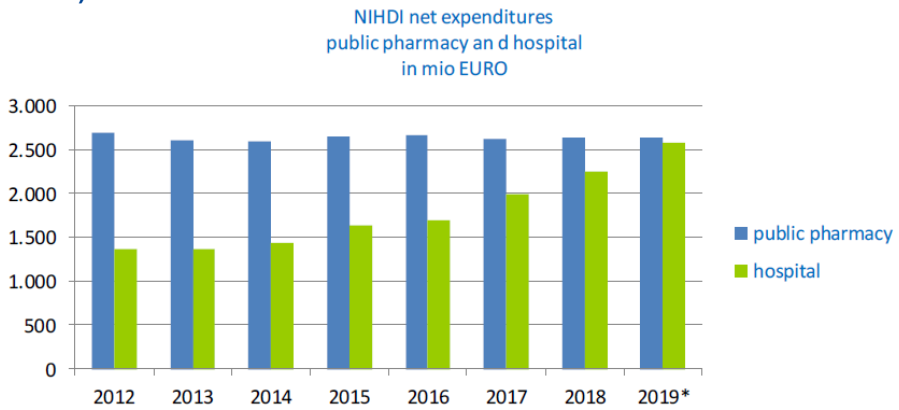
[c] See: https://www.whocc.no/atc_ddd_index/

Table 1 – Annual net expenditures of the NIHDI for medicines (2012 – 2019)

Net expenditures NIHDI (x €1 000 000)								
	2012	**2013**	**2014**	**2015**	**2016**	**2017**	**2018**	**2019***
Public pharmacy	2 692.9	2 619.3	2 604.8	2 651.8	2 665.0	2 626.3	2 647.6	2 647.3
Hospital	1 367.0	1 371.4	1 444.8	1 642.0	1 702.4	1 991.4	2 255.1	2 579.7
Total	4 059.8	3 990.7	4 049.6	4 293.7	4 367.4	4 617.7	4 902.6	5 227.0
Growth %								
		'12- '13	**'13- '14**	**'14- '15**	**'15- '16**	**'16- '17**	**'17- '18**	**'18- '19**
Public pharmacy		-2.7	-0.6	1.8	0.5	-1.5	0.8	0.0
Hospital		0.3	5.4	13.6	3.7	17.0	13.2	14.4*
Total		-1.7	1.5	6.0	1.7	5.7	6.2	6.6*

Source: MORSE report (2020).[1]
** 2019 information for hospital expenditures is based on extrapolated data.*

Figure 1 – Annual net expenditures of the NIHDI for reimbursable pharmaceutical specialties in public pharmacies and hospitals (2012 - 2019)



Source: MORSE report (2020).[1]
** 2019 information for hospital expenditures is based on extrapolated data.*

1.1.2 The increasing cancer drug prices

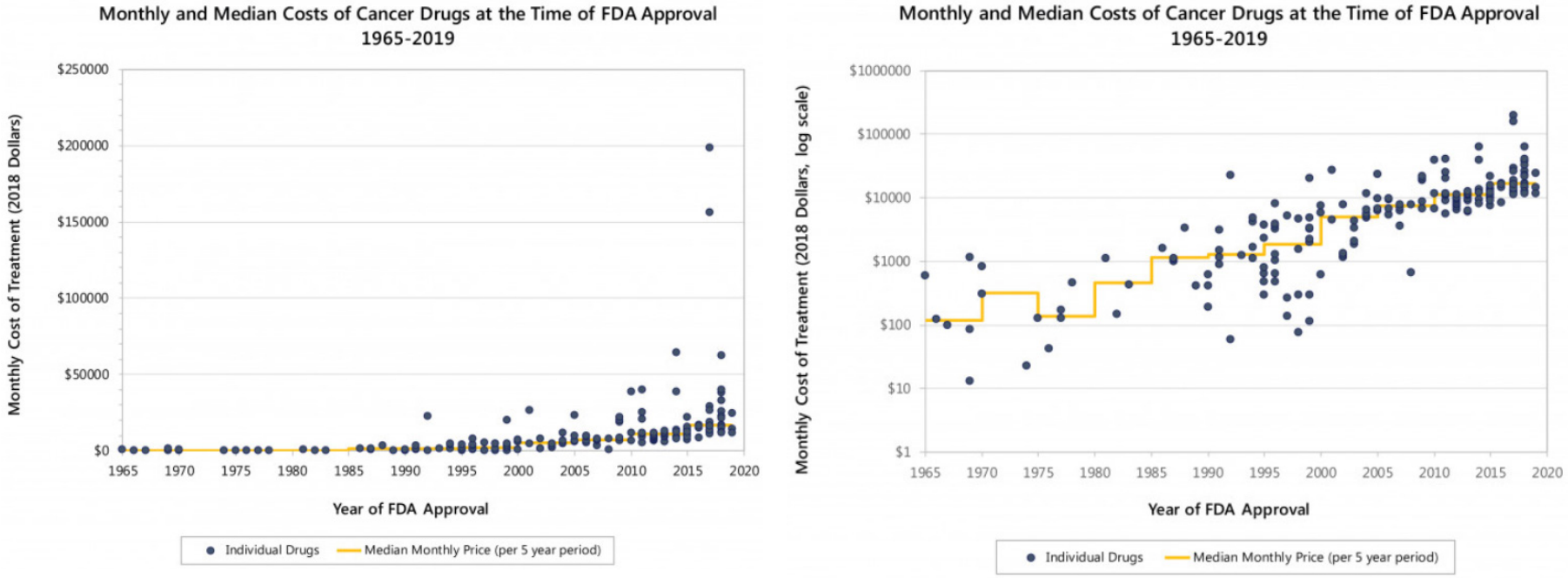
A major and driving contributor to the increased cancer drug expenditures is the pricing of innovative oncology drugs (a higher cost per treatment). Other contributors include new indications and adjuvant use, a higher number of new cancer patients and prevalent cases, longer treatment durations and more combination treatments.[3]

For new oncology drugs in the US, the price per month of treatment has increased exponentially over the last decades (see Figure 2, note the log scale on the y-axis of the second figure). This is also a global observation made by the Organisation for Economic Cooperation and Development (OECD). Global sales of cancer drugs are expected to continue to grow by 10% per year until 2023.[4] OECD identified the high drug prices in field of oncology and the lack of justification for the health benefits they confer as a main challenge.[5]

The prices of new anticancer agents seem to be decided by pharmaceutical companies according to what the market will bear, not by the development costs nor the clinical benefit. There is little correlation between the actual efficacy of a new drug and its price.[6] This suggests that

current pricing models may be inadequate to incentivize the development and utilization of high-value treatments.[7]

Figure 2 – The monthly treatment cost of new cancer drugs, by year of FDA approval



Source: Peter B. Bach, MD, Memorial Sloan Kettering Cancer Center (https://www.mskcc.org/research-programs/health-policy-outcomes/cost-drugs)
Remark: prices are adjusted for inflation.

1.1.3 Patient benefit, no longer a hard requirement for marketing authorisation

This sharp increase in expenditures creates the expectation of a substantial increase in life expectancy and quality of life in treated cancer patients. In this report, it will be assessed to what extent patient benefits can be observed in Belgium.

Patients, clinicians, HTA bodies and payers expect pharmaceutical companies to provide data for their drug showing increased overall survival and/or a better quality of life. Such data are however not required to obtain

marketing approval. This is a result of the split of the two government bodies, regulators and HTA institutes/payers.

In fact, regulators, without approval by HTA bodies or payers, have progressively lowered the evidence requirements and increasingly adopted expedited approvals for new cancer drugs, accepting small trials, surrogate endpoints and substandard comparators.[8] The trials with the patient population, comparators and outcomes as recommended by the regulators may not be fit for purpose to perform HTA nor to inform physicians wanting to practice evidence-based medicine.[9] Companies do not feel the need to extend the pivotal trials beyond the demands of regulators, especially as there is a lack of alignment between regulators, HTA organisations, and payers. This may lead to a multitude of evidence required from clinical trials and clinical practice that the company may not be able to deliver.[10]

In addition, indications granted by the regulator were sometimes broadly worded and had to be restricted by the payer. This has led to guidance for the regulator to better define the approved indication.(https://www.ema.europa.eu/en/news/enhancing-consistency-wording-therapeutic-indications-support-healthcare-decision-making)

There are multiple challenges and incompatibilities to demonstrate unambiguously patient benefits in cancer patients in terms of overall survival and/or quality of life while obtaining early marketing approval and allowing rapid patient access.

A first challenge is the comparison needed to show a benefit. Often, there are no comparative data. For example, between 2006 and 2016, over half of EMA conditional marketing authorisations for cancer drugs were based on single-group studies.[11] Conclusions of comparisons of medical interventions are most reliable when obtained using a randomised clinical trial (RCT), as only randomisation balances for unknown variables predictive of treatment outcome. Real-world observational data are therefore not a valid surrogate for a RCT. In addition, the comparator arm should reflect current (read cost-effective) usual care, not a suboptimal treatment nor a treatment that in itself is not cost-effective. Of the clinical studies that supported the US Food and Drug Administration's (FDA's) approval of new oncology drugs between 2005 and 2012, less than one in five had active comparators, required to evaluate the relative efficacy.[11] Absence of an active comparator can lead to uncertainty regarding the relative benefits and harms of treatments at the time of market approval.[11] Regulators and HTA bodies often differ in opinion on the choice of the comparator arm.[12]

Second, the key patient outcomes, survival and quality of life are often not addressed in the pre-market trials. On this topic too, regulators and HTA bodies have different views.[12] All too often, progression free survival (PFS) or tumour response is used instead of overall survival because the read-out comes earlier. This is shortening the clinical development time and reducing the pivotal trial cost by about half.[13] This is even more the case for drugs that qualify for expedited programmes, aiming at accelerated approval. Between 2012 and 2016, the duration of clinical development was almost 1 year shorter for drugs in the FDA's expedited programmes than for drugs that were not.[11] Although surrogate measures reduce the duration, size, and cost of clinical studies, thereby facilitating faster patient access to promising new treatments, they further magnify the uncertainty associated with the lack of active comparators.[11] This way the company also avoids the risk of (immediate) failure because no overall survival benefit can be demonstrated. Although certain surrogate measures are well validated, many of the surrogate measures used for approval decisions are not comprehensively validated. Surrogate measures are particularly common in cancer trials. More than four-fifths of pivotal studies that supported the approval of cancer drugs in the USA relied on surrogate measures alone. The relationship between surrogate measures (e.g., tumour response or progression-free survival) and clinical outcomes (e.g., overall survival or quality-of-life) is often poor.[14]

Third, generalization of trial findings to the routine care setting is not straightforward and this is not only because the restricted trial population does not fully reflect the real target population. Besides access issues to the expensive drugs, it is a challenge for healthcare systems to bring high quality and sophisticated companion diagnostics to the routine care setting so targeted drugs can be given to the right patients.[15]

Payers may hesitate to reimburse novel interventions if the patient benefit is not clearly demonstrated, leading to delays or even no patient access. This is a situation that occurs quite frequently in the field of cancer

treatment leading to large variations in patient access across countries and even regions.[16]

Fortunately, regulators and HTA bodies in Europe have started meetings of parallel scientific advice to companies embarking on long and costly confirmatory trials.[17, 18] However, as the HTA recommendations remain non-binding, companies may not include the routine target population, the best available active comparator nor the patient-relevant endpoint recommended by HTA agencies. Developers of innovations should embrace early dialogues with international associations of payers and HTA bodies such as EUnetHTA and more importantly, take the advice on board in the pivotal trials.

In cases where patient benefit in terms of overall survival and/or quality of life has been well documented, it is rather straightforward for healthcare payers to judge if the price of the intervention is reasonable and routine patient access can be supported. In this context one should not forget that a cost decrease (public or not public as for example in managed entry agreements, in Belgium: articles 111, 112 and 113)[19] does not increase the patient benefit of the therapy. Lowering the cost can make an intervention more cost-effective but only in case there is proven patient benefit (effectiveness). Discounts can also make the budget impact more acceptable for the healthcare payer.

1.2 Are the extra expenditures associated with patient benefits?

1.2.1 Cancer drugs as one of many contributors to cancer survival

Cancer survival for breast, colon, lung and prostate correlates with health expenditure per capita spent on cancer overall.[3] This observation is made based on the survival by cancer type, pooled for all stages at diagnosis. A variable to be considered in this analysis is the possible effect of better and more sensitive cancer diagnostics and for some cancer types, the effect of introducing screening programmes. Other types of therapeutic interventions such as advances in supportive care, surgery and radiotherapy may also have an impact. In 2016, Peter Wise argued in the BMJ[20] that, referring to a meta-analysis published in 2004, with the exception of testicular cancer, Hodgkin's disease, cancer of the cervix, lymphoma and ovarian cancer, cytotoxic chemotherapy has increased five year survival in the more common cancers by less than 2.5%. Gains in overall survival could also have come from other developments, such as early diagnosis, improved radiotherapy, surgery techniques, etc.

While being typically the cancer population where new cancer drugs are first introduced, the population of patients diagnosed at a more advanced stage of cancer are probably less affected by improvements in diagnostics and screening. Cancer registries containing information on the disease stage at diagnosis might therefore be a real world data source to explore improvements in overall survival associated with the uptake of innovative drugs in these patients.

1.2.2 *Small and uncertain patient benefit of new cancer medicines*

Two studies have systematically examined the patient benefit of cancer medicines at the time of EMA approval and beyond.

Davis et al.[21] performed a systematic evaluation of approvals of 48 oncology drugs for 68 indications by the EMA in the period 2009-2013. The authors checked if data on overall survival and quality of life benefits of cancer drugs were available both at time of approval and in the postmarketing period. In a third (24/68) there was a significant prolongation of overall survival, ranging from 1.0 to 5.8 months, median 2.7 months. Improvement in quality of life was shown in only 10% (7/68). After a median of 5.4 years' follow-up (minimum 3.3 years, maximum 8.1 years), a significant improvement in survival or quality of life was shown for 35/68 (instead of 29/68 at market entry), whereas this remained uncertain for about half of the oncology drugs on the market for over three years. Furthermore, of 23 indications associated with a survival benefit, the benefit was judged to be clinically meaningful in only half of these cases (11/23, 48%). The authors conclude that "this systematic evaluation of oncology approvals by the EMA in 2009-13 shows that most drugs entered the market without evidence of benefit on survival or quality of life. At a minimum of 3.3 years after market entry, there was still no conclusive evidence that these drugs either extended or improved life for most cancer indications. When there were survival gains over existing treatment options or placebo, they were often marginal."[21]

Grössmann et al.[22] studied the EMA website and the European public assessment reports (EPARs) and identified 102 anticancer therapies that received marketing authorisation between January 2009 and May 2015. The therapies were in solid tumors (n=71) and 31 in the field of hemato-oncology (n=31). For 43/102 (42%) dossiers there was no or negative information on median OS at the time of EMA approval. At least three years later the OS data were still missing/negative for 29 out of the 102 (28%) anticancer therapies. Of these 29 therapies, 17 had orphan drug designation, 6 were marketed under conditional approval and 25 had additional monitoring requirements. The authors conclude that many oncology drugs with ambiguous benefit-risk profiles fail to demonstrate a survival benefit several years after entering the market. Therefore, the combination of rapid access and the removal of ineffective drugs from the market requires the implementation of systematic, transparent and automated monitoring and publication mechanisms for all new drugs. The authors highlighted the need for a prolonged monitoring period (more than 3 years) after EMA approval.[22]

Key points

- **Launch prices of cancer drugs have continued to increase in the past years. This is one of the main reasons for the sharp increase in healthcare payer expenditures in Belgium of ATC class L01X (other antineoplastic agents), from €140 million in 2007 to more than €1 billion in 2019.**
- **Regulators often approve cancer drugs based on surrogate endpoints or single-arm studies, which do not always translate into improvements in the outcomes that are most important to patients, i.e. overall survival and quality of life. Literature shows that for most cancer indications also after market entry there is still no conclusive evidence on patient benefit. These uncertainties on relative efficacy combined with a high cost put governments and payers in a difficult position when it comes to deciding which treatments to fund.**
- **The aim of this project is to assess to what extent there is an increase in expenditures on oncology drugs for a selection of cancer indications, and whether this translates in a longer overall survival and/or a better quality of life for the cancer patients.**

2 OBJECTIVES

2.1 Opportunity cost or displacement effect

The request for this study comes from the NIHDI (RIZIV – INAMI). The problem statement was formulated as follows in the application: “The reimbursement of new care, in particular pharmaceutical specialties, may mean that useful, cost-effective and valuable care cannot (longer) be paid for or can no longer be purchased. This is the so-called 'displacement effect'. It must be investigated whether the expenditures on new, innovative pharmaceuticals in the pre-eminently innovative field of oncology in recent years has been worthwhile. In other words: how much health benefit has the expenditure on innovative pharmaceuticals in oncology yielded in recent years? If the real health gain, which can perhaps only be estimated on the basis of the theoretical health gain based on the results of clinical studies (and thus overestimated), is limited, a displacement effect may play a role. If the real health gain is high, an overall positive value can be attached to the expensive pharmacological care in oncology.”

The applicant openly asks whether there is a justification for the expensive treatments used in recent years. The investment in the oncology area is impressive and may be a hurdle to investment in other therapeutic areas in case of a fixed budget.

Both the Commission for the Reimbursement of Medicines (CRM, Commissie Tegemoetkoming Geneesmiddelen/Commission de Remboursement des Médicaments – CTG/CRM) and the Medicines Contract Working Group are interested in this study. This topic also fits within the social debate about how many resources the community spends in oncology and which health-economic results this entails.

The aim is to provide insights supporting the decision-making about reimbursement of medicines in oncology, whether or not through a contract between NIHDI and the pharmaceutical company.

2.2 Research questions

In the initial research proposal, the first research question was “whether the cost-effectiveness (ICER) of the class of oncology drugs in Belgium could be calculated, taking into account the efficacy data from the clinical studies (possibly effectiveness from clinical practice) and the gross expenditure for the most recently reimbursed oncology drugs (gross, because refunded by contract).” In case this could be calculated, the second research question was “what health gain has the expenditure on the class of oncology drugs brought in Belgium? What is the global average cost-effectiveness of these products?”

However, it is practically impossible to calculate a detailed cost-effectiveness for all oncology medications. We also do not consider it appropriate to calculate a global average cost-effectiveness for an entire class of pharmaceuticals, since the cost-effectiveness of individual oncology medications can vary enormously and an average is difficult to interpret and can lead to incorrect conclusions.

In a classical HTA report, the safety, efficacy/effectiveness and cost-effectiveness of a specific intervention in a well-defined population would be studied. However, a detailed HTA report for one specific oncology drug would also not answer the original research question. Therefore, the research team opted to gather relevant information on survival, expenditures and (cost-)effectiveness for a broad selection of oncology drugs in multiple indications. We did not aim to asses the treatment effect of innovative oncology drugs based on Belgian observational data. Although no conclusions on causal relationship can be made (see discussion section), we tried to identify in how far increases in oncology drug expenditures were associated with improvements in survival.

Finally, the research questions of this report are as follows:

- First research question: What is the evolution in overall survival in a broad selection of oncology indications and the budget impact of introducing new cancer drugs in the last 15 years?
- Second research question: What is known in the literature about the benefits (e.g. impact on overall survival and QoL) and cost-effectiveness for a broad selection of new cancer drugs?

Next to providing an answer to these research questions, we also aim to formulate areas for improvement. Therefore, different topics are tackled in the discussion of this report. Our policy recommendations are published in a separate synthesis, which is published simultaneously with this report.

3 METHODOLOGY

3.1 Part 1: Databases, statistical analyses, and presentation of results

3.1.1 Belgian Cancer Registry (BCR) data selection and linkage with Intermutualistic Agency (IMA) data and vital status

3.1.1.1 Selection of the study population in the Belgian Cancer Registry database

A total of 960 748 invasive tumours diagnosed in 2004-2017 from 861 140 different patients, with a known National Number for Social Security and an official residence in Belgium, were identified in the population-based Belgian Cancer Registry (BCR) database (see Box 1). When excluding non-melanoma of the skin, 891 310 tumours from 814 434 patients remained. For about one out of eight of those patients multiple invasive tumour diagnoses are recorded, which results in 714 948 (87.8%) patients with a single invasive tumour (excluding non-melanoma of the skin).

Box 1 – The Belgian Cancer Registry

In Belgium, reporting all newly diagnosed cancer cases to the Belgian Cancer Registry (BCR) is compulsory for hospitals and for pathology laboratories. Completeness of incidence has been estimated to be at least 98% of all cancer cases in Belgium from 2004 onwards.[23] The cancer registry database comprises, among others, the following patient and tumour characteristics: sex, age at diagnosis, incidence date (i.e. the date of first histopathological confirmation of the tumour or, if not available, the date of the technical procedure or clinical investigation leading to the diagnosis of cancer), topography and histology of the tumour (ICD-O-3), and clinical and pathological TNM stage at diagnosis (UICC TNM 5th edition for incidence years 1999-2002; 6th edition for incidence years 2003-2009; 7th edition for incidence years 2010-2016; 8th edition as from incidence year 2017 onwards).

The Belgian Cancer Registry has a legal basis to use the patient's unique National Number for Social Security.

The following selections have been done to study several groups of patients with a diagnosed cancer. For more details, we refer to Table 2:

- (Female) Breast cancer
- Chronic myeloid leukaemia (CML)
- Colorectal adenocarcinoma
- Squamous cell carcinoma (SCC) of the head and neck :
  - Oral cavity SCC
  - Oropharynx SCC
  - Hypopharynx SCC
  - Larynx SCC
- Malignant melanoma of the skin
- Malignant epithelioid mesothelioma of pleura
- Multiple myeloma
- Non Hodgkin Lymphoma :
  - Mantle cell lymphoma
  - B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL)
  - Diffuse Large B-cell Lymphoma (DLBCL)
- Non small cell lung cancer (NSCLC)
- Epithelial ovarian cancer
- Prostate cancer
- Renal cell carcinoma

The selection was not based on specific criteria but came forward during a first meeting between KCE and BCR experts. Based on a discussion with the external experts group, lung cancer was restricted to non-small-cell lung cancer and mesothelioma was added during the selection of oncology drugs (see further in Chapter 3.2 part 2). The final selection criteria for the included tumours based on ICD-O-3/ICD-10 is included in Table 2. ICD-10 refers to the 10th revision of the International Statistical Classification of Diseases and Related Health Problems from the World Health Organization (WHO). ICD-O-3 refers to the International Classification of Diseases for Oncology, third revision also from the WHO.

Table 2 – Selection criteria for the included tumours based on ICD-O-3.2*/ICD-10**

Cancer type	Topography	Morphology: Histology	/Behaviour
Chronic myeloid leukaemia	/	9863 9875	/3
Mantle cell lymphoma	/	9673	/3
B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL)	/	9670 9823	/3
Diffuse Large B-cell Lymphoma (DLBCL)	/	9680 9684	/3
Colorectal cancer, adenocarcinoma	C18-C19 (colon) C20 (rectum) (ICD-10)	8140-8141 8143-8145 8190-8231 8244 8260-8263 8310 8401 8480-8490 8510 8550-8551 8560 8570-8574 8576	/3
Female breast cancer	C50 (ICD-10)	/	/3
Squamous cell carcinoma of the			
- Oral cavity	C02.0-C02.3, C02.9, C03.0-C05.0, C06.0-C06.9	8004 8020-8022 8032 8050-8076 8078 8082-8084 8123 8560	/3
- Oropharynx	C01.9;C02.4, C02.8, C05.1-C05.2, C05.8-C05.9, C09.0-C10.3, C10.8-C10.9, C14.2	8004 8020-8022 8032 8050-8076 8078 8082-8084 8120-8121 8123 8560	/3
- Hypopharynx	C12.9-C13.2, C13.8-C13.9	8004 8020-8022 8031-8032 8050-8076 8078 8082-8084 8120 8123 8560	/3
- Larynx (RARECAREnet)	C32.0-C32.3, C32.8-C32.9	8004 8020-8022 8031-8032 8050-8076 8078 8082-8084 8120 8123 8560	/3
Malignant melanoma of the skin	C43 (IDC-10)	/	/3
Multiple myeloma	C90 (ICD-10)	/	/3
Non-small-cell lung cancer	C34 (ICD-10)	8010-8040 8046-8245 8247-8576	/3
Epithelial Ovarian Cancer+(RARECAREnet)	C56.9	8000 8001 8003-8005 8010 8011 8012 8020-8022 8030-8034 8040 8050 8051-8052 8070-8076 8083-8084 8120 8122 8123 8130 8140-8141 8143 8146 8147 8190 8200-8201 8210-8211 8221 8230 8231 8255 8260-8263 8290 8310 8313 8315 8320 8323 8330 8333 8380-8384 8401 8430 8440-8463 8470-8490 8500 8504 8510 8512 8514 8525 8542 8550-8551 8560 8562-8576 8950-8951 8980 9000 9014-9015 9110	/3
Renal cell carcinoma (RARECAREnet)	C64	8005 8050 8140-8141 8143 8147 8190 8200 8201 8211 8221 8230-8231 8251 8255-8263 8270 8290 8300 8310 8311 8312 8315-8320 8323 8330 8333 8401 8430 8440 8342 8450 8480-	/3

		8490 8500 8503-8504 8510-8512 8514 8525 8542 8550-8551 8562 9110	
Prostate cancer	C61 (ICD-10)	/	/3
Malignant epithelioid mesothelioma of pleura	C45.0	9052	/3

** ICD-O-3 2nd revision: http://www.iacr.com.fr/index.php?Itemid=577*
*** ICD-10: https://icd.who.int/browse10/2010/en*

3.1.1.2 Linkage with health insurance data

Since 2009, the Belgian Cancer Registry is authorized to link data from its database with data on reimbursed cancer-related diagnostic and therapeutic procedures and pharmaceuticals (in-hospital as well as out-hospital).[24] These data are obtained from all seven Belgian health insurance companies via the Intermutualistic Agency (IMA, InterMutualistisch Agentschap – Agence InterMutualiste (IMA – AIM)).[d] Via this linkage procedure, the Belgian Cancer Registry receives for each registered patient, health insurance data starting from 1 January of the year preceding the incidence year, until 31 December of the fifth year after the incidence year. These data are further mentioned as IMA data. For this study only the IMA data until the end of 2018 (year of health care act) were taken into account. Since IMA data were available until accountancy period June 2019 and a delay of two years should be taken into account to consider IMA data as 100% complete, reported expenditures for the 2nd half of 2017 and 2018 cannot be considered as complete.

For this study on innovative drugs, records from the linked IMA database available for the Belgian Cancer Registry were selected when the reimbursed pharmaceutical product can be categorized in the ATC (Anatomical Therapeutic Chemical Classification System) categories 'L01' (ATC level 2) or 'L02BA01', 'L02BA03', 'L02BB01', 'L02BB03', 'L02BB04', 'L02BG03', 'L02BG04', 'L02BG06', 'L02BX03', 'L03AC01', 'L03AX03', 'L04AX02', 'L04AX03', 'L04AX04', 'L04AX06' (ATC level 5) from the WHO. These categories include all oncology drugs.

Pharmaceutical products under consideration could be found in the IMA database for 547 347 (57.0%) patients from the originally selected 861 140 patients with at least one invasive tumour during 2004-2017. From the 714 948 with a single invasive tumour, 406 042 (56.8%) patients received at least one of those pharmaceutical products.

3.1.1.3 Vital status

Information with regard to the vital status of the included patients was retrieved from the Crossroad Bank of Social Security (Kruispuntbank van de Sociale Zekerheid / Banque Carrefour de la Sécurité Sociale) based on the patients' unique social security identification number (NISS/INSZ). Using this active follow-up method, patients were followed up until 31 January 2020. Hence, all included patients until incidence year 2017 had at least two year follow-up for survival.

[d] In principle, the IMA database contains the reimbursement data of all Belgians. In reality, this database represents about 98% of all residents (e.g. frontier workers and employees of international institutions affiliated to a non-Belgian health insurance fund, foreign students, etc. are not included).(source: metadata.ima-aim.be/nl/app/bdds/Pp)

3.1.2 Statistical analyses

3.1.2.1 Descriptive analyses

In order to identify which innovative drugs were used for the treatment of different cancer types, only patients with unique invasive tumours (excluding non-melanoma of the skin) were considered. The products administered to those patients during the year of incidence and the five following years were considered further in the study. This restriction is necessary because IMA data cannot directly be linked to a specific diagnosis and this methodology eliminates the possibility that drugs were used for another cancer type of the same patient when multiple tumours were diagnosed. Numbers at the fifth level of the ATC-classification were stratified by incidence year of the tumour and the combined tumour stage, in which the pathological stage at time of primary surgery prevails over the clinical stage at time of diagnosis, except when there is clinical proof of distant metastases (cM1).

Once the drugs for the selected cancer indications were selected (see part 3.2), all patients with the specific cancer type were taken into account (no exclusion of patients diagnosed with multiple invasive tumours) to investigate the evolution of the number of patients diagnosed with a specific cancer type who were treated with a specific innovative pharmaceutical product (e.g. bevacizumab for patients diagnosed with an epithelial ovarian cancer), the products administered/delivered during the year of incidence or the five following years were taken into account.[e] The number of patients who received at least one dose of the specified drugs during the incidence year of the tumour or the following 5 years were stratified by incidence year of the tumour and combined tumour stage.

For each cancer indication (and selected tumour stages), global expenditures per pharmaceutical product were calculated per calendar year and illustrated with stacked area charts for the first year after incidence date and the first two years after incidence date; the mean cost per patient for the first two years after incidence date was calculated per calendar year and illustrated using line charts.

Prices for selected pharmaceutical products (see part 3.2.2) have been monitored in appendix (data source: RIZIV – INAMI).

Furthermore, medical futility for the selected cancer types was investigated. Patients diagnosed with combined stage IV of one of those cancer types between 2004 and 2017 and who died before June 2018 were selected out of the cancer registry database. It was then investigated whether those patients received at least one administration of the full list of oncology drugs included in this study (see 1.1.1.1) within 7, 14 and 30 days before death.

3.1.2.2 Survival analysis

Estimation of observed and relative survival

Observed survival (OS) proportions were estimated using the Kaplan-Meier method [KM].[25] Relative survival was calculated as the ratio of the observed survival and the expected survival for a similar group of persons from the general Belgian population (stratified on sex, age, calendar year and region). The Ederer II method was applied to estimate the expected survival using the Belgian national lifetables [E2].[26]

The date of diagnosis (incidence date) was taken as time origin for the survival analysis. Patients censored at the date of diagnosis were omitted for the survival analysis. When multiple registrations of the same cancer type were available for a patient, only the first occurring diagnosis is considered, as the survival time of the subsequent diagnoses are not independent of the first.

[e] As an example, if the incidence date is 31/03/2008, then data from 1/1/2008 till 31/12/2013 are available.

3.1.2.3 *Statistical software*

Statistical analyses were performed with SAS 9.4 (SAS Institute, Cary, NC, USA).

Expenses charts were performed with Microsoft Excel 2013.

3.1.3 Graphics and Tables

For all selected cancer types, the following tables and figures will be presented, on the patients selected for the survival analysis:

A table presenting the following information:

- Patient characteristics: sex, age at diagnosis and WHO performance status for three incidence periods (2004-2008, 2009-2013 and 2014-2017).
- Kaplan-Meier (KM) graph per incidence period (2004-2008, 2009-2013 and 2014-2017): observed survival probability (in %, y-axis) versus time since diagnosis in years (x-axis).
- Time trend with incidence year: 1-, 2-, 3-, 4-, and 5-year observed survival probability (y-axis) for incidence years 2004-2017 (x-axis). The 3-year observed survival probability (mean, 95%CI) are also provided next to the figure.
- Median survival time (y-axis) for incidence years 2004-2017 (x-axis). Next to the graph, the median survival time with its 95%CI.

For cancers where staging is applicable, information is presented for stage IV cancers. Information for the other stages is provided in the appendix. Next to KM-graphs with observed survival probabilities, also graphs with relative survival probabilities are presented in the appendix.

For selected cancers, additional analyses were performed with an additional cut-off point in time at the introduction of innovative drugs in order to have a more prcise estimation of the effect of the drug(s) on observed and relative survival.

A table presenting information on drug expenditures:

- Oncological drug expenses (left y-axis) per calendar year (2004-2018, x-axis) for the selected cancer type (all stages if staging applicable). All oncology drugs are included in this figure at ATC5 level (see included L01, L02, L03 and L04 categories in part 1.1.1.1). The expenditures per molecule are cumulative curves – the larger the surface area for a molecule, the higher the expenditures. The names of the oncology drugs with the largest expenditures are added. The figure also presents the number of patients with drug expenses (right y-axis). Information presented for calendar year 2018 are not 100% complete and also for the second half of 2017 there might be a very small proportion of missing data.[f]
- Oncological drug expenses (y-axis) per incidence year (2004-2017, x-axis) for the first two years after incidence for the selected cancer type (stage IV if staging applicable). All oncology drugs are included in this figure at ATC5 level (see included L01, L02, L03 and L04 categories in part 1.1.1.1). The expenditures per molecule are cumulative curves – the larger the surface area for a molecule, the higher the expenditures. The names of the oncology drugs with the largest expenditures are added. Incidence year 2017 is the last year added on this graph. The figure also presents the total number of patients with this cancer and the number of patients with drug expenses (right y-axis). For incidence years 2015-2017, information is potentially lacking for a small proportion of patients: i.e. those patients that had drug expenditures within two years after diagnosis that were not yet present in the IMA database (June 2019) in which a delay up to two years is possible.[g]

[f] Expenditures during the second half of calendar year 2017 might not yet be included in the IMA database of June 2019 in which a delay up to two years might exist.

[g] Also data for the second half of 2015 might not be 100% complete. For example, a patient with a diagnosis in the second half of 2015 might have expenditures within two years of diagnosis (i.e. in the second half of 2017),

- Mean oncology drug cost per patient for the first two years after incidence (y-axis), per incidence year (x-axis) for the selected cancer type (stage IV if staging applicable). Costs for all oncology drugs are included (see included L01, L02, L03 and L04 categories in part 1.1.1.1). Two lines are presented: mean costs versus 1) all patients with this specific cancer; 2) only patients with this specific cancer that have oncology drug expenses.
- In the above figures, the number of patients with drug expenditures is provided to better interpret the (increase of) drug expenditures: are these changes due to more patients being treated with oncological drugs (volume effect), or do expenditures also increase due to higher treatment costs per patient (price effect)?

Finally, there are also drug uptake tables for a selection of drugs in the 12 cancer types (see part 3.2 for the selection of drugs). These tables present the proportion of patients who received at least one dose of a specific drug during the incidence year or a 5-year period after the incidence year. Results are expressed per incidence year (2004-2017). With a 5-year follow-up period after the incidence year and a potential delay of two-year in the IMA data, information for the incidence years 2012-2017 might not be 100% complete.[h] For clarification, uptake mentioned in incidence years before the year of reimbursement is thus possible and points at patients who are still alive when reimbursement started.

3.2 Part 2: Selection of drugs

3.2.1 Selection criteria and process

In view of NIHDI's initial research question, it was decided to select drugs from a wide number of cancer types. At the scoping phase of the project, in November 2019, the following 13[i] common cancer types (as single cancer diagnosis) were selected: Chronic myeloid leukaemia, Colon cancer, Colorectal cancer, Female Breast cancers, Head and Neck cancers, Small-cell lung cancers, Malignant melanoma of skin, Multiple myeloma, Non-Hodgkin Lymphoma, Non-small-cell lung cancers, Ovarian cancer, Rectum cancer, and Renal cancer.

The following criteria were considered for the selection of drugs in these cancer types:

1. The evolution in survival, both observed and relative, during the period 2004-2016 (data for 2017 were not yet available at the beginning of the project). Figures were provided by BCR for the 13 selected cancers and were available per tumour stage at time of diagnosis (where staging is applicable).
2. The budget impact of the included oncology drugs (see part 1.1.1.1) in the 13 cancer types.

- The average cost per patient of the oncology drugs under consideration for the 13 cancer types. We also take the number of patients treated with this drug within the cancer types into account.
- The top 10 oncology drugs in the yearly overall budget impact for all drug cancer types combined (i.e. also outside the previously mentioned 13 cancer types). We selected information from the most

h For example, for the incidence year 2012, oncology drugs used in the fifth year after diagnosis (second half 2017), might not yet be included in the IMA database (accountancy period until June 2019 was available for this study).

i This was part of the preliminary exploratory investigation. External experts provided further input. In part 3.2.2, we present the final selection of 12 cancer types that are further elaborated in this report.

recent available year. In first instance, this was the year 2016. More recently, we updated this with information for the year 2017.[j]

- The uptake of oncology drugs. Where tumour staging is applicable, we looked at the uptake of oncology drugs in stage IV cancers because most innovative drugs are first introduced in advanced cancer patients. We looked at innovative molecules for which the uptake by molecule in stage IV patients reached a minimum of 15% for at least one year during the period 2004-2016. In an update, information for 2017 was added. We did not further consider classic chemotherapy with high uptake.

Next to these criteria, we also looked whether the drug was still reimbursed in 2019 and that we would not only select oncology drugs that are reimbursed in a managed entry agreement (MEA).

Based on the above criteria, in December 2019, a list of suggested oncology drugs for inclusion in this report was provided to a wide list of stakeholders[k] and external experts. We provided the following text to these external stakeholders and experts: "*We like to hear from you if you think of other examples that could be covered in this report than the ones we list below. Both positive and negative examples are welcome ('positive': i.e. examples that have a major impact on the survival and/or quality of life of the patients; 'negative': examples with limited benefit in terms of OS and/or QoL but with a major budget impact). The examples that you provide will be treated anonymously (i.e. the focus is on the examples and the underlying reason for suggesting them, no matter which expert provides the example). We are especially looking forward to receive 'positive' examples of new cancer drugs introduced between 2004 and 2016 such that the effect on overall survival in the target population can possibly be documented using the 'real-world' cancer registry data.*" We explicitly asked for 'positive' examples to avoid the potential criticism that such examples would deliberately not be included and our report would be biased.

Finally, information for incidence year 2017 was added in March-April 2020. Based on this additional information (e.g. on the first used immunotherapy nivolumab and pembrolizumab in NSCLC), oncology drugs that were introduced more recently on the market were added to the list.

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j In 2016, the top 10 drugs with the highest NIHDI expenditures were: trastuzumab (L01XC03): €53 287 223; bevacizumab (L01XC07): €51 066 865; lenalidomide (L04AX04): €41 831 079; pemetrexed (L01BA04): €28 988 393; rituximab (L01XC02): €25 743 827; imatinib (L01XE01): €17 483 663; bortezomib (L01XX32): €17 147 524; pertuzumab (L01XC13): €16 504 813; ibrutinib (L01XE27): €15 895 587; pomalidomide (L04AX06): €14 353 384.

In 2017, the top 10 drugs with the highest NIHDI expenditures were: nivolumab (L01XC17): €96 668 854; lenalidomide (L04AX04): €46 658 986; trastuzumab (L01XC03): €44 047 169; bevacizumab (L01XC07): €40 198 433; pembrolizumab (L01XC18): €28 525 180; ibrutinib (L01XE27): €21 999 774; pertuzumab (L01XC13): €18 442 545; rituximab (L01XC02): €17 288 972; pemetrexed (L01BA04): €16 421 256; enzalutamide (L02BB04): €16 178 026.

k Stakeholders/Experts from the following institutes were contacted by email: University Hospital Antwerp, Brussel, Ghent, Leuven, Liège, Louvain, NIHDI, Kom op tegen Kanker, Test Aankoop, Vlaams Patiëntenplatform (VPP), Ligue des Usagers des Services de Santé (LUSS), Intermutualistic Agency (IMA), Mutualités Libres/Onafhankelijke Ziekenfondsen (MLOZ), Christelijke Mutualiteit/Mutualité Chrétienne (CM/MC), Socialistische Mutualiteit/Mutualité Socialiste (SocMut/MutSoc), The Federal Public Service (FPS) Public Health, and Jules Bordet Institute. The patient representatives (VPP and LUSS) mentioned they relied on the expertise of the other invited experts to provide input.

3.2.2 Selected cancer types and drugs

The following table provides an overview of the 40 different oncology drugs that were selected within 12 cancer types to be elaborated further in this report. This was based on an initial proposal of the research team and changes based on the suggestions of the external experts.[I] Lung cancer was limited to non-small cell lung cancer, the cancer types colon, colorectal and rectum cancer were taken together and mesothelioma was added.

Table 3 – List of selected drugs in 12 cancer types

Female Breast cancers	pertuzumab, trastuzumab emtansine, palbociclib+, abemaciclib+, and ribociclib+
Chronic myeloid leukaemia	imatinib, nilotinib, dasatinib, bosutinib+, and ponatinib+
Colorectal cancer (Colon and rectum*)	bevacizumab, cetuximab, panitumumab, aflibercept, and regorafenib
Head and Neck cancers	cetuximab
Malignant melanoma of skin	ipilimumab, pembrolizumab, nivolumab, dabrafenib, vemurafenib, and trametinib
Mesothelioma	pemetrexed+
Multiple myeloma	lenalidomide, pomalidomide, bortezomib and daratumumab+
Non Hodgkin Lymphoma**	rituximab, ibrutinib and obinutuzumab+
Non-small-cell lung cancer	erlotinib, gefitinib, ~~pemetrexed-~~, afatinib & crizotinib, nivolumab*** and pembrolizumab***
Ovarian cancer	bevacizumab
Prostate cancer	enzalutamide
Renal cancer	sunitinib, pazopanib, everolimus, sorafinib, axitinib, temsirolimus, and nivolumab

+/-: the cancer drugs that were added/deleted, based on the suggestions from external experts.
** It was decided to group colon cancer (ICD-10 C18-C19) and rectum cancer (ICD-10 C20) and look at colorectal adenocarcinoma (ICD-10 C18-C20). ** During the expert meeting, it was decided to limit Non-Hodgkin Lymphoma to the following three types: chronic lymphocytic leukaemia & small lymphocytic lymphoma, Diffuse Large B-cell Lymphoma, and Mantle cell lymphoma *** Based on the updated information including incidence year 2017, immunotherapy (nivolumab and pembrolizumab) is also added for this cancer type.*

[I] One of the suggestions for inclusion was related to vaccines for the prevention of cervical cancer. However, this was out of the scope of this project.

3.3 Part 3: Literature searches

3.3.1 Search medical literature

For the medical literature, a rapid review approach was chosen to be able to include a high number of research questions with the given time limits and limited human resources.[27]

To identify relevant published systematic reviews we conduced systematic searches of literature in the following databases:

- Medline (https://ovidsp.ovid.com/ovidweb.cgi)
- The Cochrane Database of systematic reviews (http://www.cochrane.org)

Individual search strategies for each tumour type were developed to search Medline through OvidSP interface. This strategy was then converted to Cochrane database syntax. All databases were searched from April 2020 onwards without publication date or language restrictions. For Medline the search for SR used a modified version of the NLM 2018 systematic reviews filter strategy by adding terms for HTA and meta-analysis. The search results were then imported in Endnote. 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. The search strategy used a combination of appropriate MeSH terms and free text words. Text words were found in Medline scope note, by analysing abstracts of relevant results and by using textmining tools. The detail of each strategy with date of the search and number of articles found is provided in Appendix.

After de-duplication, one researcher (LEV) selected possibly relevant SRs based on title and abstract. The same researcher further selected possibly relevant SRs based on the full text of the selected SRs. Reasons for exclusions based on full text evaluations were documented.

To be included, systematic reviews had to have the following characteristics:

- Searched minimal 2 databases
- Clearly defined in- and exclusion criteria
- Critical appraisal of included studies
- Characteristics of included studies reported

Selection of SRs was limited to the most recent publication years, until a recent high quality SR was identified for all relevant indications that are reimbursed in Belgium. Given their high quality methodology, priority was given to recent Cochrane systematic reviews, if available. Selected SRs were not updated.

Critical appraisal of included SRs was done using the AMSTAR 2 checklist.[28]

Results for overall survival (OS) and quality of life (QOL) were extracted from the included SRs by one researcher (LEV) and listed in summary tables. Other outcomes, such as (severe adverse) events were reported only if they were available in the same SRs that were included for OS or QoL.

3.3.2 Search economic literature

Also for the economic literature, a rapid review approach was chosen to be able to handle the large number of selected cancer types and oncology drugs.

In first instance, in January 2020, HTA reports related to the selected cancer types and oncology drugs were searched by consulting the Centre for Reviews and Dissemination (CRD) HTA database. This was done separately for all 12 cancer types using the relevant Medical Subject Headings (MeSH). In May 2020, the UK websites of both the National Institute for Health Research (NIHR) and the National Institute for Health and Care Excellence (NICE) were searched. The main reason to focus on these UK evaluations is because 1) we experience these reports are transparently reported and cover a wide range of the selected drugs we are interested in, and 2) our experience with these reports that they are of high quality. Our initial focus is not primarily on the cost-effectiveness of individual therapies, which is unknown in case of confidential price negotiations. Our focus is in the first place on the issues in the cost-effectiveness calculations identified by the independent evidence review groups (ERGs). We come back to this decision to rely on these UK reports in our discussion.

To be selected, the reports needed to reflect the relevant cancer type and selected oncology drug, perform a critical assessment of the medical literature, and include a 'reference case' economic evaluation referring to the results of this critical assessment. Performing a critical assessment of the medical literature was added as a selection criteria because of the large amount of published economic evaluations where there is no clear critical assessment of the medical input. Processing all these primary economic evaluations is practically infeasible for this report. Furthermore, there is also a known publication bias in economic evaluations.[m]

[m] An old systematic review, published in 2006, already indicated that "most published analyses report favourable incremental cost effectiveness ratios. Studies funded by industry were more likely to report ratios below [specific] thresholds. Studies of higher methodological quality … were less likely to

Therefore, we preferred to focus on economic evaluations that are part of an HTA report or systematic review that also includes a critical assessment of the medical literature. Full details of the search strategy, search terms and identified reports are provided in the appendix for all 12 cancer types.

For all selected economic evaluations, we gathered information related to: the measurement of QoL with a generic utility instrument to support the conduct of an economic evaluation; the results of the economic evaluation; the main sources of uncertainty and main variables for which the results were sensitive; and the conclusions. We also included information on (confidential) prices and an overview table containing information on: population, intervention and comparator; incremental costs (IC), incremental effects (IE) and incremental cost-effectiveness ratios (ICERs), and remarks related to the use of a generic utility instrument and the most uncertain variables or important variables in sensitivity analysis. All this information is available in the appendices. In the main report, a summary of our findings is reported.

3.4 Part 4: RIZIV reimbursement criteria

Current reimbursement criteria in Belgium were taken from the RIZIV/INAMI website in both Dutch and French between 2/1/2020 and 5/11/2020.[n] Information regarding start date of reimbursement for the different reimbursed cancer drugs was obtained from RIZIV/INAM (Anouk Waeytens & Inneke Van De Vijver, personal communication). Information about possible changes in the details for specific cancer types was not available.

Key points

- **Data from the Belgian Cancer Registry (BCR) of about 891 000 tumours from about 814 000 patients, diagnosed between 2004-2017, were available for this study.**
- **BCR data were linked with data from the Intermutualistic Agency (IMA) until June 2019. Since there is a possible delay up to 2 years in the IMA data, information for more recent years might not be 100% complete. Therefore, IMA data until the end of 2018 (year of health care act) were taken into account in this study. IMA data for products administered to patients during the year of incidence and the five following years were available.**
- **Vital status of included patients is retreived from the Crossroad Bank of Social Security. Data was available until January 2020, resulting in at least two year follow-up data for survival.**
- **For this report, 40 different oncology drugs were selected within 12 cancer types to be elaborated further in this report.**
- **Given the large number of selected drugs and number of indications, we will mainly rely on findings from existing systematic reviews.**

report ratios below $20 000/QALY."[29] Their results supported concerns that already exist for decades about the presence of significant and persistent bias in both the conduct and reporting of cost effectiveness analyses.[30, 31] This concern still exists.

[n] https://ondpanon.riziv.fgov.be/SSPWebApplicationPublic/nl/Public/ProductSearch, https://ondpanon.riziv.fgov.be/SSPWebApplicationPublic/fr/Public/ProductSearch

4 RESULTS PER CANCER TYPE

4.1 Breast cancer

4.1.1 Introduction

Breast cancer (BC) is the most commonly diagnosed cancer and the worldwide leading cause of cancer-related deaths in women.[32] In Belgium, in 2018, BC ranked first in terms of incidence and 10 905 new cases were diagnosed.[33]

Although significant improvements in the diagnosis and treatment of early BC have been made, between 6 to 10% of women with newly diagnosed BC have stage IV (metastatic) disease.[34, 35] In Belgium, in the incidence period 2014-2017, 6.4% of patients were diagnosed with primary metastatic (stage IV) disease (see Appendix). Furthermore, 30% of early stage BC patients eventually evolve into metastatic stage.[36] Metastatic BC remains incurable and the therapy aims at prolonging survival and improving quality of life.[37]

BC is classified according to the positivity, or not, of hormone receptors (HR) and the overexpression of human epidermal growth factor receptor 2 (HER2), that are both involved in cell proliferation. HR include estrogen receptors (ER) and progesterone receptors that are coexpressed by the majority of tumours.[38] More than 80% of BCs are positive for ER whereas HER2 amplification is only found in 10-20%.[39-43] Tumours with HER2 expression are characterized by a decreased responsiveness to treatments and a worse prognosis.[39, 44]

Stage-IV median survival depends on the molecular subtype and vary from 1 year in tumours negative for HR and HER2 (triple negative BC), to 3 years in less aggressive disease (Luminal A- like subtype).[37, 39, 45, 46]

Before new targeted therapies emerged in the late nineties, metastatic BC treatment options included hormonotherapy and various chemotherapy drugs involving the combination of cyclophosphamide-methotrexate-fluorouracil (CMF), anthracycline, vinorelbine or taxane agents.[36] Survival has been prolonged due to the development of targeted therapy against HER2 pathway such as trastuzumab that is a monoclonal antibody blocking HER2 preventing cell proliferation.[41] Later, pertuzumab, another recombinant humanised monoclonal antibody, has also been approved and is reimbursed since 2014 in Belgium. For metastatic BC overexpressing HER2, while trastuzumab associated with chemotherapy has been the standard treatment for several years, the combination of pertuzumab and trastuzumab with chemotherapy is now recommended as standard first line therapy regardless of HR status.[47, 48]

Targeted therapy (trastuzumab, pertuzumab, lapatinib) has also been tested in adjuvant and neoadjuvant settings.[49] Dual blockades with two antibodies against HER2 (trastuzumab and pertuzumab) along with chemotherapy have been used in those settings.[50, 51]

For people who have relapsed during trastuzumab and chemotherapy-based therapy, trastuzumab emtansine, allowing a cell-specific delivery of chemotherapy, is now a therapeutic option.[52] It has been approved as adjuvant therapy for locally advanced tumours[53] and for metastatic BC in patients previously treated with trastuzumab and taxanes.[54]

Blockers of HR are indicated in all patients with detectable ER expression.[55, 56] Such endocrine drugs include tamoxifen, aromatase inhibitors, fulvestrant, and progestins.[52] Besides, in premenopausal patients, the addition of drugs suppressing the ovarian function by interfering with the LHRH (luteinizing hormone-releasing hormone) is recommended.[52, 55]

Intrinsic resistance to hormone therapy occurs and the majority of people develop disease progression.[57] In this setting, the addition of cyclin dependent kinase (CDK)4/6 inhibitors (abemaciclib, palbociclib, and ribociclib) to the endocrine therapy has shown benefits in first line[58, 59] but also after relapse under hormonetherapy[60, 61], regardless of menopausal status.[62] CDK4/6 inhibitors have been approved in 2015.

Another potential therapy is the combination of endocrine drugs with the mammalian target of rapamycin (mTOR) inhibitor, everolimus. The phosphoinositide 3 kinase (PI3K)/Akt/mTOR is involved in resistance to endocrine therapy.[63] In post-menopausal women, the combination of endocrine therapy and everolimus has proved beneficial in progression free survival.[64, 65]

Finally, isoform-specific PI3K inhibitors have been developed for tumours mutated for PI3KCA gene: taselisib in combination with fulvestrant has been shown to prolong progression-free survival among postmenopausal women who had previously been treated with endocrine therapy.[63, 66]

Table 4 presents the selected drugs for breast cancer.

Table 4 – Selected drugs for breast cancer

Drug	Year#	Trade Name	Company$	Mechanism of action
Pertuzumab	2014	Perjeta	Roche	Pertuzumab is a recombinant humanised monoclonal antibody that specifically targets the extracellular dimerization domain (subdomain II) of the human epidermal growth factor receptor 2 protein (HER2)
Trastuzumab emtansine	2014	Kadcyla	Roche	Kadcyla, trastuzumab emtansine, is a HER2-targeted antibody-drug conjugate which contains the humanised anti-HER2 IgG1, trastuzumab, covalently linked to the microtubule inhibitor DM1 (a maytansine derivative) via the stable thioether linker MCC
Palbociclib	2017	Ibrance	Pfizer	Palbociclib is a selective, reversible inhibitor of cyclin-dependent kinases (CDK) 4 and 6
Abemaciclib	2019	Verzenios	Eli Lilly	Abemaciclib is a selective inhibitor of cyclin-dependent kinases 4 and 6 (CDK4 and CDK6)
Ribociclib	2018	Kisqali	Novartis	Ribociclib is a selective inhibitor of cyclin-dependent kinase (CDK) 4 and 6

#year of start reimbursement first indication in Belgium; $ of the originator.

4.1.2 Observational data

4.1.2.1 Patient characteristics, survival and expenditures

Overall reported cases of female metastatic BC (stage IV) has increased over the three incidence periods[o], globally affecting all age groups (Table 5A). No noticeable improvement in observed survival is observed over the three incidence periods (Table 5B). The 3-years observed survival probability did not considerably vary throughout the incidence periods with a value of 47.2% (95%CI 43.1-51.3) in 2004 and 51.2% (95%CI 47-55.1) in 2017 (Table 5C). Similarly, the trend of median survival time has remained rather constant and roughly ranges between 2.5 and 3.1 years (Table 5D).

Also for stage I and II breast cancer, no improvement in overall and relative survival is seen during the studied period. For stage III patients, a slight increase in 4 and 5-year survival is noted, with a 4-year survival of 70.7% (95%CI 68.0-73.3) for patients diagnosed in 2004 and 74.7% (95%CI 71.8-77.3) for patients diagnosed in 2016. Observed 5-year survival was 64.1% (95%CI 61.2-66.8) for patients diagnosed in 2004 and 70.7% (95%CI 67.9-73.3) for patients diagnosed in 2015 (see Appendix).

For the global BC population, yearly oncology drug expenditures has sharply gone up from 2004. While these expenses were about €8.5 million in 2004, they were already more than €80 million in 2008 and peaked at a high of €102 million in 2017 (Table 3A). A slight decrease of expenditures is seen in 2018, but IMA data for reimbursement of drugs is incomplete for that year. The marked rise in expenditures is particularly due to the uptake of trastuzumab and later to other newly reimbursed drugs (e.g. pertuzumab and palbociclib).

The amount of stage IV patients treated with oncology drugs increased from 506 in 2004 to 652 in 2017. The proportion of stage IV patients among all BC also went up from 5.1% in 2004-2008 period to 6.4% in the 2014-2017 period (Appendix). While drug expenses during the first two years after diagnosis were about €4.1 million for patients diagnosed in 2004, this amount abruptly tripled for patients diagnosed in 2014 to €13 million and reached €16 million for patients diagnosed in 2017 (Table 6B). This steep increase corresponds to the reimbursement of pertuzumab that is reimbursed since 2014. The mean cost per stage IV breast cancer patient with drug expenses for the first two years after incidence sharply rose from less than €11 000 before 2014 to €25 000 in 2017 (Table 6C).

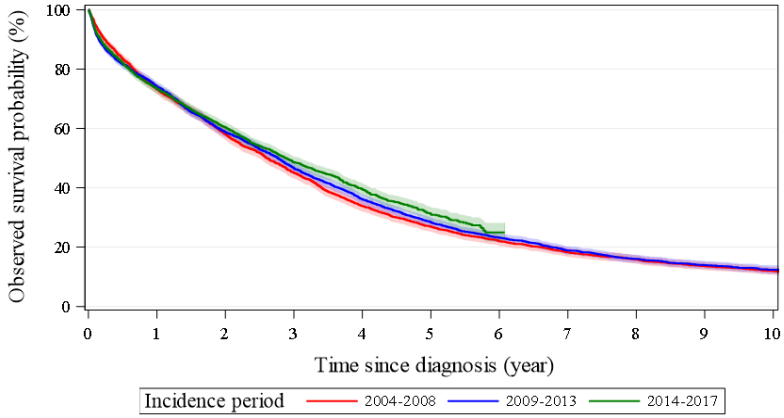
[o] remark: the 3rd incidence period covers 4 years, while the first two incidence periods cover 5 years.

Table 5 – Female breast cancer (2004-2017), combined stage IV (observed survival): A) Patient characteristics; B) Kaplan-Meier graph per incidence period; C) Time trend with incidence year*; D) Median survival time* **

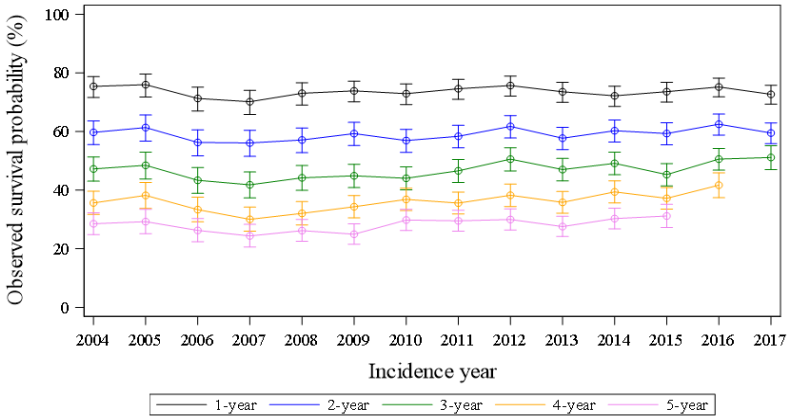
A

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

B

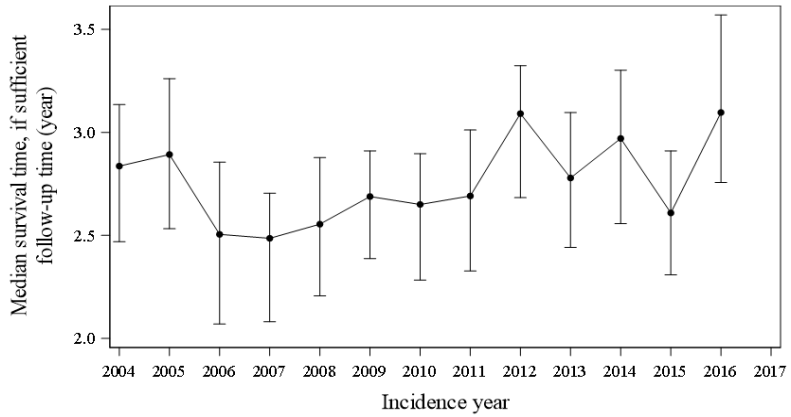


C



Year: 3-y OS [95%CI]
2004: 47.2 [43.1, 51.3]
2005: 48.5 [43.8, 53.0]
2006: 43.4 [38.9, 47.7]
2007: 41.8 [37.4, 46.2]
2008: 44.2 [39.9, 48.4]
2009: 44.9 [40.9, 48.8]
2010: 44.0 [40.1, 47.9]
2011: 46.6 [42.6, 50.4]
2012: 50.6 [46.6, 54.4]
2013: 47.0 [43.1, 50.8]
2014: 49.1 [45.2, 52.9]
2015: 45.3 [41.5, 49.1]
2016: 50.6 [46.8, 54.2]
2017: 51.2 [47.0, 55.1]

D

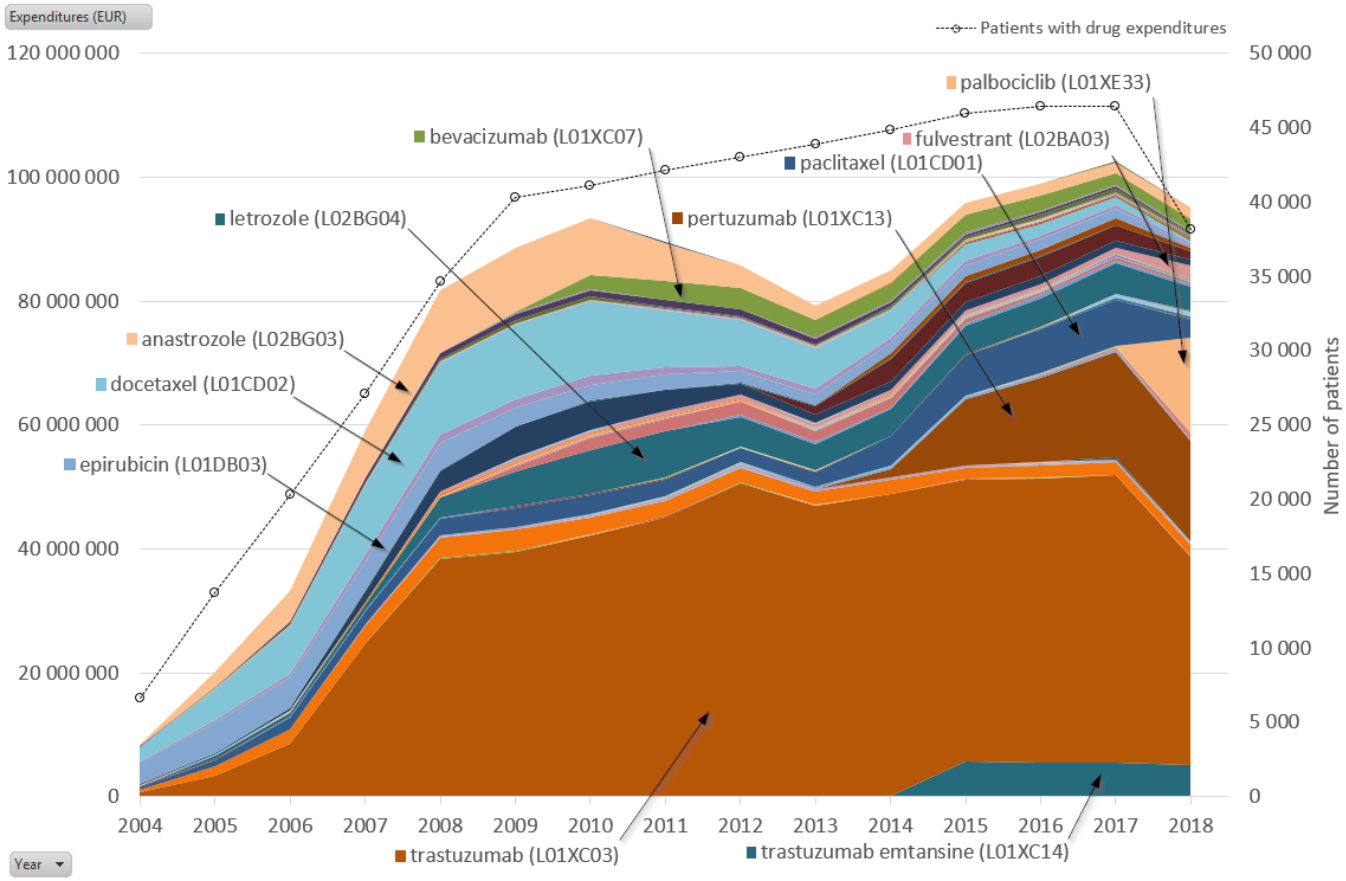


Year: Med. ST [95%CI]
2004: 2.8 [2.5, 3.1]
2005: 2.9 [2.5, 3.3]
2006: 2.5 [2.1, 2.9]
2007: 2.5 [2.1, 2.7]
2008: 2.6 [2.2, 2.9]
2009: 2.7 [2.4, 2.9]
2010: 2.7 [2.3, 2.9]
2011: 2.7 [2.3, 3.0]
2012: 3.1 [2.7, 3.3]
2013: 2.8 [2.4, 3.1]
2014: 3.0 [2.6, 3.3]
2015: 2.6 [2.3, 2.9]
2016: 3.1 [2.8, 3.6]
2017: >3

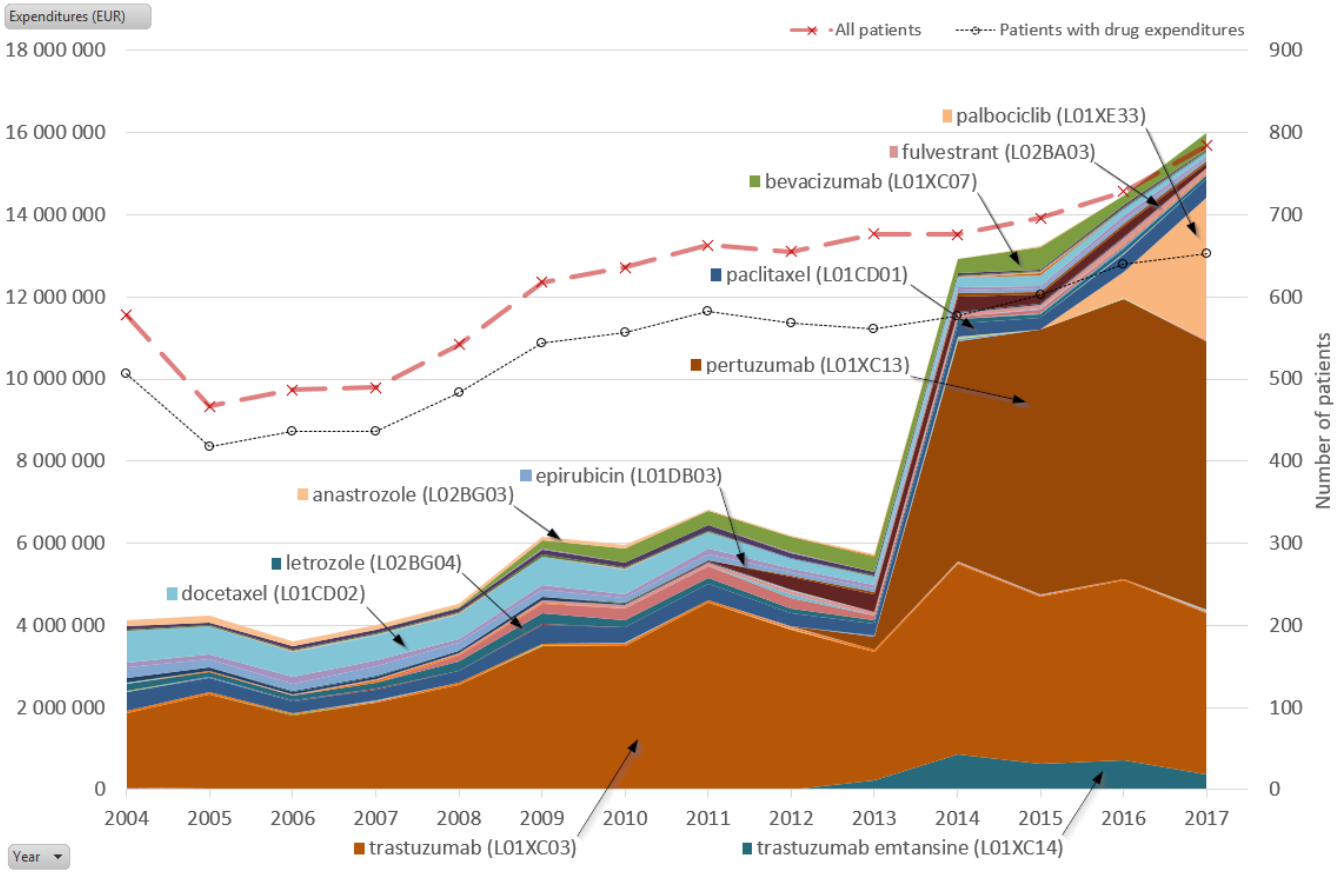
*Med. ST: median survival time; 3-y OS: 3-year observed survival; * the error bars represent the 95%CI. ** When the upper error is not plotted, the upper limit could not be determined with the available follow-up data. Source: BCR.*

Table 6 – Female breast cancer: drug expenditures

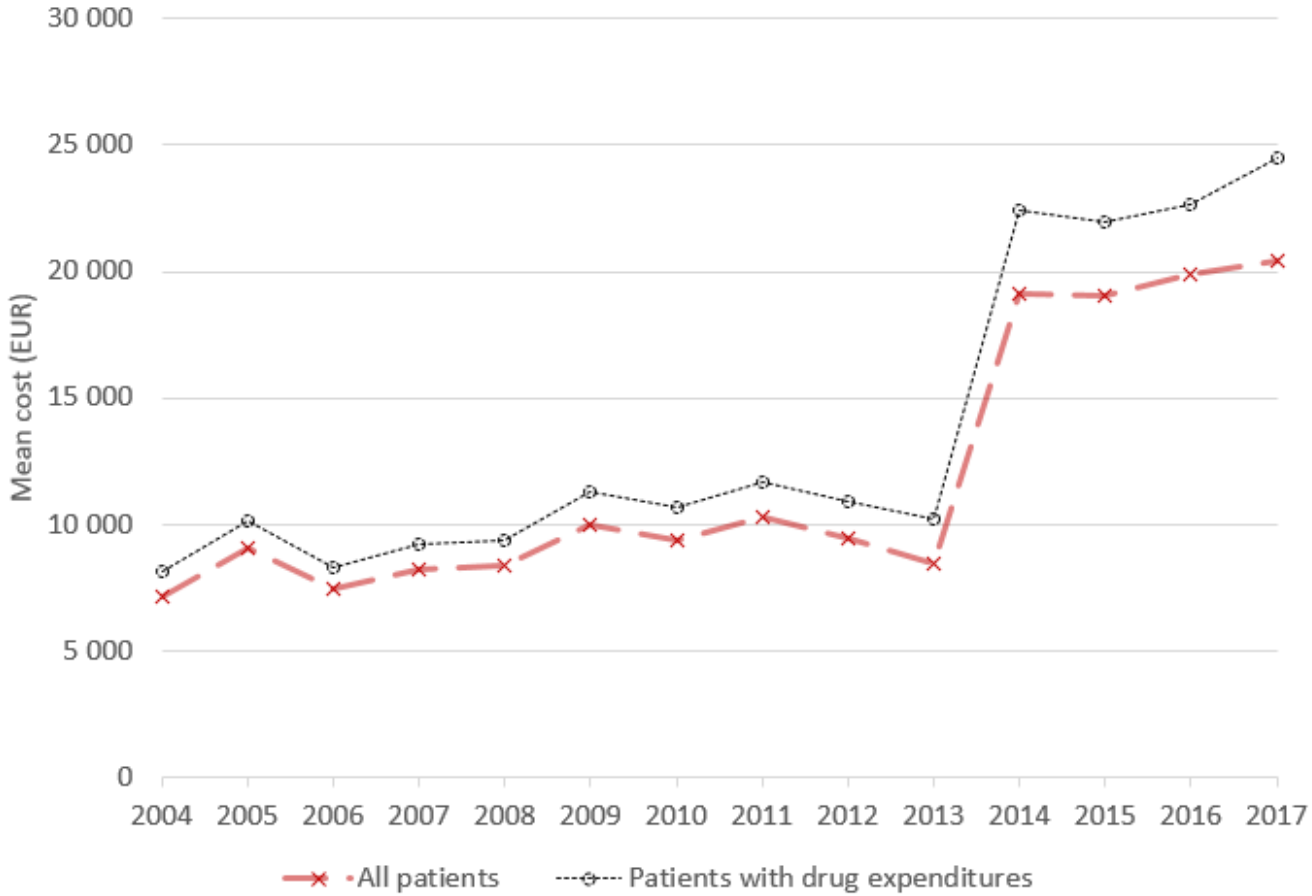
A) Oncological drug expenses per calendar year (all stages)



B) Expenses for the first two years after incidence per incidence year (stage IV)



C) Mean cost per patient for the first two years after incidence per incidence year (stage IV)



Source: BCR-IMA.

4.1.2.2 *Drug uptake for a selection of drugs during the first 5 years after diagnosis*

Pertuzumab is reimbursed in Belgium since 2014 (Table 4). Thirteen percent of stage-IV patients who were diagnosed in 2014 received the molecule during the five-year period after diagnosis (Table 7). Its 5-year uptake rose to 16.7% for the incidence year 2015 and relatively maintained the same level. It reached 16.1% in 2017. However, 5-year follow-up data are not present for the last years in our table.

Trastuzumab emtansine is reimbursed since 2014. Its uptake reached its maximum in the incidence group of 2014 at the high of 7.1% and decreased thereafter to 2.9% in 2017. However, we have to remember that the follow-up period is less than 5 years for the more recent incidence years. Observed numbers in these recent years have thus to be interpreted with caution. Palbociclib has been reimbursed from 2017. Uptake was already 18.4% in the incidence group of 2017. Both other cyclin dependent kinase ribociclib and abemaciclib were reimbursed later in 2018 and 2019, respectively. The uptake of ribociclib remained marginal and abemaciclib has not been used in the studied incidence years.

Uptake during the first five years after diagnoses remained below 5% for all selected drugs in patients with stage I-II-III breast cancer (see Appendix).

Table 7 – Proportion of patients who received at least one dose during 5-year period after diagnosis (breast cancer stage IV)

Drug/incidence year (n)	2004 (578)	2005 (467)	2006 (487)	2007 (490)	2008 (542)	2009 (618)	2010 (636)	2011 (663)	2012$ (655)	2013 (677)	2014 (676)	2015 (696)	2016 (728)	2017 (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. $ IMA data were only available up to the second trimester of 2019 and might have a delay of two years. Five-year follow-up data are thus not 100% complete from incidence year 2012 onwards (see part 3.1.3). # Ribociclib and abemaciclib were reimbursed since 2018 and 2019, respectively. Source: BCR-IMA.*

4.1.3 Medical literature: efficacy

For patients with early HER2-positive BC, in adjuvant and/or neo-adjuvant settings, a clear benefit in overall survival has not been proven for dual anti-HER2 blockade therapy (pertuzumab/trastuzumab) along with chemotherapy compared with single blockade (trastuzumab) and chemotherapy (see 4.1.3.1).[32, 49] This regimen is associated with rather acceptable side-effects. It leads to more hepatic, digestive or skin toxicities but no significant cardiotoxicity.[32]

Regarding stage IV HER2-positive BC, the same dual blockade strategy conjointly with paclitaxel has proved to be beneficial as first-line treatment in terms of overall survival when compared with trastuzumab alone (see 4.1.3.2).[48] The survival gain was 15.7 months in the CLEOPATRA trial.[47]

In second-line treatment, trastuzumab emtansine (T-DM-1) may improve overall survival in comparison with other treatments such as lapatinib (anti HER2) and capecitabine (chemotherapy), but results of the meta-analysis remained inconclusive. TDM-1 was associated with hepatic toxicity and thrombocytaemia but less frequently with gastro-intestinal side-effects (see 4.1.3.3).[67]

Regarding the HER2 negative/HR positive tumours, prolongation of overall survival has been shown by adding cyclin dependent kinase 4/6 inhibitors to endocrine therapy (see 4.1.3.4).[68, 69] However, gastrointestinal and haematologic side effects were more frequently observed. The risk of neutropenia is particularly high.

4.1.3.1 HER2(+) Breast cancer: neo-adjuvant and adjuvant setting (pertuzumab)

Reference + search date	Intervention and comparator + indication	OS	Quality of life	Other outcomes
Yu 2020[32] Search date: December 2018	In patients with HER2-positive early breast cancer (adjuvant and/or neo-adjuvant) Intervention: trastuzumab-containing dual anti-HER(2) therapy (+ chemotherapy) comparator: trastuzumab single-agent anti-HER2 therapy (+ chemotherapy)	trastuzumab + pertuzumab vs trastuzumab HR 0.89 (95%CI 0.66-1.19)		
Wu 2019[49] Search date: April 2018	Patients who undergo neoadjuvant treatment for HER(+) breast cancer Interventions C: chemotherapy P: Pertuzumab T: trastuzumab			Pathologically complete response CTP vs CT: OR 0.41 (95%CI0.20-0.84) CTP vs CP OR 0.33 (95%CI 0.15-0.67) CT vs CP OR 0.78 (95%CI 0.34-1.71) Serious adverse events CTP vs CT

				OR 0.71 (0.23-2.12) CTP vs CP OR 0.82 (95%CI 0.25-2.55) CP vs CT OR 0.87 (95%CI 0.29-2.63)

4.1.3.2 HER2(+) Breast cancer: metastatic disease or locally advanced disease – first line (pertuzumab)

Reference + search date	Intervention and comparator + indication	OS	Quality of life	Other outcomes
Feng 2019[48] Search date: 16 December 2017	Patients with advanced or metastatic HER2-positive breast cancer comparator: trastuzumab + paclitaxel (PT) intervention: pertuzumab + trastuzumab + paclitaxel (PTP)	PTP vs PT: HR 0.68 (95%CI 0.56-0.83)		

4.1.3.3 HER2(+) Breast cancer: metastatic disease or locally advanced disease – second line (pertuzumab, trastuzumab emtansine)

Reference + search date	Intervention and comparator + indication	OS	Quality of life	Other outcomes
Paracha 2020[67] Search data: 3 January 2018 Funded by F. Hoffmann-La Roche AG	HER2-positive locally advanced breast cancer (LABC) with early relapse (within 6 months) following adjuvant therapy, or for HER2-positive unresectable mBC in which patients had progressed after treatment with trastuzumab plus taxane Interventions: trastuzumab emtansine (T-DM1) capecitabine (Cap) lapatinib (Lap) pertuzumab (Per) Trastuzumab (Tras)	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 HR 1.03 (95%CI 0.51-1.82) 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)		

4.1.3.4 HER2(-) Breast cancer: metastatic disease or locally advanced disease

Reference + search date	Intervention and comparator + indication	OS	Quality of life	Other outcomes
Li 2020[68] Search date: 8 April 2019	women of any menopausal status who were 18 years old or older with HR+/HER2− advanced breast cancer (with or without prior chemotherapy, with or without prior endocrine therapy) Intervention: CDK4/6 inhibitor (palbociclib, ribociclib or abemaciclib) + endocrine therapy comparator: endocrine therapy alone	HR 0.79 (95%CI 0.67-0.93) (including 2 studies with palbociclib and 1 with ribociclib)		All grade neutropenia RR14.24 (95%CI 10.91-18.59) Fatigue RR 1.24 (95%CI 1.08-1.41) Nausea RR 1.63 (95%CI 1.44-1.84) Diarrhea RR 1.71 (95%CI 1.23-2.37)
Wang 2019*[69] Search date: unclear	advanced HR+/HER2− breast cancer Intervention: CDK4/6 inhibitors + endocrine therapy comparator: endocrine therapy alone	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)		

** In the SR of Wang et al, no critical appraisal was performed and the details of included studies were not reported but results of the meta-analysis is reported here as the same studies were included as in Li et al. 2020 but with OS results of more trials (5).*

4.1.3.5 Discussion

No improvement of survival was observed observed in Belgium, in spite of a substantial increase of expenditures. The lack of a visible improvement of survival may be explained by several factors. First, .maximum uptake of pertuzumab, trastuzumab emtansine and palbociclib is 16.7%, 7.1% and 18.4% only. Abemaciclib and ribociclib are reimbursed since 2019 and 2018 only, hence follow-up in our report is too short to see a possible effect. In addition, for second line treatment of metastatic breast cancer with pertuzumab or trastuzumab emtansine, no clear survival benefit has been proven. A survival benefit may thus be absent or very limited. If more specific data were available at BCR, an evolution in survival may be seen for HER(+) metastatic breast cancer after the introduction of pertuzumab and trastuzumab emtansine. It must be noted however that the increase in cost per patient would also be much higher than in our current analysis including all patients.

Findings with other countries

In the Netherlands, a nation-wide population-based study that followed-up metastatic BC patients through the national cancer registry reported an increment of median survival over time: 1.42 years in the period 1995 - 1999 and 1.95 years in the period 2005-2008. The improvement was most pronounced for patients younger than 50 years. The increased efficacy of chemotherapy and the introduction of targeted therapy are the most likely explanations for this improvement (targeted therapy was administered only in the second studied period).[70] Other authors in the Netherlands reported an increase of survival in all stages from 1990 to 2014 but survival of

stage IV turned to remain poor. At ten-year, a slight increase from 6 to 9% was noted for stage IV patients.[71]

In Australia, a population-based study that followed-up patients through the national cancer registry from 2000 to 2014, reported a decreased risk of death overtime: for all stages, compared with the reference period (2000-2004), the adjusted Hazard Ratio for death was 0.75 (95%CI 0.67 to 0.83) in 2005–2009, whereas it was 0.57 (95%CI 0.48 to 0.67) for women diagnosed in 2010–2015.[72]

Population-based data in Germany (region of Augsburg) reported trends in survival of cancer in the whole region-population from 2005 to 2013. A substantial rise for 3 year-relative survival probability was reported for BC. The 3-year relative survival probability among patients (all stages) diagnosed in 2005-2007 was 89.9% (95%CI 87.9-92.0), 92.7% (95%CI 91.0-94.6%) among patients diagnosed in 2008-2010 and 95% (95%CI 93.3-96.7%) for patients diagnosed in 2011-2013. Nevertheless, survival was not analysed according to the stage of disease.[73]

In Canada, a decrease in mortality rates was observed in patients diagnosed between 1992 and 2010.[74] However, the analysis did not provide information on the stage of the disease nor the treatments. More recent data specifically identified patients diagnosed with HR-positive/HER2 negative metastatic BC across 3 time cohorts (2003-2005, 2007-2009, and 2011-2013) in the province of British Colombia. Among those selected patients, 90% received at least 1 line of systemic therapy for metastatic disease (mainly hormone therapy and chemotherapy). None of the patients in our cohort received a CDK inhibitor. Survival did not improve over the three selected periods. As such, median survival was 24.4 months (95%CI 21.6-27.3) for patients diagnosed in 2003-2005, 23.1 months (95%CI 20.7-25.5) for those diagnosed in 2007-2009 and 23.1 months (95%CI 20.6-25.6) for those diagnosed in 2011-2013.[75]

Limitations

- Data over particular types of tumour such as triple negative BC or oligometastatic disease were not available in our analysis.
- Moreover, there is still limited data on the impact of late changes in systemic treatment because many molecules have recently come to the market. Longer-time follow-up might presumably reveal further improvement of survival for patients diagnosed in 2016-2017, particularly the impact of drugs such as CKD inhibitor. No data on abemaciclib and ribociclib has been reported yet as there is no data on the uptake during the studied period.
- Since clinical trials mostly compare two treatments, integrating the efficacy of all tested regimens remains difficult as often head-to-head comparison are lacking.[76]
- Apart from the potential effect of new drugs, changes in imaging practices enabling the detection of metastasis could also impact survival.
- Bisphosphonate therapy that may improve survival in early BC stages, was not included in the analysis.[77] Information on other drug expenditures outside of our selection (e.g. gosereline) are also not included in our analysis.

4.1.4 Economic literature: cost-effectiveness

For more information about the economic evaluations in the identified HTA reports, we refer to Appendix.

Confidential prices

In all evaluations, there are confidential price discounts for the intervention and/or the included comparators. The use of confidential prices makes it impossible for external researchers to calculate exact ICERs. In all identified reports, the exact ICER used for decision making is unknown. In cases where there are also discounts for the comparator or subsequent treatments, even the ICER based on the company's submission is not the ICER used for decision making. For example, in an assessment of

abemaciclib, 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).[78] Exceptionally, in an evaluation of ribociclib, the discount for one of the comparators was also included in the company's confidential analysis because the marketing authorization for the intervention and comparator drug was both held by the same company.[79]

Quality of life

In some identified studies, no generic utility instrument is used in the underlying trial.[80-82] In other studies, QoL is measured in the underlying trial with a generic utility instrument (EQ-5D).[78, 83-88] Unfortunately, also in these studies, the calculation of QALYs gained is confronted with some difficulties.

First, in some studies, a head-to-head comparison of the intervention and comparator used in the economic evaluation is lacking.[78, 84, 86, 87] In one of these studies, the reviewers mention they have "a general preference for the treatment-specific utility estimates from MONARCH 3, because they reflect benefits and harms of treatments directly assessed by patients. But equivalent treatment-specific utilities are not available for all comparators."[89]

Second, another limitation is that utilities are only measured up to disease progression.[83, 85] In an evaluation of pertuzumab, "the company state in the cost-effectiveness section … that "the schedule of EQ-5D administration was designed to capture differences in QoL across the various stages of disease, not between treatment arms". This same schedule was used for all HRQoL measures in the APHINITY trial.[90] The rationale for this approach is unclear to the ERG."[91] Indeed, "the EQ-5D questionnaire was not administered to patients who presented with disease progression (either non metastatic or metastatic) in the APHINITY study."[91] As a result, assumptions need to be made to assess the (long-term) impact on QoL and QALYs. Also in an evaluation of palbociclib, "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."[92]

Finally, we note that none of the studies fully transparently presents the utility measurements, i.e. utilities per treatment arm and for all moments in time it was measured. Only general statements are made such as in an evaluation of ribociclib where it is mentioned that "quality of life scores showed no clinically meaningful changes from baseline and no meaningful differences between treatment arms."[93]

Uncertainty & influential parameters

The modeled utility parameters are important variables with a major impact on the ICERs in several analyses.[78, 80, 84, 85, 87] Next to the uncertainties on the impact on QoL (see above), the impact on overall survival is the greatest uncertainty in all identified evaluations.[78, 80-88]

First, there is the problem of a lack of head-to-head trials.[78, 82, 84, 86, 87] For example, in an evaluation of abemaciclib, "The cost-effectiveness estimates are based on an indirect comparison. Also, survival data are incomplete. Therefore the cost-effectiveness estimates are highly uncertain."[78] Or in another example of ribociclib: "the results of an indirect comparison of ribociclib and fulvestrant with exemestane and everolimus are very uncertain,"[87] which results in very uncertain cost-effectiveness estimates.

In addition, there is also the remark that immature data are used in a number of analyses.[78, 81, 83, 86-88] For example, in an evaluation of pertuzumab, "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."[81] In some cases, there is an explicit request for more mature data. In an evaluation of palbociclib, the reviewers mention that "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."[85] In an evaluation of abemaciclib, "the ERG is concerned with the high degree of uncertainty embedded in the OS analysis of relative treatment effectiveness of ABE-FUL compared with all other treatments. Given the immaturity of OS data in MONARCH 2, the ERG advises caution when interpreting all analysis undertaken involving these data."[78] "more mature data on the effect of abemaciclib plus fulvestrant on OS are required."[78] Also in a 2019 evaluation of ribociclib, "ribociclib with fulvestrant increases progression-free survival compared with fulvestrant alone but overall survival data are immature,"[87] and "more mature data on the effect of ribociclib plus fulvestrant on OS are required."[79] Similar remarks are made in a 2017 evaluation of this product where it is mentioned that "the overall survival data from 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."[88]

Next, the link between surrogate and final outcomes is questioned. For example, in an evaluation of pertuzumab, "the extent to which invasive disease-free survival translates into long-term overall survival benefit is not known."[83] Or in an assessment of palbociclib, "an assumption of overall survival gain equal to the progression-free survival gain is not supported by any evidence."[85] In the 2019 evaluation of ribociclib: "the economic analyses still have some remaining uncertainty in the results, mainly because of the potentially implausible assumption of a full surrogacy between PFS and OS. Immature overall survival data in the first-line model make this difficult to assess fully."[79] "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."[79] In the 2017 evaluation of ribociclib, the reviewers refer to another analysis of palbociclib to make their point: "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."[93]

The intervention's acquisition cost also has a major impact on the ICERs. For example, in an evaluation of pertuzumab, the "acquisition cost has a notable impact on the generated ICER values."[83] Related to this, the treatment duration or time to treatment discontinuation was also an important variable which was uncertain in analyses of palbociclib,[84] abemaciclib,[78] and ribociclib.[87, 88]

Finally, also costs of subsequent treatments impact an intervention's cost-effectiveness.[78, 81, 84, 88] For example, in an assessment of palbociclib, "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."[84] In contrast, with the discounts for subsequent treatments, "most of the plausible estimates are likely to be higher than what NICE normally considers an acceptable use of NHS [National Health Services] resources."[84] Also in an assessment of pertuzumab, "the committee raised concerns about the company's precise drug costs. The company used list prices for the CDF [Cancer Drugs Fund] -funded treatments, but the NHS may be paying lower prices for these drugs which would increase the ICER."[81]

Results

The above mentioned price negotiations and uncertainties have their impact on the transparency and reliability/uncertainty of the results from the underlying economic evaluations. There is no single assessment where the authors conclude an intervention being cost-effective if the official list prices are used. In all dossiers, confidential prices are negotiated.

The ICERs are as follows (see more details in appendix):

- **Pertuzumab**
  - HER2-positive early stage breast cancer:[83]

    "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."[83]

    "The ERG's base case ICER for the node-positive population was calculated to be £60 679 per QALY gained."[91]

    "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."[83]
  - HER2-positive metastatic breast cancer:[80]

    "The ERG considers that a revised ICER of £******* per QALY gained best reflects the cost effectiveness of pertuzumab use in this population."[94]
  - HER2-positive, locally advanced, inflammatory or early-stage breast cancer at high risk of recurrence:[81]

    "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."[81]
- **Trastuzumab emtansine**
  - HER2-positive, unresectable, locally advanced or metastatic breast cancer, who previously received trastuzumab and a taxane, separately or in combination:[82]

    No information is provided on the ICERs with price discounts for the intervention. "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."[82]
- **Palbociclib**
  - Hormone receptor-positive, HER2-negative advanced breast cancer:[84]

    The exact ICERs are commercial in confidence and cannot be reported. "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."[84]

    "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"[84]
  - Previously untreated, hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer:[85]

    Using list prices, "the company's base case cost effectiveness results [£150 869 per QALY gained] and the results generated following the application of either of the ERG's combined revision scenarios [£132 872 & £213 206 per QALY gained], are all considerably higher than the range normally considered acceptable by NICE."[92]

    "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."[85]

- **Abemaciclib**
  - Advanced hormone receptor-positive, HER2-negative breast cancer after endocrine therapy:[78]

    "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."[78]
  - Previously untreated, hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer:[86]

    "This version of the model (with list prices for all drugs) gave similar results to the company base case: an ICER of just under £200 000 per QALY gained for abemaciclib + NSAI compared with NSAI alone, compared with about £250 000 in the company's base case."[89]

    "The committee noted that there is no evidence of a difference between the 3 treatments … and that it is appropriate to consider a class effect for the CDK 4/6 inhibitors … . It concluded that, assuming the clinical effectiveness of abemaciclib, palbociclib and ribociclib is comparable, a cost-comparison approach is preferred."[86]

    "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."[86]

- **Ribociclib**
  - Hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer who have had previous endocrine therapy:[87]

    Results are confidential. "The most plausible ICERs for ribociclib with fulvestrant are uncertain with very small QALY gains"[87] "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."[87]
  - Previously untreated, hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer:[88]

    "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."[88]

Elements such as the absence of a head-to-head comparison, the use of immature data or the lack/uncertainty around QoL measurements (see above) means that the cost-effectiveness cannot always be determined with great certainty. Exact ICERs used by decision makers are not presented since they are considered as commercial in confidence.

No information on incremental costs or effects is presented in many analyses.[78, 81-84, 87] In others, only information on incremental costs is kept confidential.[80, 88] This confidentiality complicates any external assessment and interpretation of results. For example, in an assessment of pertuzumab, the biosimilar discount is also taken into account.[83] However, because the costs and incremental costs are presented as being confidential, it is not clear whether this discount is also taken into account in the comparator arm (which should be the case to make an appropriate comparison).

Exceptionally, in an evaluation of pertuzumab, the reviewers refer to lower ICER threshold values because of the uncertainty in the clinical evidence and cost-effectiveness: “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. … 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.”[83]

In contrast, often higher ICERs are accepted under the argument that the so-called ‘end-of-life’ criteria are met. In an evaluation of pertuzumab, this criteria was not met, but even then, a ‘special consideration’ was made: “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.”[80] “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.”[80] “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.”[80] and finally, “the committee accepted that the ICER, taking into account the commercial access arrangement, provides for an acceptable use of NHS resources.”[80]

In the identified evaluations, often interventions for which the ICERs are above the range that NICE considers a cost-effective use of resources, are recommended for the Cancer Drugs Fund:

- In the evaluation of trastuzumab emtansine, the results of the first evaluation (without discount) indicate that “the ERG's base-case ICER was … £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.”[82] In a second analysis incorporating the patient access scheme, there was “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.”[82] In a third analysis, after accepting the criteria for end-of-life consideration, “the ICER incorporating the patient access scheme remained well above the range that could be considered a cost-effective use of NHS resources.”[82] While finally, in the analysis for the Cancer Drugs Fund reconsideration, “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.”[82]
- In an evaluation of palbociclib, the intervention could not be recommended for routine use in the NHS because the plausible estimates are likely to be higher than what NICE normally considers an acceptable use of NHS resources.[84] Nevertheless, “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”[84]
- Also in an evaluation of abemaciclib,[78] the ICERs for abemaciclib plus fulvestrant compared with each of the selected comparators were substantially above what could be considered a cost-effective use of NHS resources. Nevertheless, “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."[78]

- Similarly, in an evaluation of ribociclib, "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."[87] But, "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."[87]

Finally, we remark that intervention's ICERs are very dependant on the comparator being used. For example, in an evaluation of abemaciclib, the intervention is considered a cost-effective use of NHS resources by comparing the intervention with palbociclib or ribociclib. In contrast, the resulting ICERs of these interventions (with list prices) in comparison with a non-steroidal aromatase inhibitor (NSAI) was just under £200 000 per QALY gained for abemaciclib + NSAI compared with NSAI alone.[86]

4.1.5 Summary

Observational data

- Overall survival has not changed for stage IV breast cancer between 2004 and 2017. The 3-years observed survival probability varied between 47.2% (95%CI 43.1-51.3) in incidence year 2004 and 51.2% (95%CI 47.0-55.1) in incidence year 2017. Median survival roughly maintained at the same level and ranged between 2.5 and 3.1 years.
- For all stages, yearly oncology drug expenditures forcefully rose from €8.5 million in 2004 to reach €102 million in 2017.
- For stage IV breast cancer, drug expenditures during the first two years after diagnosis increased over the years from €4.1 million in 2004 to €16 million in 2017.
  - This rise is mainly ascribed to the reimbursement of pertuzumab in 2014
  - The number of patients with stage IV breast cancer with oncology drug expenditures went up overtime: 506 in 2004 to 652 in 2017. This does not explain the major increase in expenditures.
  - The mean cost per stage IV breast cancer patient with drug expenses for the first two years after incidence promptly increased from less than €11 000 before 2014 to €25 000 in 2017
- For stage IV patients, five-year uptake of trastuzumab progressively grew and reached 16.7% in the incidence year 2015. It relatively leveled off afterwards but 5-year follow-up data are still not complete. The uptake of trastuzumab emtansine peaked at 7.1% in the incidence group of 2014 and decreased down to 2.9% in 2017 but the observational 5 years period has not yet been completed for the latter group. Palbociclib has been reimbursed from 2017. Its uptake peaked reached 18.4% in the incidence-group of 2017. Ribociclib and abemaciclib have been recently reimbursed. Uptake of ribociclib was very low and abemaciclib has not been used in the studied incidence years
- For stages I, II, III, the uptake during the first five years after diagnoses remained below 5% for all selected drugs.

Medical literature

- For HER2+ breast cancer:
  - In adjuvant and neo-adjuvant setting, dual anti-HER2 blockade therapy (pertuzumab-trastuzumab) in combination with chemotherapy has not shown a significant survival benefit in HER2 positive breast cancer.
  - In stage IV, first-line treatment with dual anti-HER2 blockade therapy (pertuzumab-trastuzumab) along with paclitaxel improves overall survival in clinical trials. .
  - In stage IV, there is no proof that second-line treatment with trastuzumab emtansine improves overall survival compared with lapatinib and capecitabine.
- For HER2- /HR+ breast cancer:
  - Use of Cyclin Dependent Kinase 4-6 inhibitors added to endocrine therapy resulted in better overall survival in clinical trials.

Economic literature

- In all identified evaluations, there are confidential price discounts for the intervention and/or the included comparators. The use of confidential prices makes it impossible for external researchers to calculate exact ICERs. In all identified reports, the exact ICER used for decision making is unknown. In cases where there are also discounts for the comparator or subsequent treatments, even the ICER based on the company's submission is not the ICER used for decision making.
- In three out of ten evaluations, no generic utility instrument was used in the underlying trial. In seven out of 10 evaluations, QoL was measured with a generic utility instrument in the underlying trial. Unfortunately, four of these underlying trials were no head-to-head comparisons. Both the lack of head-to-head comparisons and the lack of measured utilities make the calculation of QALYs difficult and surrounded with major uncertainty.
  - In some trials where QoL is measured, the questionnaire was not administered anymore after disease progression. As a result, assumptions need to be made to assess the (long-term) impact on QoL and QALYs.
  - None of the studies fully transparently presents the utility measurements, i.e. utilities per treatment arm and for all moments in time it was measured. Only a general statement is made. For example, in one of the evaluations, the following is mentioned: "quality of life scores showed no clinically meaningful changes from baseline and no meaningful differences between treatment arms."
- Next to the large uncertainty on the modelled utility parameters, the impact on overall survival is identified as the greatest uncertainty in all evaluations. This large uncertainty is mainly linked to both the lack of head-to-head trials (in five evaluations) as well as the use of immature data (in six evaluations).
  - The link between surrogate and final outcomes is questioned. The extent to which invasive disease-free survival translates into long-term overall survival benefit is not known. In one of the assessments, one of the main concerns of the ERG was the assumption in the economic model that any gain in PFS is 100% translated into OS gain. This was in contrast with the results 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.[93]
- Related to the cost of the initial treatment, the treatment duration or time to treatment discontinuation also have an important impact on ICERs.
- Elements such as the absence of a head-to-head comparison, the use of immature data or the lack/uncertainty around QoL

measurements (see above) means that the cost-effectiveness cannot always be determined with great certainty.

- There is no single assessment where the authors conclude an intervention being cost-effective if the official list prices are used. In all dossiers, confidential prices are negotiated. Exact ICERs used by decision makers are not presented since they are considered as commercial in confidence.
- The choice of the comparator can have a major impact on the calculated ICER. In one case (TA563), abemaciclib is considered a cost-effective use of NHS resources by comparing the intervention with palbociclib or ribociclib. In contract, the ICER was almost £200 000 per QALY gained when the intervention (with list price) was compared with a non-steroidal aromatase inhibitor (NSAI).
- Exceptionally, in one of the evaluations, the reviewers explicitly refer to lower ICER threshold values because of the uncertainty in the clinical evidence and cost-effectiveness: "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."[83]
- More often, relatively high ICERs that are in excess of what is considered to be a cost-effective use of NHS resources, are accepted under the argument of the so-called 'end-of-life' criteria that are met. In one case, these criteria were not met, but 'special consideration' was called upon to accept the higher ICER. In other cases, interventions with relatively high ICERs above the range that NICE considers a cost-effective use of resources, are recommended for the Cancer Drugs Fund.

4.2 Chronic Myeloid Leukaemia

4.2.1 Introduction

Chronic myeloid leukaemia (CML) is a rare form of cancer with 158 new diagnoses in Belgium in 2018 (source: BCR). CML is a haemopoietic stem cell disorder characterised by the reciprocal translocation between the long arms of chromosomes 9 and 22. The abnormal chromosome 22 was first observed in Philadelphia and is hence often called the Philadelphia chromosome. This translocation results in the juxtaposition of v-ABL oncogene and the BCR housekeeping gene leading to the production of the oncogene BCR-ABL1 gene. This fusion tyrosine kinase is susceptible to drug targeting.[95]

Before the development of tyrosine kinase inhibitors, the median survival was 5-7 years.[95] Currently, prognosis is rather good, with a 5-year observed survival of 84.5% for patients diagnosed in 2015 (source: BCR).

Historically, CML was treated with interferon α and possibly cytarabine or allogenic stem cell transplantation.[95] Imatinib was the first tyrosine kinase inhibitor (TKI) used for the treatment of CML. It is reimbursed in this indication since 2004. Since 2007-2008, the two second-generation tyrosine kinase inhibitors nilotinib and dasatinib are also reimbursed in Belgium, first as second-line therapy and later as first-line therapy. Bosutinib (second-generation TKI) and ponatinib (third-generation TKI) are reimbursed since 2014 and 2016 respectively for patients who are resistant to other TKIs. TKIs are oral and administered daily and induce their maximum effect gradually.[95] This means patients often receive treatment during several years.

Drugs selected for CML are listed in Table 8.

Table 8 – Drugs selected for CML

Drug	Year#	Trade Name$	Company$	Mechanism of action
imatinib	2002	Glivec	Novartis	small molecule protein-tyrosine kinase inhibitor that inhibits the activity of the Bcr-Abl tyrosine kinase (TK), as well as several receptor TKs
nilotinib	2008	Tasigna	Novartis	inhibitor of the ABL tyrosine kinase activity of the BCR-ABL oncoprotein both in cell lines and in primary Philadelphia-chromosome positive leukaemia cells.
dasatinib	2007	Sprycel	Bristol-Myers Squibb	inhibits the activity of the BCR-ABL kinase and SRC family kinases
bosutinib	2014	Bosulif	Pfizer	Bosutinib is a kinase inhibitor. Bosutinib inhibits the abnormal BCR-ABLkinase that promotes CML.
ponatinib	2016	Iclusig	INCYTE Bioscience	Ponatinib inhibits the tyrosine kinase activity of ABL and T315I mutant ABL

4.2.2 Observational data

4.2.2.1 Patient characteristics, survival and expenditures

Patient characteristics of patients with newly diagnosed CML did not change substantially over the years (Table 9A).

An improvement in overall survival and relative survival over the years was seen. Survival probability 3 years after diagnosis increased from 75.2% (95%CI 66.8-81.8) for patients diagnosed in 2004 to 88.7% (95%CI 81.9-93.0) for patients diagnosed in 2017 (Table 9C). Five-year overall survival increased from 69.8% (95%CI 61.0-76.9) in the 2004 cohort to 84.5% (95%CI 77.7-89.4) in the 2015 cohort. An additional analysis comparing observed survival before and after the introduction of dasatinib and nilotinib (cut-off point 2010) shows a better survival for patients diagnosed after 2010 (Figure 3).

Median survival was already 14.3 years for patients diagnosed in 2004, hence follow-up was insufficiently long to see a possible evolution over the years (Table 9D).

For the Flemish region, data on incidence are available from the year 2000 onwards. The biggest improvement in observed survival was seen between 2000-2003 and 2004-2008 (Table 10B). Three-year observed survival was 56.6% (95%CI 45.3-66.5) for patients diagnosed in 2000, 75.4% (95%CI 63.4-83.9) for patients diagnosed in 2004 and 86.0% (95% CI 75.5-92.2) for patients diagnosed in 2017 (Table 10C). Median survival was 6.3 years for the 2000 cohort and more than 12 years for patients diagnosed in 2004 (or later) (Table 10D).

Overall drug expenditures increased steadily from about €1.5 million to more than €23 million over the period 2004-2016. Over this period, the number of CML patients being treated with oncology drugs during that calendar year increased from about 100 to almost 800 patients due to the long-term treatment.

When only looking at the expenditures the first two years after diagnosis, the increase is less steep (from almost €5 million in 2004 up to €10 million in 2015 and then slightly decreasing to less than €7 million in 2017.

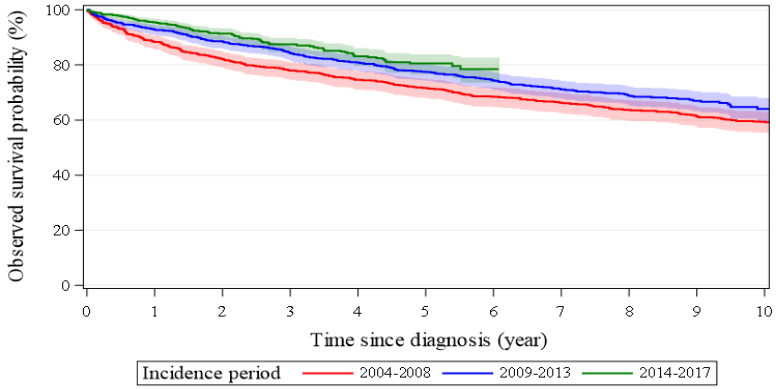
Mean cost for the first two years after diagnosis per patient who received any oncolytic drugs was €41 000 in 2004, increased to €64 500 in 2015, and then decreased to less than €39 000 in 2017.

Table 9 – Chronic myeloid leukaemia (2004-2017) (observed survival): A) Patient characteristics; B) Kaplan-Meier graph per incidence period; C) Time trend with incidence year*; D) Median survival time* **

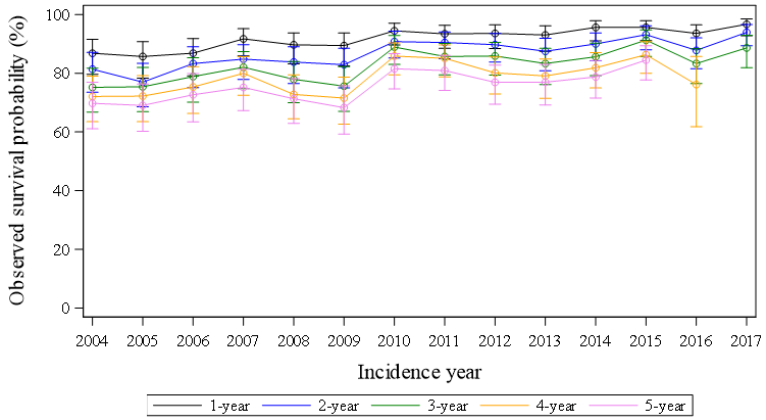
A

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

B

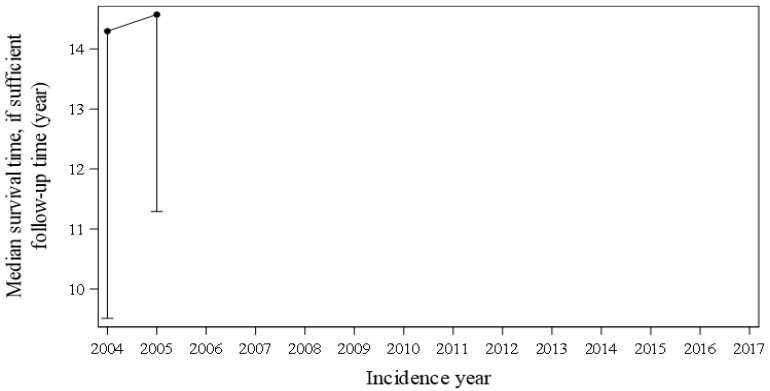


C



Year: 3-y OS [95%CI]
2004: 75.2 [66.8, 81.8]
2005: 75.4 [66.9, 82.0]
2006: 78.9 [70.2, 85.3]
2007: 82.1 [74.8, 87.4]
2008: 77.9 [70.0, 84.0]
2009: 75.6 [67.0, 82.3]
2010: 88.9 [83.0, 92.9]
2011: 85.7 [79.4, 90.2]
2012: 85.9 [79.4, 90.5]
2013: 83.3 [76.1, 88.5]
2014: 85.6 [79.2, 90.2]
2015: 91.3 [85.8, 94.8]
2016: 83.3 [76.5, 88.3]
2017: 88.7 [81.9, 93.0]

D



Year: Med. ST [95%CI]
2004: 14.3 [9.5, .]
2005: 14.6 [11.3, .]
2006: >14
2007: >13
2008: >12
2009: >11
2010: >10
2011: >9
2012: >8
2013: >7
2014: >6
2015: >5
2016: >4
2017: >3

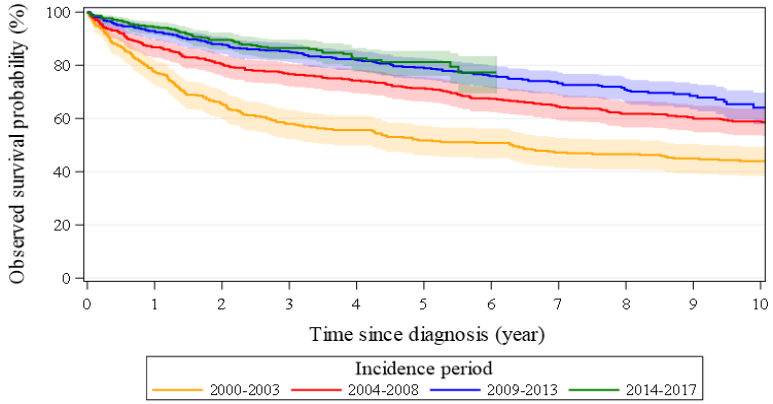
*Med. ST: median survival time; 3-y OS: 3-year observed survival; * the error bars represent the 95%CI. ** When the upper error is not plotted, the upper limit could not be determined with the available follow-up data. Survival results based on small number of persons initially at risk (N<35) can be too variable to be practically meaningful and are therefore not reported. Source: BCR.*

Table 10 – Chronic myeloid leukaemia Flanders (2000-2017) (observed survival): A) Patient characteristics; B) Kaplan-Meier graph per incidence period; C) Time trend with incidence year*; D) Median survival time* **

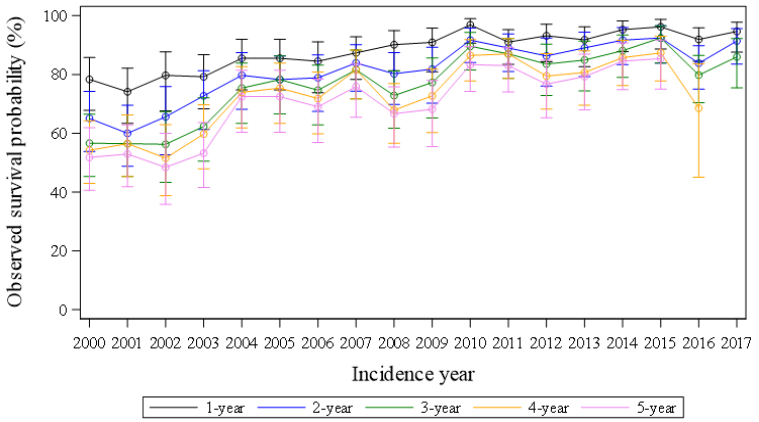
A

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

B

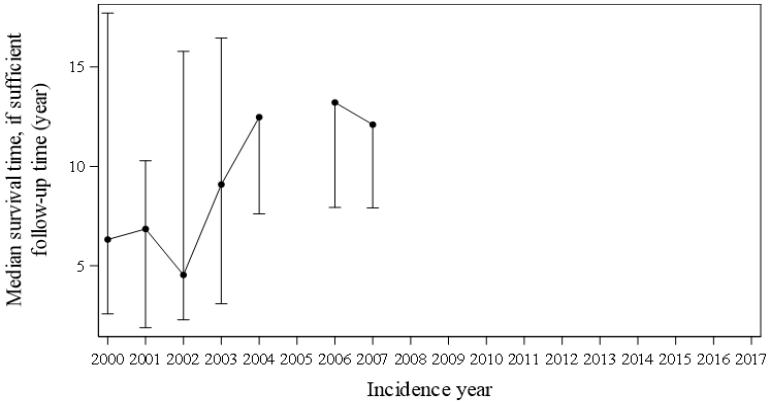


C



Year: 3-y OS [95%CI]
2000: 56.6 [45.3, 66.5]
2001: 56.5 [45.3, 66.2]
2002: 56.3 [43.3, 67.4]
2003: 62.3 [50.5, 72.1]
2004: 75.4 [63.4, 83.9]
2005: 78.3 [66.6, 86.3]
2006: 74.6 [62.8, 83.2]
2007: 81.6 [71.7, 88.3]
2008: 72.8 [61.7, 81.2]
2009: 77.3 [65.2, 85.6]
2010: 89.6 [81.5, 94.3]
2011: 87.0 [78.7, 92.2]
2012: 83.6 [72.9, 90.3]
2013: 84.9 [74.4, 91.3]
2014: 88.1 [79.0, 93.4]
2015: 92.4 [83.9, 96.5]
2016: 79.8 [70.4, 86.5]
2017: 86.0 [75.5, 92.2]

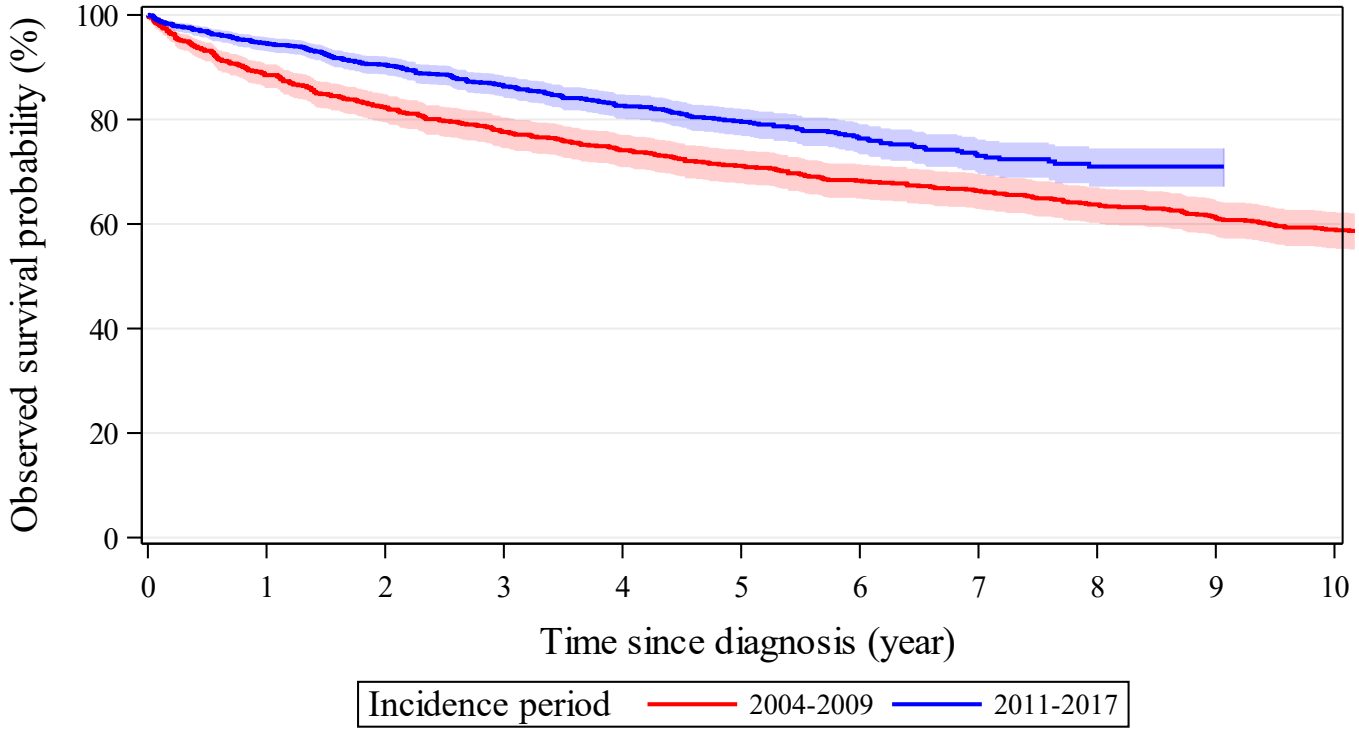
D



Year: Med. ST [95%CI]
2000: 6.3 [2.6, 17.7]
2001: 6.8 [1.9, 10.3]
2002: 4.5 [2.3, 15.8]
2003: 9.1 [3.1, 16.5]
2004: 12.5 [7.6, .]
2005: >15
2006: 13.2 [7.9, .]
2007: 12.1 [7.9, .]
2008: >12
2009: >11
2010: >10
2011: >9
2012: >8
2013: >7
2014: >6
2015: >5
2016: >4
2017: >3

*Med. ST: median survival time; 3-y OS: 3-year observed survival; * the error bars represent the 95%CI. ** When the upper error is not plotted, the upper limit could not be determined with the available follow-up data. 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. Source: BCR.*

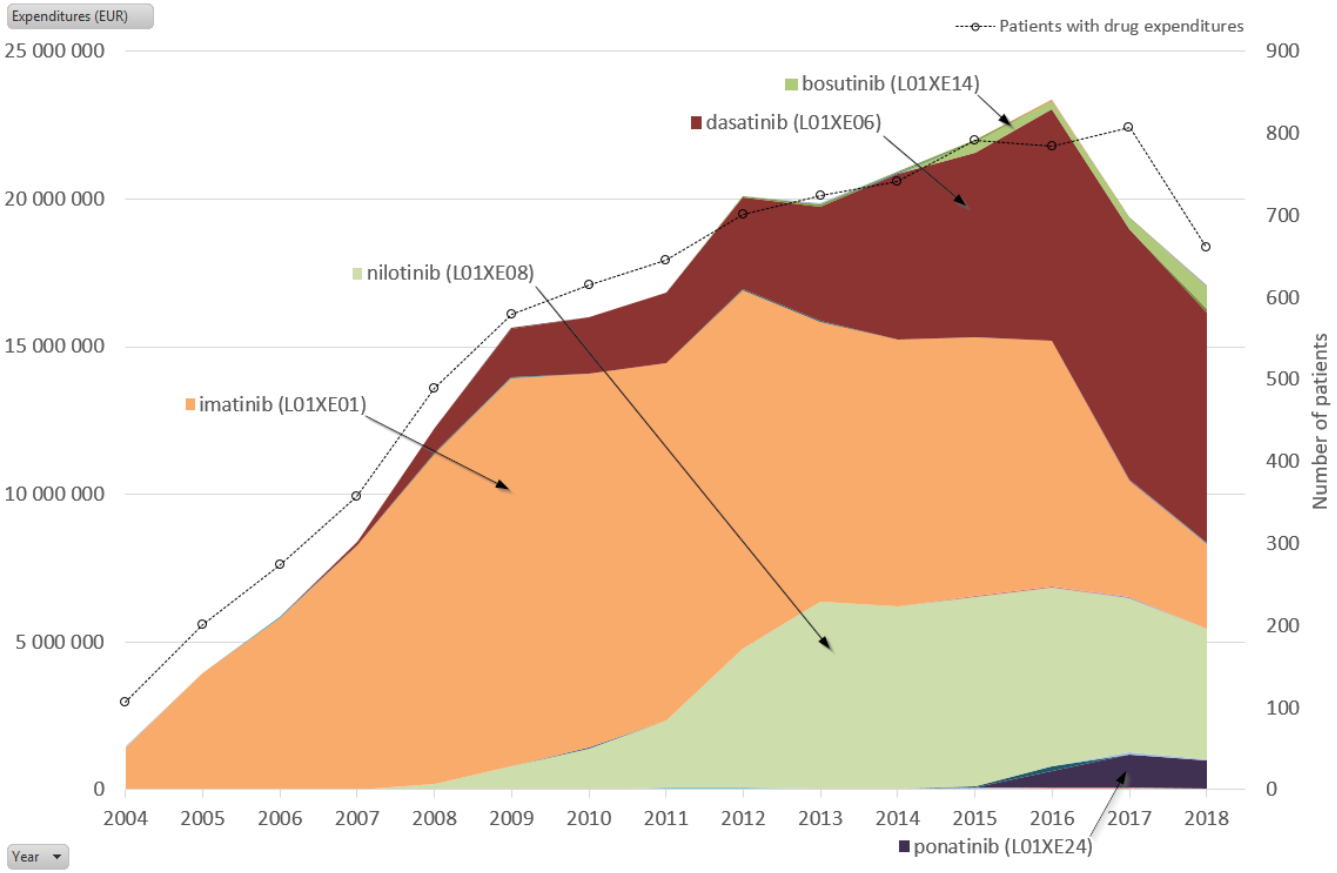
Figure 3 – Chronic myeloid leukaemia (2004-2017) (observed survival): Kaplan-Meier graph 2004-2009 vs 2011-2017



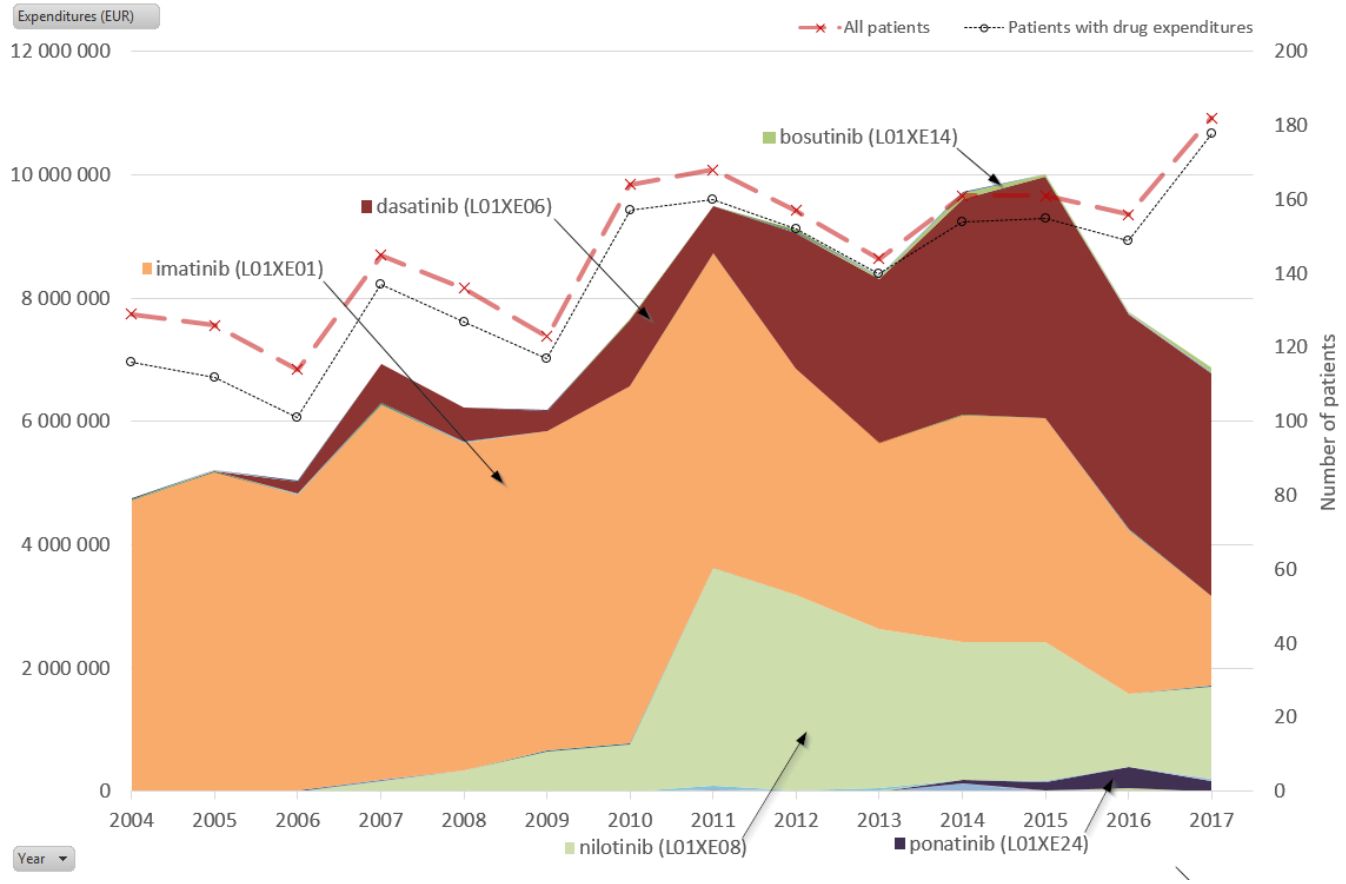
Source: BCR.

Table 11 – Chronic myeloid leukaemia: drug expenditures

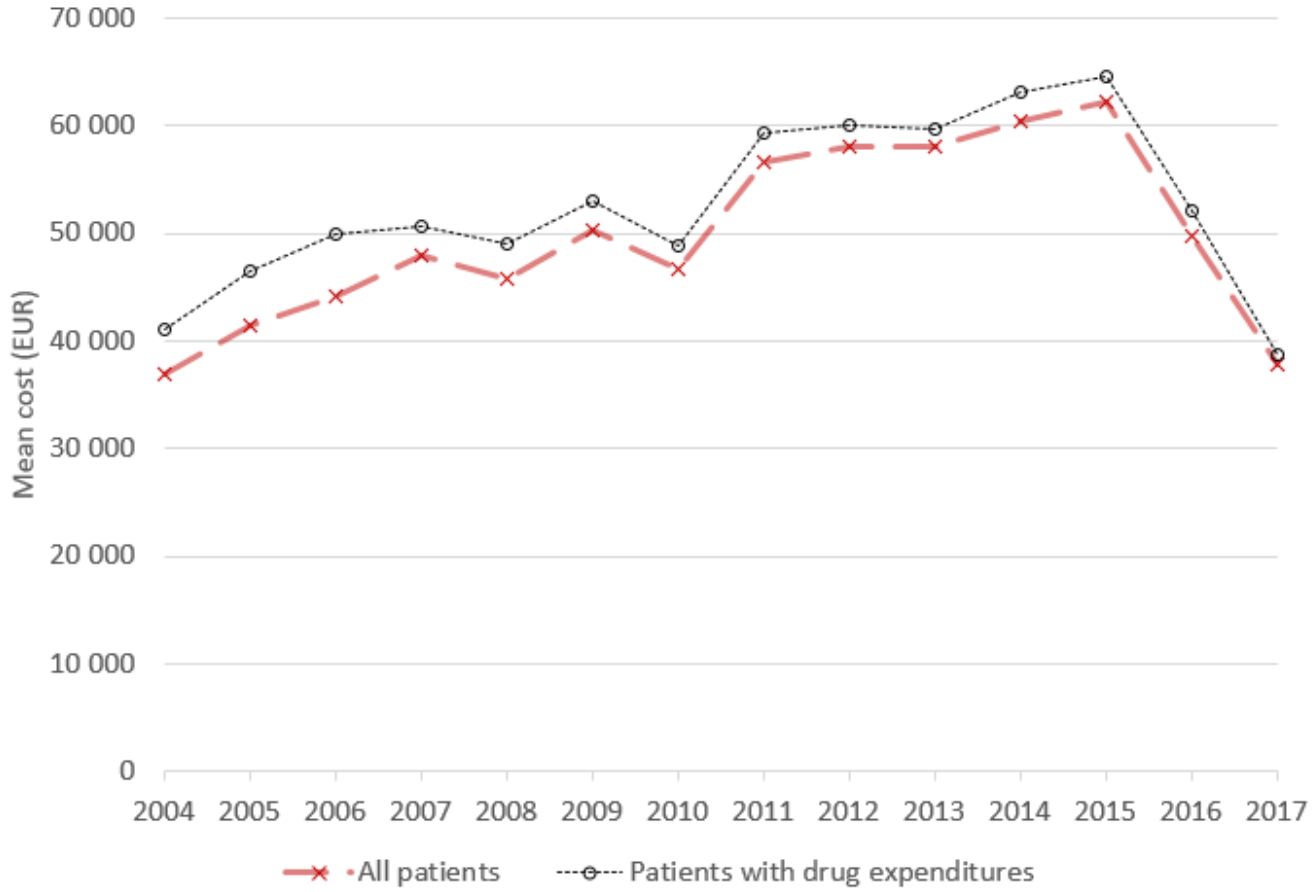
A) Oncological drug expenses per calendar year



B) Expenses for the first two years after incidence per incidence year



C) Mean cost per patient for the first two years after incidence per incidence year



Source: BCR-IMA.

4.2.2.2 *Drug uptake for a selection of drugs during the first 5 years after diagnosis*

Imatinib had already a high uptake of 79% in patients diagnosed 2004 and the uptake further increased to a maximum of 88.6% in patients diagnosed in 2009. From the 2011 cohorts onwards, uptake fell below 70% and even below 60% for the 2015 and 2017 cohorts.

The first cohort with an uptake of nilotinib more than 10% was the group of patients diagnosed in 2007. Uptake increased to a maximum of 45% in the 2012 cohort, then started to decrease to 17.9% in the 2016 cohort.

Dasatinib has got an uptake higher than 10% since the 2006 cohort, increasing to a maximum uptake of 46.6% in the 2015 cohort.

Bosutinib and ponatinib had a maximum uptake of 5 to 6% only during the first 5 years after diagnosis.

Table 12 – CML: proportion of patients who received at least one dose during 5-year period after diagnosis

Drug/incidence year (n)	2004 (129)	2005 (126)	2006 (114)	2007 (145)	2008 (136)	2009 (123)	2010 (164)	2011 (168)	2012$ (157)	2013 (144)	2014 (161)	2015 (161)	2016 (156)	2017 (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. $ IMA data were only available up to the second trimester of 2019 and might have a delay of two years. Five-year follow-up data are thus not 100% complete from incidence year 2012 onwards (see part 3.1.3). Source: BCR-IMA.*

4.2.3 *Medical literature: efficacy*

Compared with the old treatment of interferon-alpha and cytarabine, imatinib achieves a dramatically higher proportion of major molecular response at 12 months. Health-related quality of life was also found to be better for patients treated with imatinib than those with IFN-α + Ara-C as first-line therapy.

The benefit in overall survival for second generation TKIs (dasatinib, nilotinib, bosutinib) and third generation TKIs (ponatinib) compared to imatinib remains unclear based on published clinical trials. Trials in imatinib-resistant CML are hampered by a high cross-over rate.

4.2.3.1 *First-line treatment*

Reference + search date	Indication – intervention -comparator	OS	Quality of life	Other outcomes
Tang 2019[96] search date unknown	Previously untreated CML diagnosed in the chronic phase Comparator: Imatinib 400 mg QD Interventions: interferon-alpha (IFN-α) + Cytarabine (Ara-C), nilotinib, dasatinib, bosutinib, ponatinib			Major molecular Response (MMR) within 12 months IFN-α + Ara-C: OR 0.00 (95%CI 0.00-0.03) Imatinib 800mg: OR 1.82 (95%CI 1.39-2.38) Nilotinib 400mg: OR 1.68 (95%CI 0.56-5.07) Dasatinib 100mg: OR 1.44 (95%CI 1.29-1.60) Bosutinib 500mg: OR 1.90 (95%CI 1.30-2.76) Ponatinib 45mg: OR 6.48 (95%CI 3.89-10.82) Complete cytogenetic response (CCyR) within 12 months IFN-α + Ara-C: OR 0.03 (95%CI 0.02-0.05) Imatinib 800mg: OR 1.60 (95%CI 1.21-2.12) Nilotinib 400mg: OR 1.90 (95%CI 1.31-2.76) Dasatinib 100mg: OR 1.34 (95%CI 1.25-1.44) Bosutinib 500mg: OR 1.11 (95%CI 0.76-1.61) Ponatinib 45mg: not reported Discontinuation of drug-related AEs IFN-α + Ara-C: OR 3.13 (95%CI 1.56-6.26) Imatinib 800mg: OR 2.83 (95%CI 1.49-5.36) Nilotinib 400mg: OR 2.01 (95%CI 0.61-6.65) Dasatinib 100mg: OR 1.48 (1.11-1.98) Bosutinib 500mg: OR 4.11 (2.34-7.19) Ponatinib 45mg: OR 7.50 (1.67-33.60) Serious AEs IFN-α + Ara-C: not reported Imatinib 800mg: OR 1.24 (95%CI 0.18-8.38) Nilotinib 400mg: OR 1.27 (95%CI 0.98-1.63) Dasatinib 100mg: OR 1.54 (95%CI 1.02-2.31) Bosutinib 500mg: OR 1.92 (95%CI 1.35-2.75) Ponatinib 45mg: not reported

Vener 2020[97] Search date: 28 May 2019	Patients with newly diagnosed chronic-phase CML Philadelphia (+). Intervention: dasatinib, nilotinib, bosutinib or ponatinib Comparator: imatinib	OS up to 60 months 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) Imatinib vs dasatinib HR 1.01 (95%CI 0.58-1.73)		
Douxfils 2016[98] search date: 21 October 2014	All patients treated with tyrosine kinase inhibitors with no restriction regarding a prior therapy Comparator: Imatinib Interventions: nilotinib, dasatinib, bosutinib, ponatinib	OS at 12 months Nilotinib OR 1.51 (95%CI 0.38-5.99) Dasatinib OR 0.42 (95%CI 0.14-1.31) Bosutinib OR 2.38 (0.82-6.89) Ponatinib OR 2.00 (0.21-19.33)		
Gurion 2016[99] search date: August 2015	Previously untreated CML diagnosed in the chronic phase Comparator: Imatinib Interventions: 2nd and 3rd generation TKIs (nilotinib, dasatinib, bosutinib, ponatinib)	All-cause mortality 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) 5 years: RR 0.95 (95%CI 0.62-1.47)		Any arterial cardiovascular events: RR 2.99 (95%CI 1.94-4.62) Pleural effusion of any grade: RR 11.14 (95%CI 3.46-35.91)
Efficace 2013[100] Search date: September 2012	Previously untreated CML Comparator: IFN-α + Ara-C Interventions: Imatinib		HRQoL better for patients treated with imatinib than those with IFN-α + Ara-C as first-line therapy	

4.2.3.2 Second- and third-line treatment

Reference + search date	Intervention and comparator + indication	OS	Quality of life	Other outcomes
Loveman 2012[101] Search data: January 2011	Population: patients with imatinib-resistant CML Comparator/intervention: high dose imatinib, dasatinib, nilotinib			No comparative evidence available given the high cross-over rate in the only identified RCT

4.2.3.3 Discussion

Survival of patients with CML clearly improved after the introduction of imatinib in 2002. To a lesser degree, a further improvement of survival is seen for patients diagnosed between 2009-2014 compared to patients diagnosed between 2004-2008. This may be due to the introduction of second generation TKIs such as nilotinib and dasatinib, although RCTs did not provide a clear proof of efficiacy in terms of overall survival. Compared to patients diagnosed between 2009-2013, no improved survival is seen for patients diagnosed in 2014-2017. Uptake of ponatinib and bosutinib remained very low in our study, too low to possibly lead to a visisble change in overall survival.

Findings in countries

In Italy, the data of CML patients in the cancer registries of two provinces were analysed. Patients were diagnosed between 1996-2012 and followed-up until 2015. Disease-specific survival probability increased sharply after the introduction of imatinib in 2002, by 35.9% at 3 years and 40.4% at 5 years. After 2002, no change in trends was observed.[102]

In Sweden, CML patients were followed-up through the national cancer registry from 1958 to 2012. The 5-year overall survival more than quadrupled from 0.18 in the 1970s to 0.82 in 2012. Between the two calendar periods 1999-2005 and 2006-2012 the 5-year relative survival has increased for all age-groups, for example from 0.88 (95%CI 0.83-0.92) to 0.92 (0.86-0.96) for patients younger than 50 years and from 0.79 (95%CI 0.69-0.86) to 0.89 (95%CI 0.78-0.96) for patients between 60 and 69 years of age.[103]

In the Netherlands, it was seen that treatment before 2000 mainly consisted of chemotherapy, while after 2007 88% of patients received TKIs. Five-year relative survival was only 36% before the introduction of TKIs and increased to 79% afterwards.[104]

Also in France, CML patients were identified in five population-based registries and survival probabilities were followed over time from January 1980 till December 2009. The 5-year relative survival probability among patients diagnosed in 1980-1986 (before the use of interferon-alpha) was 40.2% (95%CI 28.7-56.4), 59.4%(95%CI 53.0-66.5) among patients diagnosed in 1987-1999 (before the use of TKIs) and 82.6% (95%CI 78.3-87.1) for patients diagnosed in 2000-2009.[105]

In Lithuania, uptake of TKIs was more modest, with 1.5%, 30.6% and 69.1% of CML patients receiving TKIs in 2000-2004, 2005-2009 and 2010-2013 respectively. The 5-year relative survival probability increased from 0.33 (95%CI 0.27-0.40) for patients diagnosed with CML in 2000-2004 to 0.55 (95%CI 0.47-0.63) for patients diagnosed in 2005-2009.[106]

Limitations

Data on uptake of the selected drugs include only the first five years after diagnosis and may thus not include all drugs taken for second-line or further lines of therapy. Data on expenditures even include only the first two years after diagnosis and represent not the full picture of expenditures of CML treatment, especially as many drugs are taken chronically.[95]

Major molecular response and complete cytogenetic response drastically improved with imatinib compared to old treatment options with clear survival improvements in observational studies. The additional survival benefit with the introduction of second- and third-generation TKIs is however less clear from clinical trials and observational studies. Cross-over may hamper the interpretation of survival results of the clinical trials.

Treatment costs for CML patients decreased in recent years, probably due to the expiry date of imatinib's patent in 2016.[107]

4.2.4 Economic literature: cost-effectiveness

For more information about the economic evaluations in the identified HTA reports, we refer to Appendix.

Confidential prices

With one exception, all drugs assessed in the economic evaluations (either as intervention or comparator) were provided under a patient access scheme (PAS) in which confidential discounts to the list prices of those drugs were negotiated with the companies. This was the case for nilotinib,[108, 109] dasatinib,[108, 109] bosutinib[110, 111] and ponatinib,[111] all used for the treatment of chronic myeloid leukaemia (CML). Of those drugs, dasatinib[108, 109] and bosutinib[110] were assessed under a Cancer Drug Fund (CDF) rapid reconsideration (see Box 1) for which a revised PAS was negotiated. The revised PAS was either a further increase in the discount rate of a previous PAS (bosutinib), or a switch from a complex to a simple PAS (dasatinib), and it had a great impact on the results (see later). In all these evaluations the ICERs were calculated including the (revised) confidential price reductions.

There was no discount on imatinib for the treatment of CML. For the assessment of this drug, results based on published list prices were used by the decision maker.[112]

Box 1 – Cancer Drug Fund rapid reconsideration

The original model of the Cancer Drug Fund (CDF) was set up by the UK Government in 2011 to provide patients with faster access to the most promising but still clinically uncertain new cancer treatments. Later on, NICE and NHS England worked together to develop a new model for the CDF which was launched in July 2016 (see NICE website[p] for the rationale and main changes). For cancer drugs that were already being funded by the CDF using the previous model, NICE elaborated and applied a rapid reconsideration process to decide how licensed drugs in the previous CDF model should now be managed and whether they can continue to be available on the NHS via the CDF. During this process, the companies involved were invited to provide new evidence submissions. The focus was on cost-effectiveness analyses of the drug due to the availability of a new patient access scheme or commercial access agreement. Only in exceptional circumstances and with prior agreement with NICE could new clinical evidence be included. Submission of new clinical evidence could however not lead to structural changes in the approach to cost-effectiveness.

p https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-technology-appraisal-guidance/cancer-drugs-fund (accessed December 2020)

Quality of life

Virtually all economic evaluations appraised in the technology assessments (TAs) were cost-utility analyses with QALYs as the outcome measure. When comparing dasatinib with nilotinib,[108, 109] however, the evaluation was limited to a cost-minimisation analysis whose appropriateness was confirmed by the appraisal committee: "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."[108, 109]

In one TA,[112] the health-related quality of life aspects (i.e. utilities) of the QALYs were obtained directly from the IRIS head-to-head trial that compared standard-dose imatinib with interferon-alfa for the first-line treatment of CML, and alongside which an EQ-5D generic instrument was administered.[112] In this TA, the utilities were modelled according to the trial's results per health state (chronic phase, accelerated phase, blast phase, etc.). However, though EQ-5D utilities were measured at different time points in each arm of the IRIS trial (i.e. at baseline, every months up to month 6, then at months 9, 12, 18 and 24) these time-dependent utilities were not transparently reported and not used as such in the model.

In all other TAs, utilities were obtained from indirect sources, because either there was no underlying head-to-head trial comparing the interventions under consideration,[108, 110, 111] or because such trial existed but did not measure the health-related quality of life aspects with a generic instrument, i.e. DADISION and ERNESTnd for dasatinib / nilotinib versus imatinib in TA426.[109] This lack of direct evidence to measure the impact on quality of life gives rise to uncertainty in the results of the economic evaluation. In those TA, utilities were obtained from the following sources:

- The set of EQ-5D utilities derived from people receiving standard-dose imatinib in the IRIS trial, which was used to model the quality-of-life of CML patients (i.e. 0.85 for the chronic phase, 0.73 for the accelerated phase and 0.52 for the blast phase), irrespective of the drugs administered (nilotinib versus high- or low-dose imatinib, nilotinib versus hydroxycarbamide, dasatinib versus low-dose imatinib).[108, 109]
- The set of EQ-5D utilities directly derived from the bosutinib pivotal study (Study 200, single arm) and that was used to assess bosutinib (against hydroxycarbamide) for the second-line treatment of CML.[110]
- The study by Szabo et al. (2010),[113] that aimed at estimating preference weights from the general population for standardized CML-related health states using the time trade-off technique. This set of utilities was used for the assessment of ponatinib (versus bosutinib, best-supportive care and induction therapy) against CML (second line treatment) and against acute lymphoblastic leukaemia (ALL).[111]

QoL input data used in the models were usually transparently reported, except in one TA of bosutinib where QoL data (and also the cost-effectiveness results) were reported as commercial in confidence.[110] The impact on QoL was usually modelled per health state, defining a single QoL value per health state modelled (e.g. chronic, accelerated and blast phases for CML), irrespective of the treatment administered.[108-111] However, in the assessment of imatinib versus interferon-alpha for the first line treatment of CML, QoL were modelled per treatment arm according to the results of the IRIS trail.[112]

Uncertainty and influential parameters

The estimation of the impact of the treatment on long-term survival was reported as being the main source of uncertainty in all TAs. Consequently, this further led to considerable uncertainty in the estimated QALYs and in the correct estimation of the incremental cost-effectiveness ratios (ICERs). The reasons for the uncertainty are multiple.

In many TAs, the committee refers to a lack of head-to-head trials directly comparing the interventions under consideration. This was the case for the assessments of nilotinib (versus high-dose imatinib),[108] dasatinib (versus nilotinib),[108, 109] bosutinib[110] and ponatinib.[111] In those cases, evidence came from indirect comparisons (e.g. for dasatinib versus nilotinib,[108, 109] ponatinib versus bosutinib[111]) and/or from non-comparative single-arm studies (e.g. Study 200 for bosutinib,[110] the PACE trial for ponatinib[111]), which generates considerable uncertainties in the results.

Another problem leading to uncertainty in the estimation of the treatment effect is the immaturity of the available data, even when head-to-head trials are available. Sometimes, the underlying head-to-head trial provided only short-term data on overall survival, such as in the IRIS trial (standard-dose imatinib versus interferon-alpha),[112] the DASISION trial (dasatinib with standard-dose imatinib)[109] and the ENESTnd trial (nilotinib with standard-dose imatinib).[109] This was also the case for the assessment of OS with bosutinib from the Study 200 single-arm trial.[110] In those TAs, the published supportive evidence from the RCT relied principally on surrogate measures of efficacy for which longer-term data was available, such as the achievement of a complete cytogenic response (CCyR) and major molecular response (MMR). In practice however it is not clear how well surrogate measures of efficacy predict overall survival and the plausibility of this relationship was largely discussed by the appraisal committee. Also related to the immaturity of the data, is the difficulty to model/extrapolate OS in the absence of enough trial data to appropriately inform the OS curve in the economic model,[111, 112] as was reported for the assessment of ponatinib: "*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 (…).*"[111]

Even when long-term data are available from the underlying head-to-head trial, uncertainties in the estimation of the treatment effect may still arise due to crossover. In the IRIS trial comparing imatinib with interferon-alpha there was a high crossover rate in the interferon-alpha group, such that "*the Committee thought that the degree of the benefit of imatinib treatment would have been underestimated (…)*". This led the committee to also consider the results of a per protocol analysis based on treatment completers.

Sensitivity of the results to drug costs (and discounts) was reported in the three TAs in which drugs funded under the original model of the CDF were reconsidered and for which a revised patient access scheme was applied (see below).[108-110]

Results

The ICERs supporting the committee's conclusions are (see more details in Appendix):

- **Standard-dose imatinib**
  - First-line treatment of adults with chronic myeloid leukaemia (CML):[112]

  a. Intention-to-treat analysis from the ERG model (no PAS): £26 000 (range £13 500 to £52 000) per QALY gained for imatinib versus IFN-α

  b. Per-protocol analysis from the ERG independent model (no PAS): £17 500 to £29 900 per QALY gained for imatinib versus IFN-α

- **Nilotinib**
  - First-line treatment of adults with CML:[109]

    ERG model (including PAS for nilotinib): £11 000 per QALY gained for nilotinib versus standard-dose imatinib

  - Second-line treatment of adults with CML (Philadelphia-chromosome-positive CML adults resistant or intolerant to standard-dose imatinib):[108]

  a. nilotinib versus high-dose imatinib (including PAS for nilotinib): "It [The committee] noted that in the base-case analysis, nilotinib dominated (that is, it was less expensive and more effective than) high-dose imatinib (…)."

  b. nilotinib versus hydroxycarbamide (including PAS for nilotinib):

     Company model: between £22 800 and £25 000 per QALY gained

     ERG model: £31 300 per QALY gained

     Committee 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".

- **Dasatinib**
  - First-line treatment of adults with CML:[109]

  a. dasatinib versus standard-dose imatinib (ERG model):
    - Including PAS for dasatinib: over £300 000 per QALY gained
    - Including revised PAS dasatinib: "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)."

  b. dasatinib versus nilotinib (ERG model):
    - Including PAS for dasatinib and nilotinib: "The committee noted that dasatinib was associated with fewer QALYs and was more costly than nilotinib in all scenarios"
    - Including revised PAS for dasatinib and PAS for nilotinib : "the committee concluded that, with the revised patient access scheme, it was likely that dasatinib is a cost-effective use of NHS resources and so should be recommended".

  - Second-line treatment of adults with CML (Philadelphia-chromosome-positive CML who are resistant or intolerant to imatinib):[108]

  a. dasatinib versus nilotinib
    - Including PAS for dasatinib and nilotinib: "Therefore the committee concluded that dasatinib could not be recommended as a cost effective use of NHS resources."
    - Including revised PAS for dasatinib and PAS for nilotinib: "It [The committee] concluded that, with the revised patient access scheme, it was likely that dasatinib was a cost-effective use of NHS resources"

- **Bosutinib**
  - Second-line (or later) treatment of adults with Philadelphia-chromosome-positive CML when they have previously had 1 or more tyrosine kinase inhibitor, and imatinib, nilotinib and dasatinib are not appropriate:[110]

  a. Bosutinib versus hydroxycarbamide
    - Including PAS for bosutinib (ERG model): chronic phase CML £40 000 to £50 000 per QALY gained, accelerated phase CML: £58 000 per QALY gained, blast phase CML: £60 000 per QALY gained.
    - Including revised PAS for bosutinib: IC, IE and ICER are reported as commercial-in-confidence. "Given the cost-effectiveness analyses including the revised patient access scheme, and taking into account the unmet need in this patient population, the committee concluded that the ICERs were within the ranges normally considered a cost-effective use of NHS resources." Bosutinib meets the end-of-life criteria for the accelerated and blast phases CML.

- **Ponatinib**
  - Treatment of adults with CML whose disease is resistant to, or who cannot tolerate dasatinib, nilotinib and imatinib:[111]

  a. Ponatinib versus bosutinib and ponatinib versus best supportive care (including PAS for ponatinib and the comparators):
    - Chronic phase CML (ERG model): "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."
    - Accelerated and blast phases CML (ERG model): "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."

- Treatment of adults with Ph+ ALL whose disease is resistant to, or who cannot tolerate, imatinib and dasatinib:[111]

a. Patients in whom stem cell transplant is suitable (ERG model):

   - Ponatinib versus best supportive care (including PAS for ponatinib): £7 156 to £29 995 per QALY gained
   - Ponatinib versus induction chemotherapy (including PAS for ponatinib): dominant to £4 138 per QALY gained

b. Patients in who stem cell transplant is not suitable (ERG model):

   - Ponatinib versus best supportive care (including PAS for ponatinib): ponatinib dominates BSC

In the early assessment of imatinib in 2003,[112] the committee concluded that using its official list price, standard-dose imatinib was a cost-effective intervention for the first-line treatment of adults with CML, when compared with interferon-alpha.

In other assessments, the interventions were considered cost-effective only if they were provided with the discounts agreed in the relevant patient access schemes and not when the official list prices were used. This was the case for nilotinib (versus standard-dose imatinib for the first-line treatment of CML,[109] and versus high-dose imatinib[108] and hydroxycarbamide[108] for the second-line treatment of CML); ponatinib (versus bosutinib and best supportive care for the treatment of CML patients who are resistant or intolerant to dasatinib, nilotinib and imatinib,[111] and versus best supportive care and induction chemotherapy for the treatment of acute lymphoblastic leukaemia[111]). The negotiated discounts were all commercial in confidence.

For the interventions whose financing through the Cancer Drug Fund was reconsidered in 2016, the committee concluded that they were cost-effective when using the revised patient access scheme proposed by the firm. This was the case for dasatinib (versus standard-dose imatinib for the first-line treatment of CML,[109] and versus nilotinib for both the first- and second-line treatment of CML[108, 109]) and bosutinib (versus hydroxycarbamide for the second-line or later treatment of CML[110]). This contrasts with the original appraisals of those cancer drugs in which the previous non-revised patient access schemes were used and that concluded that none of the interventions were cost-effective (i.e. TA251[114] for dasatinib used first line, TA241[115] for dasatinib used second line and TA299[116] for bosutinib). For example, using the non-revised patient access scheme, the ICER for dasatinib versus standard-dose imatinib was above £300 000 per QALY gained which was substantially outside the range normally considered as cost-effective in the UK. With the revised patient access scheme, the committee concluded that "it was likely that dasatinib was a cost-effective use of NHS resources and so should be recommended for untreated Philadelphia-chromosome-positive CML."[109]

Despite the uncertainty surrounding the results in many TAs, the interventions were all appraised positively by the committee and were all recommended for reimbursement. However, the ICERs backing up the committee's conclusions were explicitly reported in only half of the cases, that is for the assessments of standard-dose imatinib[112] and nilotinib[108, 109] against CML, and ponatinib[111] against ALL. For those drugs, the decision-making ICERs were (nearly) all below the relevant UK cost-effectiveness threshold of £20 000 - £30 000 per QALY gained. For the first-line treatment of CML, the decision-making ICERs were £17 500 to £29 900 per QALY for standard-dose imatinib versus interferon-alpha in the relevant per-protocol analysis,[112] and £11 000 per QALY for nilotinib versus standard-dose imatinib.[109] For the treatment of imatinib-resistant CML, nilotinib dominated (i.e. it was less expensive and more effective than) high-dose imatinib,[108] and, although the ERG ICER of nilotinib versus hydroxycarbamide was £31 300 per QALY, the committee accepted that the ICER for nilotinib was likely to be less due to some plausible adjustments.[108] For adults with Ph+ acute lymphoblastic leukaemia whose disease is resistant to, or who cannot tolerate, imatinib and dasatinib, the ICER for ponatinib versus induction chemotherapy ranged between dominance to £4 138 per QALY.[111] Compared with best supportive care, ponatinib was either dominant in patients in who stem cell transplant is not suitable or ranged between £7 156 to £29 995 per QALY for patients in who stem cell transplant is suitable.[111]

ICERs were not reported when the assessment was a Cancer Drug Fund rapid reconsideration of a drug provided with a (in 2016) revised and confidential discount (i.e. dasatinib for the first- and second-line treatment of CML,[108, 109] and bosutinib for the second-line treatment of CML[110]). Exact ICERs were also kept confidential in an evaluation of ponatinib against CML because of confidential patient access schemes for both ponatinib and its comparator, bosutinib.[111] For dasatinib (with revised PAS), the committee reported that the cost-effectiveness estimates were below the relevant cost-effective threshold, i.e. £20 000 - £30 000 per QALY.[108, 109] However for bosutinib (versus hydroxycarbamide) and ponatinib (versus bosutinib and best supportive care), the committee departed from this usual threshold and accepted that higher ICERs (up to £50 000 per QALY gained) would still represent a cost-effective use of NHS resources as both drugs met the end-of-life criteria[q] for the accelerated and blast phases[r] CML.[110, 111]

Details about the incremental costs and effects were not reported in any of the documents available for review.

4.2.5 Summary

Observational data

- Observational data indicate that overall survival improved over the years for CML patients. The survival probability at 3 years after diagnosis increased from 75.2% of patients diagnosed in 2004 to 88.7% of patients diagnosed in 2017. Five-year survival increased from 69.8% in the 2004 cohort to 84.5% in the 2015 cohort. For the Flemish region, with available data from the year 2000 onwards, the biggest improvement in observed survival was seen between the 2000-2003 and 2004-2008 period.
- Mean cost for the first two years after diagnosis per patient who received oncolytic drugs was about €41 000 in 2004, increased to €64 500 in 2015, then decreased to less than €39 000 in 2017.
- Imatinib had already a high uptake of 79% in patients diagnosed in 2004 and the uptake further increased to a maximum of 88.6% in patients diagnosed in 2009. From the 2011 cohorts onwards, uptake fell below 70% and even below 60% for the 2015 and 2017 cohorts. The first cohort with an uptake of nilotinib more than 10% was the group of patients diagnosed in 2007. Uptake increased to a maximum of 45% in the 2012 cohort, then started to decrease to 17.9% on the 2016 cohort. Dasatinib has got an uptake higher than 10% since the 2006 cohort, increasing to a maximum uptake of 46.6% in the 2015 cohort. Bosutinib and ponatinib had a maximum uptake of 6% only during the first 5 years after diagnosis.

[q] End of Life (EOL). To qualify as 'life-extending treatment at the end of life', a treatment must fulfill the following two criteria: 1) the treatment is indicated for patients with a short life expectancy, normally less than 24 months; 2) there is sufficient evidence to indicate that the treatment has the prospect of offering an extension to life, normally of a mean value of at least an additional three months, compared with current NHS treatment.

[r] End of life criteria were not met for the chronic phase CML. For this phase, both ponatinib (with PAS) and bosutinib (with revised PAS) were considered cost-effective at the standard NICE threshold.[110, 111]

Medical literature

- Imatinib
  - Compared with the old treatment of interferon-alpha and cytarabine, imatinib achieves a much higher proportion of major molecular response at 12 months. Health-related quality of life was also found to be better for patients treated with imatinib than those with IFN-α + Ara-C as first-line therapy.
- Dasatinib, nilotinib, bosutinib, ponatinib
  - The benefit in overall survival for second generation TKIs (dasatinib, nilotinib, bosutinib) and third generation TKIs (ponatinib) compared to imatinib remainds unclear based on published clinical trials.

Economic literature

- All but one drugs assessed in the TAs were provided under a (revised) patient access scheme (PAS) in which confidential discounts to the drug list prices were negotiated with the companies. There was no discount on one drug (imatinib) that was provided at list price.
- All studies referred to utilities measured with a generic utility instrument, being the EQ-5D questionnaire, or the time trade-off technique. The quality of life input data were usually transparently reported. Utilities were however mostly obtained from indirect sources because of a lack of head-to-head trial or, when such a trial existed, because quality of life was not collected with a generic utility instrument. None of the economic evaluations in the TAs modelled the utilities per treatment arm and at different points in time.
- In all TAs the appraisal committee acknowledged the uncertainty around the ICERs, which reflected the considerable uncertainty in the elicitation of the clinical benefits of the drugs (i.e. the impact on overall survival and quality of life). The main reasons for this were the absence of head-to-head trials directly comparing the cancer treatments and/or the immaturity of the available data originating from short-term studies from which only surrogate outcomes (e.g. complete cytogenic response, major molecular response) could be derived.
- In all TAs, the impact of the treatment on long-term survival was a key driver of the ICER estimates, together with the drug cost (and discounts). The underlying reason for the uncertain impact on overall survival was most of the times related to the lack of head-to-head trials and/or the immaturity of the available data.
- With one exception, the interventions were considered cost-effective only if they were provided with the discounted prices agreed in the (revised) PAS (i.e. nilotinib, dasatinib, bosutinib and ponatinib against CML; and ponatinib against ALL). In an early TA (2003) however, the intervention was cost-effective when using it official list price (standard-dose imatinib against CML).
- (With inclusion of the discounts) All interventions were recommended as a cost-effective use of NHS resources. Most of them were assessed at the £20 000 - £30 000 per QALY threshold, but some of them at the £50 000 per QALY threshold as they met the end-of-life criteria (bosutinib and ponatinib against accelerated and blast phase CML).
- All TAs suffer from a lack of transparency as the decision-making ICERs were reported in only half of the cases, and details about IC and IE were never reported.

4.3 Colorectal cancer

4.3.1 Introduction

Colorectal cancer (CRC) is the second most common cancer diagnosed in women and the third most common in men. Its incidence is expected to increase in the next decades.[117] In Belgium, 7 860 new colorectal cancers were diagnosed in 2018.[33] Approximately 25% of newly diagnosed people have metastatic disease at initial diagnosis (synchronous metastasis) and 50% will develop metastatic disease in the long run (metachronous metastasis).[118, 119] Most of the time, neoplastic precursor lesions progressively undergo genetic and epigenetic abnormalities and progress to CRC over the years. Hence, besides the TNM staging and histological analysis, the further description of such molecular disorders enabled a better characterization of the tumours and led to the development of more targeted therapeutic agents.[117]

Systemic therapy is the treatment of choice for metastatic disease. Until the introduction of modern chemotherapy agents such as oxaliplatin and irinotecan, fluorouracil was the sole molecule used in metastatic CRC.[120] Nowadays, therapy for metastatic colorectal cancer typically includes chemotherapy along with drugs directed towards specific disease features. Those therapeutic agents include anti-VEGF (Vascular Endothelial growth Factor), anti-EGFR (Epidermal Growth Factor Receptor) monoclonal antibodies.[117]

Monoclonal antibodies against EGFR (cetuximab, panitumumab) showed efficacy in various phase III trials, in advanced colorectal cancer. Genetic alterations of oncogenes (RAS, BRAF) involved in the downstream pathway of EGFR predict resistance to EGFR inhibition.[121] Vascular endothelial growth factor (VEGF) participate in cancer development by promoting angiogenesis in many tumour types, including CRC. Bevacizumab, a monoclonal anti-VEGF antibody and aflibercept, a recombinant fusion protein that traps VEGF and inhibits its activity, did show benefit in the treatment of advanced CRC and are now approved in metastatic CRC patients, respectively in first and second-line therapy.[122-124]

Regorafenib is a new multikinase inhibitor targeting the intracellular pathways of angiogenesis and oncogenesis. It is reimbursed in Belgium since 2015 for patients with chemorefractory metastatic CRC.[123, 124]

Drugs selected for colorectal cancer are listed in Table 13.

Table 13 – Selected drugs for colorectal cancer

Drug	Year#	Trade Name	Company$	Mechanism of action
Bevacizumab	2008	Avastin	Roche	Monoclonal antibody that inhibits the binding of VEGF to its receptors
Panitumumab	2008	Vectibix	Amgen	human IgG2 monoclonal antibody that binds to the human EGFR
Cetuximab	2006	Erbitux	Merck	monoclonal IgG1antibody that is specifically directed against the epidermal growth factor receptor (EGFR)
Aflibercept	2014	Zaltrap	Sanofi	Aflibercept binds to VEGF-A, with higher affinity than its native receptors, as well as the related ligands PlGF and VEGF-B
Regorafenib	2015	Stivarga	Bayer	Regorafenib is an oral tumour deactivation agent that potently blocks multiple protein kinases, including kinases involved in tumour angiogenesis (VEGFR1, -2, -3, TIE2)

#year of start reimbursement first indication in Belgium; $ of the originator.

4.3.2 Observational data

4.3.2.1 Patient characteristics, survival and expenditures

Characteristics of stage IV colorectal cancer patients did not change significantly over time (Table 14A). Observed survival (Table 14B) and relative survival (Appendix) did not change substantially over time. Three-year observed survival probability was 21.5% (95%CI 19.2-23.8) for patients diagnosed in 2004 and 28.2% (95%CI 25.4-31.0) for those diagnosed in 2017 (Table 14C). Median survival remained stable between 1.3 and 1.6 years (Table 14D). Evaluation of the evolution of overall survival by RAS-mutation status was not possible based on the data available at BCR.

Overall drug expenditures for colorectal cancer increased between 2004 and 2009, mainly based on the increasing yearly number of patients treated with oncological drugs (about 2 900 patients in 2004 versus 8 600 patients in 2009). In 2004, about €6.6 million was spent on oncological drugs for colorectal cancer patients. This substantially increased to about €55 million in 2009. From 2009 onwards, the yearly number of treated patients did not further increase substantially, but overall expenditures were higher than the years before 2009, mainly due to the additional costs spent for bevacizumab (Table 15A). In the period 2010-2016, the yearly expenditure for this drug varied between €19.3 million (2010) and €26.9 million (2014). Overall drug expenditures for colorectal cancer patients was about €56 million in 2016.

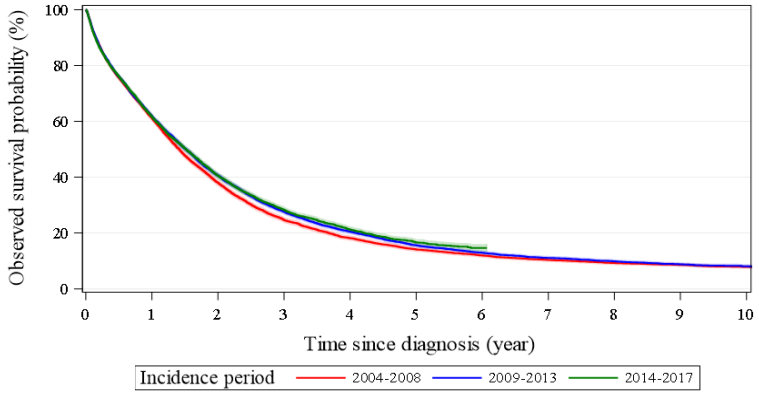
Drug expenditures for stage IV colorectal cancer patients during the first two years after diagnosis clearly increased from the incidence years 2008-2009 onwards, mainly caused by the expenditures for bevacizumab (Table 15B). Up till 2007, total expenditures for the first two years after incidence were less than €13 million. For incidence years 2010-2016, this is always above €20 million, with expenses above €11 million for bevacizumab. Mean cost per patient during the first two years after diagnosis was about €10 600 for patients diagnosed in 2004 and increased to more than €18 000 for patients diagnosed in 2009 or later. Highest mean cost per patients was noted for patients diagnosed in 2011 at about €20 100 per patient.

Table 14 – Colorectal cancer (2004-2017), combined stage IV (observed survival): A) Patient characteristics; B) Kaplan-Meier graph per incidence period; C) Time trend with incidence year*; D) Median survival time* **

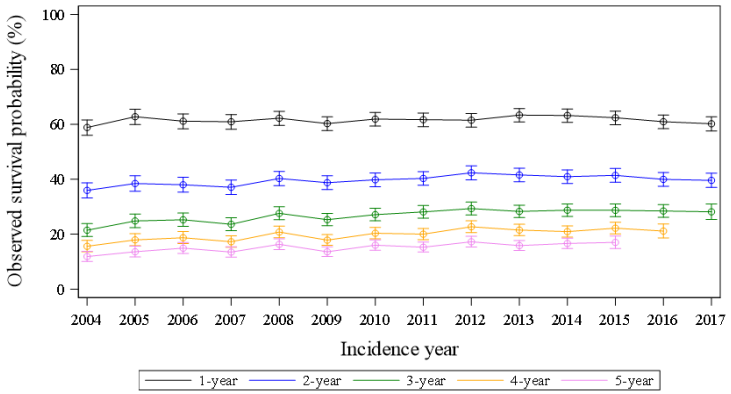
A

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

B

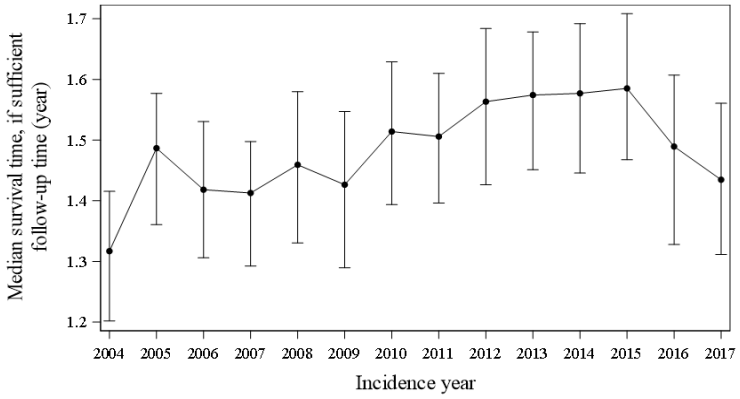


C



Year: 3-y OS [95%CI]
2004: 21.5 [19.2, 23.8]
2005: 24.8 [22.4, 27.4]
2006: 25.3 [22.9, 27.7]
2007: 23.6 [21.3, 26.0]
2008: 27.6 [25.3, 30.0]
2009: 25.3 [23.1, 27.5]
2010: 27.1 [24.9, 29.4]
2011: 28.1 [25.9, 30.4]
2012: 29.3 [27.0, 31.7]
2013: 28.3 [26.1, 30.6]
2014: 28.7 [26.5, 31.0]
2015: 28.7 [26.4, 31.0]
2016: 28.4 [26.2, 30.8]
2017: 28.2 [25.4, 31.0]

D

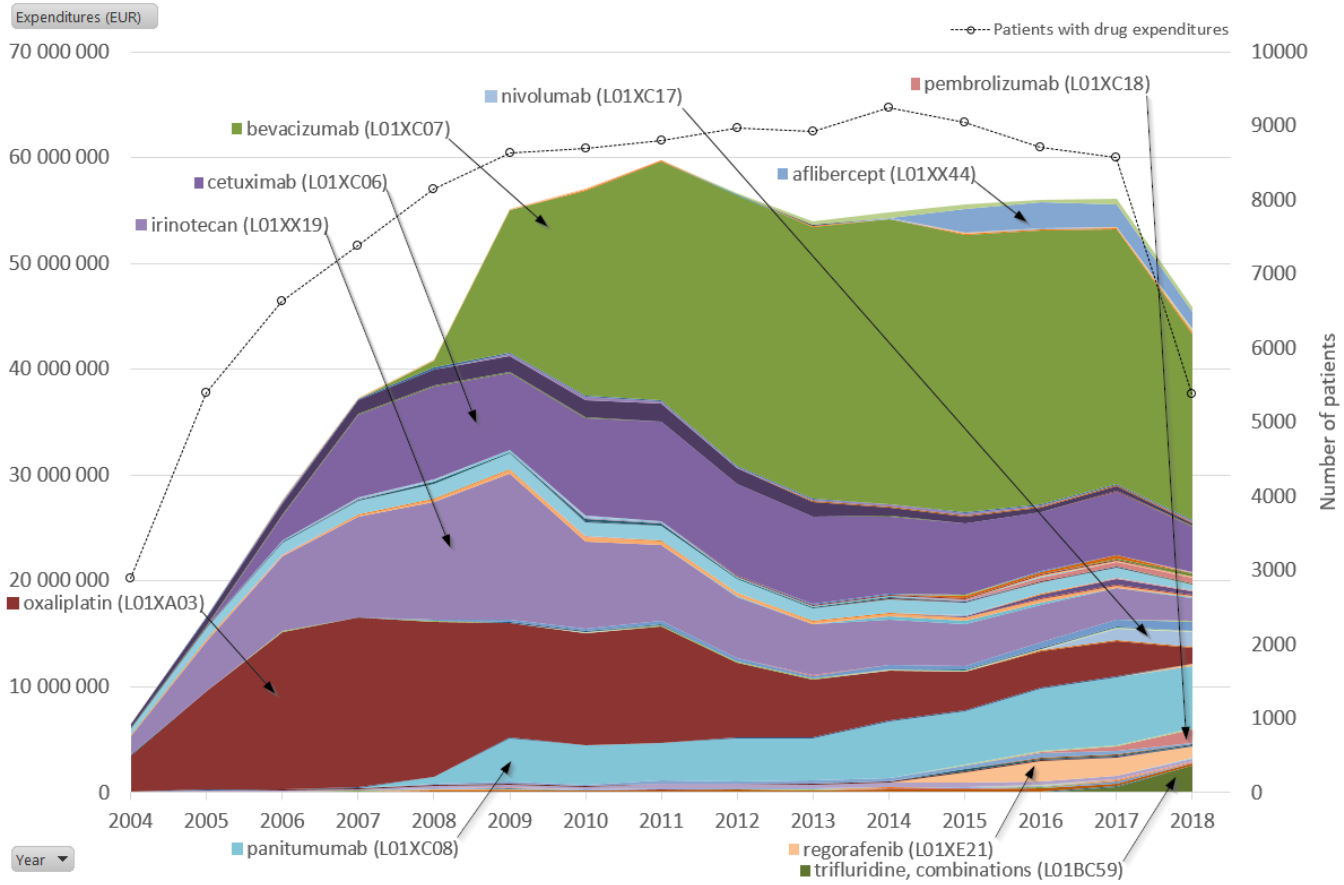


Year: Med. ST [95%CI]
2004: 1.3 [1.2, 1.4]
2005: 1.5 [1.4, 1.6]
2006: 1.4 [1.3, 1.5]
2007: 1.4 [1.3, 1.5]
2008: 1.5 [1.3, 1.6]
2009: 1.4 [1.3, 1.5]
2010: 1.5 [1.4, 1.6]
2011: 1.5 [1.4, 1.6]
2012: 1.6 [1.4, 1.7]
2013: 1.6 [1.5, 1.7]
2014: 1.6 [1.4, 1.7]
2015: 1.6 [1.5, 1.7]
2016: 1.5 [1.3, 1.6]
2017: 1.4 [1.3, 1.6]

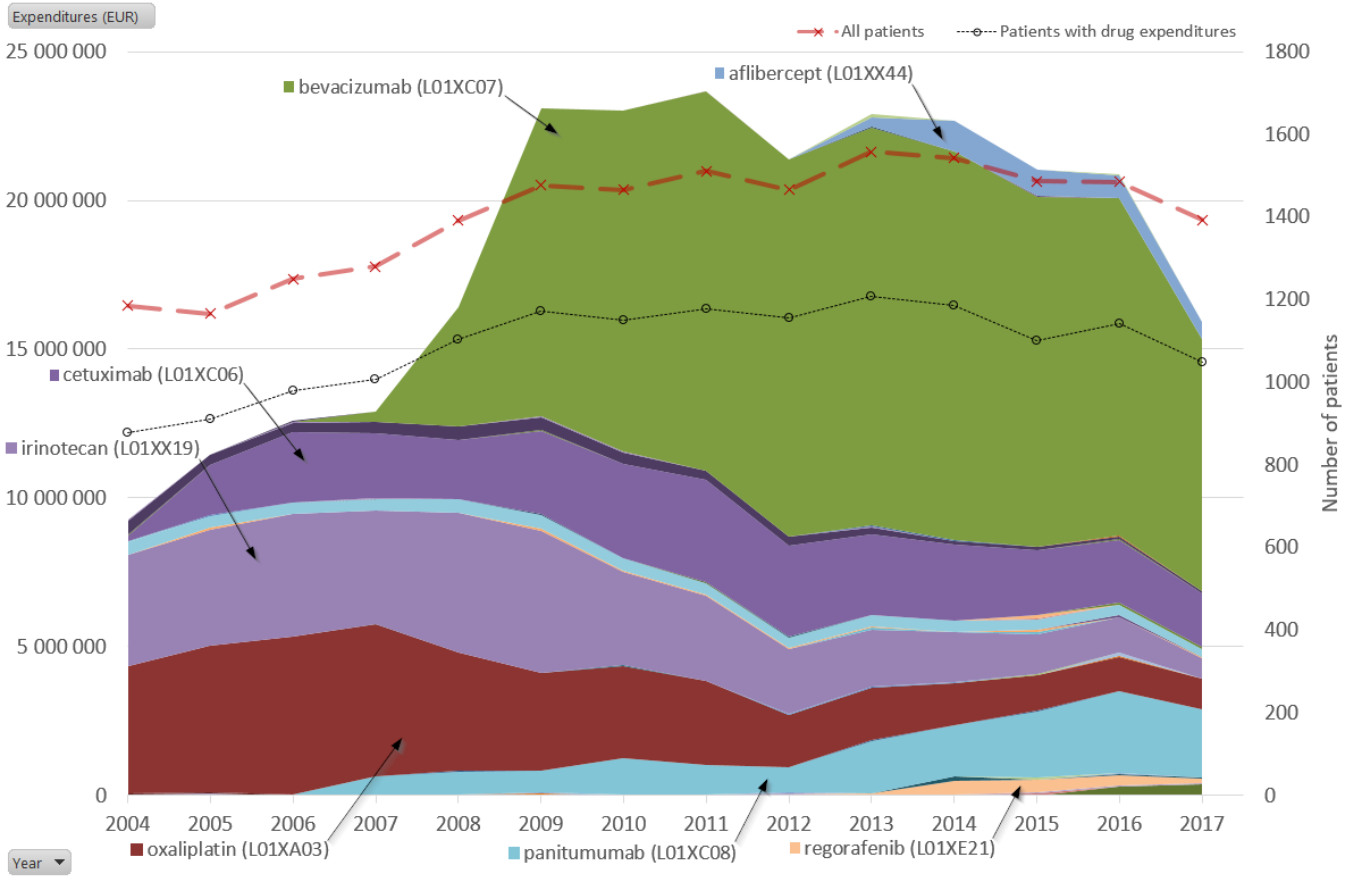
*Med. ST: median survival time; 3-y OS: 3-year observed survival; * the error bars represent the 95%CI. ** When the upper error is not plotted, the upper limit could not be determined with the available follow-up data. Source: BCR.*

Table 15 – Colorectal cancer: drug expenditures

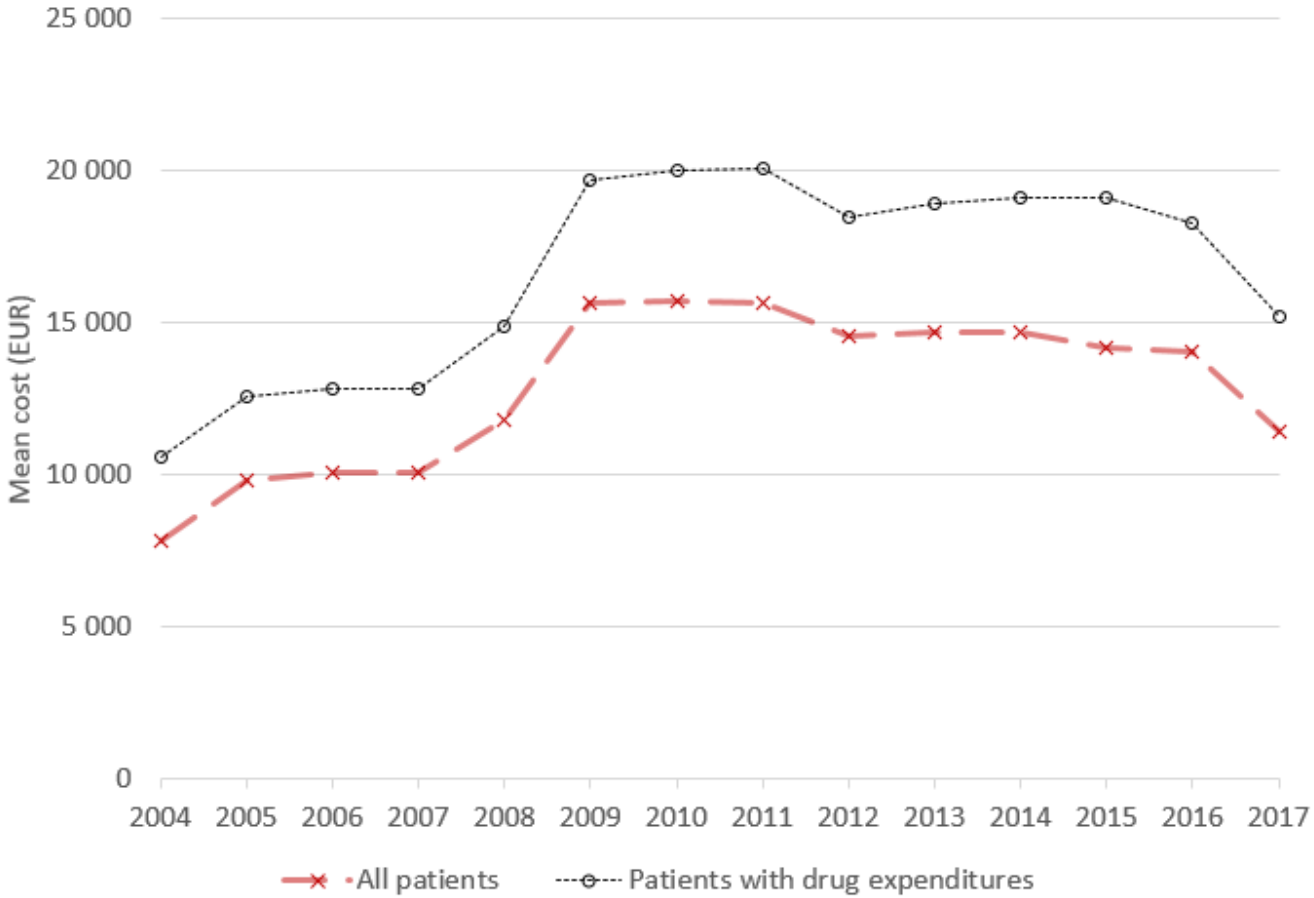
A) Oncological drug expenses per calendar year (all stages)



B) Expenses for the first two years after incidence per incidence year (stage IV)



C) Mean cost per patient for the first two years after incidence per incidence year (stage IV)



Source: BCR-IMA.

4.3.2.2 *Drug uptake for a selection of drugs during the first 5 years after diagnosis*

The uptake of bevacizumab, the first anti-VEGF therapy reimbursed in colorectal cancer, reached an uptake during a 5-year period after diagnosis higher than 20% for patients diagnosed from 2008 onwards and even higher than 40% for patients diagnosed from 2010 onwards. Other anti-VEGF therapy reimbursed more recently (aflibercept and regorafenib) had an uptake during the first five years after diagnosis below 3% for all cohorts.

Panitumumab, an anti-EGFR targeted drug, reached a maximum uptake of 10 to 12% in patients diagnosed between 2008 and 2017. The uptake of cetuximab, another anti-EGFR agent, remained below 8% for all incidence years.

Table 16 – Colorectal cancer stage IV: proportion of patients who received at least one dose during 5-year period after diagnosis

Drug/incidence year (n)	2004 (1185)	2005 (1166)	2006 (1249)	2007 (1280)	2008 (1391)	2009 (1476)	2010 (1466)	2011 (1511)	2012$ (1466)	2013 (1557)	2014 (1543)	2015 (1486)	2016 (1485)	2017 (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. $ IMA data were only available up to the second trimester of 2019 and might have a delay of two years. Five-year follow-up data are thus not 100% complete from incidence year 2012 onwards (see part 3.1.3). Source: BCR-IMA.*

4.3.3 *Medical literature: efficacy*

In the first-line setting, anti-EGFR monoclonal antibodies (panitumumab, cetuximab) may have a survival benefit in RAS wild type patients, but the effect is probably small and results appear only statistically significant for the combination with irinotecan-based chemotherapy.[125] Bevacizumab added to first-line chemotherapy appears to result in a small survival benefit, but the effect may be limited to combination with fluoropyrimidine monotherapy. If added to 5-FU with irinotecan or oxaliplatin, a survival benefit is not clearly proven (see 4.3.3.1).[126]

In the second-line setting, bevacizumab added to chemotherapy has a more clear survival benefit compared to chemotherapy alone, at the cost of an increase in adverse events.[120] Also aflibercept, if added to FOLFIRI chemotherapy, can improve overall survival in the second-line setting (see 4.3.3.2).[120]

If compared to best supportive care, anti-EGFR therapy results in a survival benefit in the second or later line therapy in RAS wild type patients.[125] When studies with the combination anti-EGFR therapy and chemotherapy compared with chemotherapy alone are added in the meta-analysis, a clear survival benefit is no longer seen (see4.3.3.2).[127]

In refractory colorectal cancer, regorafenib modestly improve overall survival, compared to best supportive care.[128]

4.3.3.1 *First-line treatment*

Reference + search date	Intervention and comparator + indication	OS	Quality of life	Other outcomes
Sun 2019[125] Search date: 20 May 2019	Patients with KRAS, NRAS or HRAS wild type metastatic colorectal cancer (stage III included) Intervention: multiple chemotherapies with anti-EGFR monoclonal antibodies (cetuximab or panitumumab) Comparator: chemotherapy without anti-EGFR monoclonal antibodies	Oxaliplatin-based chemotherapy + anti-EGFR therapy overall HR 0.89 (95%CI 0.78-1.02) First-line HR 0.92 (95%CI 0.83-1.02) Iriniotecan-based chemotherapy + anti-EGFR therapy overall HR 0.89 (95%CI 0.80-0.98)		
Baraniskin 2019[126] Search date: May 2018	Patients with diagnosis of metastatic colorectal cancer without prior chemotherapy Intervention: chemotherapy + bevacizumab Comparator: chemotherapy alone	Overall HR 0.85 (95%CI 0.78-0.94) Fluoropyrimidine monotherapy HR 0.83 (95%CI 0.70-0.98) chemotherapy regimens based on 5-FU + irinotecan or oxaliplatin HR 0.92 (95%CI 0.81-1.04)		
Chan 2017[127] Search date: 9 September 2016	Patients with KRAS wild type metastatic (stage IV) colorectal cancer Intervention: anti-EGFR monoclonal antibodies + chemotherapy Comparator: chemotherapy alone	HR 0.87 (95%CI 0.75-1.02)	2 studies showed neutral or equivocal results	

4.3.3.2 *Second-line (or later) treatment*

Reference + search date	Intervention and comparator + indication	OS	Quality of life	Other outcomes
Mocellin 2017[120] Search date: May 2016	Patients with distant or locally advanced unresectable colorectal cancer (stage IV disease) that progressed, recurred or did not respond to first-line therapy Intervention: bevacizumab + chemotherapy Comparator: chemotherapy	HR 0.79 (95%CI 0.70-0.88)		Serious adverse events: RR 1.72 (95%CI 1.23-2.43)
Sun 2019[125] Search date: 20 May 2019	Patients with KRAS, NRAS or HRAS wild type metastatic colorectal cancer Intervention: EGFR monoclonal antibodies (cetuximab or panitumumab) Comparator: best supportive care	HR 0.65 (95%CI 0.54-0.78)		
Chan 2017[127] Search date: 9 September 2016	Patients with KRAS wild type metastatic colorectal cancer Intervention: anti-EGFR monoclonal antibodies + chemotherapy/best supportive care Comparator: chemotherapy alone/best supportive care	Second line HR 0.93 (95%CI 0.82-1.05) Third line HR 0.79 (95%CI 0.50-1.24)	1 study in third line patients showed improved quality of life with anti-EGFR antibodies. 2 studies in second-line treatment showed neutral or equivocal results.	
Sonbol 2019[128] August 2018	patients with refractory metastatic colorectal cancer Intervention: Regorafenib comparator: best supportive care	HR 0.67 (95%CI 0.48-0.93)	"Trials showed a similar deterioration in quality of life in both the regorafenib and comparator groups.	
Mocellin 2017[120] Search date: May 2016	Patients with distant or locally advanced unresectable colorectal cancer (stage IV disease) that progressed, recurred or did not respond to first-line therapy Intervention: FOLFIRI + aflibercept Comparator: FOLFIRI	aflibercept HR 0.82 (95%CI 0.71-0.94) bevacizumab, aflibercept or ramucirumab + FOLFIRI HR 0.82 (95%CI 0.74-0.90)		

4.3.3.3 Discussion

In spite of a high uptake of bevacizumab and its survival benefit seen in clinical trials, no improvement in overall survival is seen for stage IV colorectal cancer patients in our observational data. The absolute difference in survival may be too small to have a meaningful impact in real world practice. For the other selected drugs, uptake remained low, hence a possible effect may not be visible in the overall population. In addition, absolute benefits for e.g. regarafinib appear to be very limited (maximum 2.5 months).

Findings in other countries

In the United States, based on the SEER registry, overall survival of patients diagnosed with metastatic colorectal adenocarcinoma was compared for three time-periods: 2004-2006, 2008-2010 and 2012-2013. No evidence of survival improvement was seen.[129]

Based on data from the Lithuanian cancer registry, the five-year relative survival of colorectal cancer patients was calculated for three time periods of diagnosis. For advanced cancer with distant spread, a slight improvement was seen: 5-year relative survival was 4.5 % (95%CI 3.6-5.6) for patients diagnosed between 1998 and 2002, 6.61% (95%CI 5.4-8.0) for patients diagnosed in 2003-2007 and 6.8% (95%CI 5.5-8.3) for patients diagnosed in 2008-2012. For advanced tumours with regional lymph node involvement, a greater improvement was seen. Five-year relative survival for these patients was 40.3% (95%CI 39.98-42.54) for patients diagnosed in 1998-2002, 49.2% (95%CI 46.6-51.9) for the 2003-2007 cohort and 52.4% (95%CI 49.6-55.1) for patients diagnosed in 2008-2012.[130]

Also in the Netherlands, data from the national cancer registry were used to assess time trends in survival. For patients diagnosed with stage IV colon or rectal cancer, an increase was seen in the use of systemic therapy with or without resection and the use of metastasectomy. The five-year relative survival of stage IV colorectal cancer patients increased from 4 to 12% between 1989-1994 and 2010-2014. For patients diagnosed in 2005-2009, five-year relative survival was 9%.[131]

Limitations

- Unfortunately, we cannot evaluate the evolution of overall and relative survival according to RAS mutation status based on available data. For RAS wild type patients, overall survival may have improved after the introduction of anti-EGFR therapy, without having a clear impact on the overall survival curves for the general colorectal cancer population.
- Furthermore, we don't know whether anti-EGFR treatment and bevacizumab were used in the first-line or second-line (or later) setting.
- Although several clinical trials result in a significant effect in terms of relative effect, the absolute gain in overall survival may be limited. For example, the 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.[132]
- Our analysis did not select drugs such as trifluridine-tipiracil or BRAF inhibitors (encorafenib), because their uptake were too recent.
- Finally, other therapeutic options such metastasectomy or ablation techniques for liver or peritoneal metastases may also have changed over time and have affected survival. Data on these type of treatment options are not available for this project.

4.3.4 Economic literature: cost-effectiveness

For more information about the economic evaluations in the identified HTA reports, we refer to Appendix.

Confidential prices

From the seven identified technology assessment reports, two were terminated because no evidence submission was received from the manufacturer or sponsor of the technology.[133, 134] In two of the five remaining reports, the interventions (bevacizumab, cetuximab and panitumumab in TA242 and bevacizumab and cetuximab in TA118) were not recommended for reimbursement and no results of analyses with

confidential prices were reported. In the remaining reports, there are confidential price discounts for the interventions under consideration.[135-137] In TA212,[137] there is also a discount for the comparator and including this discount has an important impact on results (see further).

Quality of life

In all of the identified assessments, there are issues with the inclusion of HRQoL in the assessments. In TA242,[138] a generic utility instrument was used in a study with cetuximab (HUI) and panitumumab (EQ-5D). However, the Committee 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."[138] Furthermore, for the assessment of bevacizumab in combination with non-oxaliplatin chemotherapy, the cost-effectiveness could not be estimated because of the absence of RCT evidence (and thus also the absence of reliable results for the impact on QoL measured with a generic utility instrument). Also in TA118,[139] there is no head-to-head trial available in which QoL is measured with a generic utility instrument.

In TA439, "none of the included publications reported HRQoL estimates for the RAS WT population."[140] "In the absence of RAS WT data, EuroQol 5-Dimensions data from two trials with Kirsten rat sarcoma (KRAS) WT populations was used."[140]

In TA212, an assessment of bevacizumab, it was noted by the Committee "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."[137]

In TA307, "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, … ."[136] Unfortunately, "data on health-related quality of life were not collected in the VELOUR trial."[136]

As mentioned before, the two remaining identified technology assessment reports were terminated because no evidence submission was received from the manufacturer or sponsor of the technology.

Uncertainty & influential parameters

Based on the lack of measuring quality of life with a generic utility instrument (see previous paragraph), it is not surprising that utility values in the assessments are highly uncertain. This was the case in all identified reports in which an assessment was made (i.e. excluding the terminated appraisals). In TA242, "the Committee concluded that the utility values in the manufacturer's model were highly uncertain."[138] In TA118: "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."[141] For TA439, there is "the lack of reported HRQoL estimates for the RAS WT population."[140] In TA212, HRQoL is one of the main areas of uncertainty within the cost-effectiveness analysis.[142] Finally, in TA307, "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."[136]

The lack of a head-to-head comparison was noted in two studies: TA118: "The Committee noted that there were currently no clinical studies available comparing cetuximab with FOLFOX [5-FU and oxaliplatin], and therefore the relative clinical effectiveness of cetuximab as a second-line treatment could not as yet be determined."[139] TA439: "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."[140] The two terminated appraisals are not further discussed, but in TA240, the manufacturer stated that at that time "there was not sufficient evidence to robustly estimate the cost effectiveness of panitumumab for this indication."[133]

Not surprisingly, overall survival estimates are one of the main factors affecting the cost effectiveness:[138, 140, 142] For example, in TA242, "for panitumumab, the estimate of overall survival was the main factor found to substantially change the ICER."[138] The importance of the applied time horizon and checking the extrapolation scenarios is linked to the importance of the overall survival estimates. For example in TA307, "the Committee agreed that, when the time horizon is much longer than the trial duration, and the life expectancy of most patients, it is particularly important to explore the assumptions underlying how overall survival is extrapolated."[136]

Other important factors were the treatment duration[138, 140, 142] or the drug acquisition costs.[138] In an assessment of cetuximab and panitumumab, the authors state that "first-line drug acquisition costs were the largest cost items."[140] This makes the results sensitive for the applied discount. In one analysis, the discount for the comparator also had a major impact on the ICER (see results for RA212 in the next section).

Results

The ICERs are as follows (see more details in appendix):

- **Bevacizumab, cetuximab and panitumumab**
- Metastatic colorectal cancer that has progressed after first-line chemotherapy:[138]
  a. Cetuximab: people with KRAS wild-type metastatic colorectal cancer:
     - Cetuximab plus best supportive care compared with best supportive care alone: £98 000 per QALY gained.
     - Cetuximab plus irinotecan plus best supportive care compared with best supportive care alone: £88 000 per QALY gained.
  b. Panitumumab: Panitumumab plus best supportive care compared with best supportive care alone: £150 000 per QALY gained.
  c. Bevacizumab: bevacizumab plus non-oxaliplatin chemotherapy compared with best supportive care: lack of relevant evidence on clinical effectiveness → not feasible to carry out a cost-effectiveness evaluation of bevacizumab.
- **Bevacizumab and cetuximab**
- Metastatic colorectal cancer:[139]
  a. Bevacizumab: first-line treatment
     - Bevacizumab combined with IFL compared with IFL alone: £62 857 per QALY gained
     - Bevacizumab combined with 5-FU/LV compared with 5-FU/LV alone: £88 436 per QALY gained.
  b. Cetuximab: patients with EGFR-expressing metastatic colorectal cancer who have previously failed on irinotecan-including therapy
     - Cetuximab combined with irinotecan vs. active/best supportive care (indirect comparison): £77 210 to £370 044 per QALY gained.
- **Cetuximab and panitumumab**
- Rat sarcoma (RAS) wild-type (WT) metastatic colorectal cancer:[135]
  a. Without discounts:
     - - Cetuximab plus FOLFIRI (folinic acid + 5-fluorouracil + irinotecan) compared with FOLFIRI: £122 554 per QALY gained.
     - - Cetuximab plus FOLFOX (folinic acid + 5-fluorouracil + oxaliplatin) compared with FOLFOX: £104 205 per QALY gained.
     - - Panitumumab plus FOLFOX compared with FOLFOX: £204 103 per QALY gained.
  b. With discounts:

- - Cetuximab plus FOLFIRI compared with FOLFIRI: <£50 000 per QALY gained.
- - Cetuximab plus FOLFOX compared with FOLFOX: likely to be similar to that for cetuximab plus FOLFIRI compared with FOLFIRI alone
- - Panitumumab plus FOLFOX compared with FOLFOX: <£50 000 per QALY gained.
- - Panitumumab plus FOLFIRI compared with FOLFIRI: likely to be similar to that for panitumumab plus FOLFOX compared with FOLFOX alone

- **Bevacizumab**
- Metastatic colorectal cancer:[137]
  - 1st line treatment

  a. without discount:
    - B-XELOX versus XELOX: £105 000 per QALY gained.
    - B-FOLFOX-6 versus FOLFOX-6: £108 000 per QALY gained.

  b. with discount for bevacizumab:
    - B-XELOX versus XELOX: £30 000 per QALY gained.
    - B-FOLFOX-6 versus FOLFOX-6: £24 600 per QALY gained.

  c. 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.

  - 2nd line treatment (without discount): B-FOLFOX-4 compared with FOLFOX-4: £102 644 per QALY gained.
    - **Panitumumab**

      Terminated appraisal because no evidence submission was received from the manufacturer.[133]
    - **Aflibercept**

      Metastatic colorectal cancer that has progressed following prior oxaliplatin-based chemotherapy:[136]

      The most plausible ICER was higher than the normally acceptable maximum ICER range of £20 000–30 000 per QALY gained.
    - **Regorafenib**

      Terminated appraisal because no evidence submission was received from the manufacturer.[134]

Of the seven identified evaluations, only one evaluation reached positive conclusion after discounts were included for the intervention. 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."[140] 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."[135]

The other evaluations reached less positive recommendations. In two evaluations, this was because no evidence was submitted by the manufacturer. As a result, "NICE is unable to recommend panitumumab with 5 fluorouracil, folinic acid and irinotecan (FOLFIRI) for previously treated metastatic colorectal cancer … "[133] and "NICE is unable to make a recommendation about the use in the NHS of regorafenib for metastatic colorectal cancer after treatment for metastatic disease … ."[134]

In three other evaluations, the interventions could not be considered a cost-effective use of resources and were not recommended for reimbursement:

- TA242: "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."[138] This was because it was not possible to confirm by how much the intervention would extend life (bevacizumab) or because the ICERs were very high (cetuximab and panitumumab) and did not represent a cost-effective use of NHS resources.[138]

- TA118: "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."[139]
- TA307: "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."[136]
- "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."[136]

In one evaluation, it is shown that it is important to include discounts not only for the intervention but also for the comparator: in TA212, "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."[137] As a result, "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."[137] Also for second-line or later treatment of metastatic colorectal cancer, "the Committee concluded that bevacizumab in combination with oxaliplatin-containing regimens could not be recommended as a cost-effective use of NHS resources."[137]

4.3.5 Summary

Observational data

- Observational data indicate that overall survival of Belgian stage IV colorectal cancer patients has not substantially improved between 2004 and 2017. Three-year observed survival probability increased slightly from 21.5% (95%CI 19.2-23.8%) for patients diagnosed in 2004 to 28.2% (95%CI 25.4-31.0%) in 2017. Median survival remained stable between 1.3 and 1.6 years.
- For all stages of colorectal cancer, oncological drug expenditures increased between 2004 and 2009, mainly based on the increasing number of patients treated with oncological drugs. From 2009 onwards, the number of treated patients did not further increase substantially, but overall expenditures were higher than the years before 2009, mainly due to the additional costs spent for bevacizumab. In 2004, about €6.6 million was spent on oncological drugs for colorectal cancer patients and this was about €56 million in 2016.
- Drug expenditures for stage IV colorectal cancer patients during the first two years after diagnosis clearly increase from the incidence

years 2008-2009 onwards, mainly caused by the expenditures for bevacizumab.

- The number of patients with stage IV colorectal cancer for which oncology drug expenditures were identified increased over the years, from 878 in 2004 to 1 048 in 2017.
- Mean cost per patient during the first two years after diagnosis was about €10 600 for patients diagnosed in 2004 and increased to more than €18 000 for patients diagnosed in 2009 or later.

Medical literature

- Anti-EGFR treatment in RAS wild type patients (panitumumab, cetuximab)
  - In the first-line setting, anti-EGFR monoclonal antibodies (panitumumab, cetuximab) may have a survival benefit in RAS wild type patients, but the effect is probably small and results appear only statistically significant for the combination with irinotecan-based chemotherapy.
  - If compared to best supportive care, anti-EGFR therapy results in a survival benefit in the second or later line therapy in RAS wild type patients. When studies with the combination anti-EGFR therapy and chemotherapy compared with chemotherapy alone are added in the meta-analysis, a clear survival benefit is no longer seen.
- Anti-VEGF therapy (bevacizumab, aflibercept, regorafenib)
  - Bevacizumab added to first-line chemotherapy appears to result in a small survival benefit, but the effect may be limited to combination with fluoropyrimidine monotherapy. If added to 5-FU with irinotecan or oxaliplatin, a survival benefit is not clearly proven.
  - In the second-line setting, bevacizumab added to chemotherapy has a more clear survival benefit compared to chemotherapy alone, at the cost of an increase in adverse events.
  - Aflibercept, if added to FOLFIRI chemotherapy, can improve overall survival in the second-line setting.
  - In refractory colorectal cancer, regorafenib can improve overall survival, compared to best supportive care.

Economic literature

- In the economic evaluations of the identified HTA reports in colorectal cancer, a confidential price discount is present for the interventions in three out of seven evaluations. In the other four evaluations, the assessment was terminated because no evidence submission was received from the manufacturer (2 cases) or the evaluations under consideration were not recommended for reimbursement (2 cases).
- The five studies that were not discontinued all have shortcomings in measuring QoL with a generic utility instrument: either there is no head-to-head trial, or no HRQoL measurement with a generic utility instrument was performed in the relevant population.
- Next to the uncertainty around the impact on HRQoL, one of the greatest uncertainties in the economic evaluations is the estimation of the treatment effect. In one assessment, it is stated that “when the time horizon is much longer than the trial duration, and the life expectancy of most patients, it is particularly important to explore the assumptions underlying how overall survival is extrapolated”
- Drug acquisition costs are the largest cost items and make the results sensitive to the applied discounts.
- None of the evaluations comes to the conclusion that the intervention would represent good value for money applying the official list prices.
- Only one of the identified economic evaluations (TA439) reaches a positive reimbursement recommendation after applying confidential discounts. Without these discounts, the researchers state the

interventions "are likely to represent poor value for money when judged by cost-effectiveness criteria currently used in the UK".

- As a result of the confidential prices, exact ICERs used for decision making are not transparently reported.
- One of the evaluations (TA212) clearly shows that also including the discounts for the comparators has a major impact on the results: Initially, without including any discount, the interventions are not considered cost-effective. In second instance, this would be the case when including a discount for the interventions. Finally, when also including a discount for the comparator, the interventions could not be recommended as a cost-effective use of NHS resources.

4.4 Head and neck cancer

4.4.1 Introduction

Head and neck cancer (HNC) is a large heterogenous group of tumours arising from various anatomical sites encompassing oral cavity, nasopharynx, oropharynx, hypopharynx and larynx. It represents the seventh most common cancer worldwide.[143, 144] In 2018, 2 730 head and neck cancers were newly diagnosed in Belgium.[33]

Nearly all cases of HNC are squamous cell carcinoma and are associated with alcohol use and smoking. Oral infection with human papilloma virus (HPV) is another increasing reported aetiology of oropharyngeal HNC.[143-145]

The majority of patients have loco-regionally advanced disease at the time of diagnosis and up to 50% of them experience a relapse after primary treatment.[144, 146]

Tumour staging varies according to the anatomical site and has recently been modified.[143, 147] Briefly, stage III corresponds to large tumour size with marked local invasion and lymph node invasion (in almost all cases), whereas stage IV concurs with more pronounced locoregional spreading of the tumour (marked invasion of surrounding structures) or with the presence of distant metastasis.[143]

Multimodal therapy combining surgery, radiotherapy or chemotherapy are the proposed therapeutic options for stage III and IV HNC. Possibilities for locally advanced HNC encompass surgery along with adjuvant chemo-radiotherapy or chemo-radiotherapy alone, when surgery is not technically feasible.[144]

In recurrent or metastatic disease, until recently, chemotherapy (platinum plus fluorouracil) in association with cetuximab was the standard of care.[144] Cetuximab is a monoclonal antibody directed against the Epidermal Growth Factor Receptor (EGFR), which is overexpressed in HNC,[148] and showed a benefit in terms of survival in the phase III-clinical trial in 2008.[149] Currently, pembrolizumab, an immune checkpoint inhibitor drug targeting PD-1 (Programmed Death-1) has been added to first-line therapy in tumours expressing Programmed Death- 1 Ligand (PD-L1).[144, 150] Nivolumab that targets PD-L1, is used in patients who progressed within 6 months of platinum therapy.[144, 150]

Cetuximab is the oncological drug on which the present report focused.

Table 17 presents the list of selected drugs for Head and Neck cancer.

Table 17 – Selected drugs for head & neck cancer

Drug	Year#	Trade Name	Company$	Mechanism of action
cetuximab	2006	Erbitux	Merck	monoclonal IgG1antibody that is specifically directed against the epidermal growth factor receptor (EGFR)

#year of start reimbursement first indication in Belgium; $ of the originator.

4.4.2 Observational data

4.4.2.1 Patient characteristics, survival and expenditures

Patient characteristics did not change substantially over time. An increase in the number of diagnosed head and neck cancers is noticed over the three incidence periods,[s] including a slight increase of proportion of women over time (Table 18A). Observed overall survival (Table 18B) and relative survival (see appendix) of stage IV head and neck cancer did not change significantly over time. Three-year observed survival was 39.0% (95%CI 35.4-42.5) for patients diagnosed in 2004 and 40.3% (95%CI 36.7-43.9) for those diagnosed in 2017 (Table 18C). Median survival was 1.8 years (95%CI 1.5-2.1) for patients diagnosed in 2004 and 2.0 years (95%CI 1.7-2.4) for patients diagnosed in 2017. An additional analysis comparing the period before and after the introduction of cetuximab shows only a slight improvement in overall survival (Figure 4).

For patients with stage III head and neck cancer, an improvement of overall and relative survival was seen in the last time period (2014-2017) compared to earlier periods (see appendix).

Overall drug expenditures for head and neck cancer (all stages) started to increase after 2006 (calendar year), due to a raise in the number of patients receiving oncological drugs and the introduction of cetuximab. A further steep increase is seen after 2016, especially linked to the use of nivolumab and to a smaller extend also pembrolizumab. In 2004, about €450 000 was spent on oncological drugs for head and neck cancer patients, in 2018 it had increased to more than €15 million (Table 19A).

The same pattern is seen for patients with stage IV head and neck cancer. From incidence year 2007 onwards, expenditures during the first two years after diagnosis increase due to the introduction of cetuximab and an increase in the number of patients treated with oncological drugs (from 447 in incidence year 2004 to 695 in incidence year 2017). A further increase is seen from incidence year 2015 onwards with the introduction of pembrolizumab and mainly nivolumab. Expenditures during the first two years after diagnosis were about €420 000 for incidence year 2004, about €3.6 million for incidence year 2015 and about €5 million in 2017. The mean amount of expenditures for oncological drugs per patient, the first two years after diagnosis, was less than €1 000 for incidence year 2004 and more than €7 000 per patient for incidence year 2017.

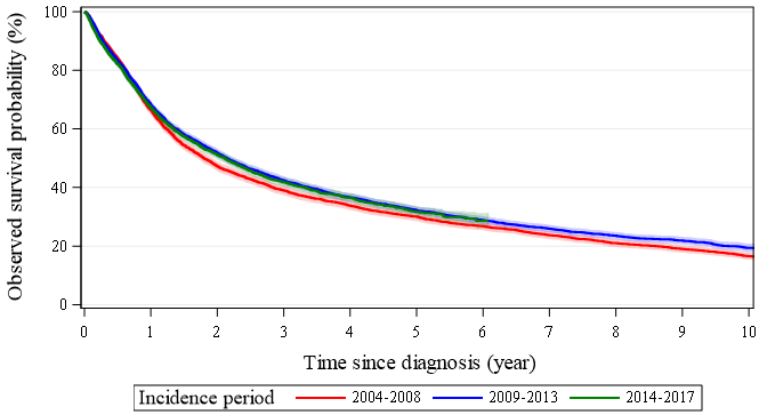
[s] We remark that the first two incidence periods (2004-2008 and 2009-2013) contain 5 years, while the third incidence period (2014-2017) only covers 4 years.

Table 18 – Head and neck cancers (2004-2017), combined stage IV (observed survival): A) Patient characteristics; B) Kaplan-Meier graph per incidence period; C) Time trend with incidence year*; D) Median survival time* **

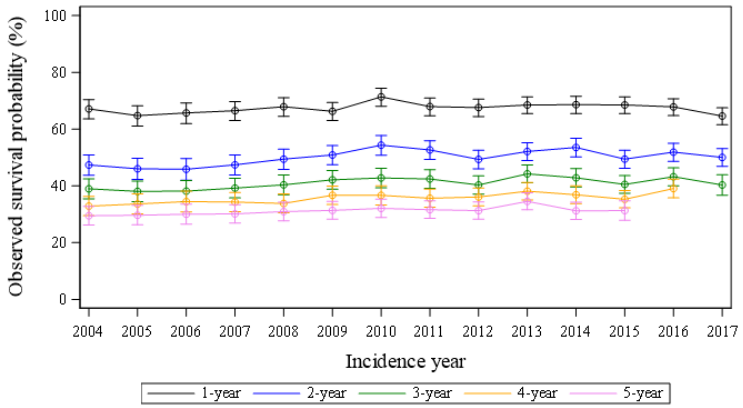
A

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

B

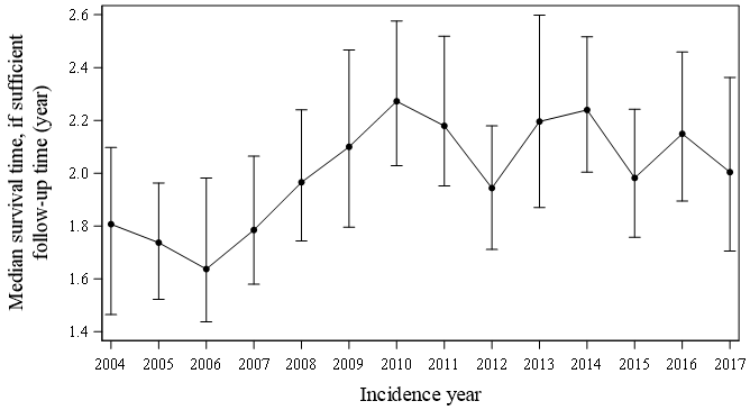


C



Year: 3-y OS [95%CI]
2004: 39.0 [35.4, 42.5]
2005: 38.1 [34.4, 41.7]
2006: 38.2 [34.4, 41.9]
2007: 39.2 [35.8, 42.7]
2008: 40.4 [36.9, 43.8]
2009: 42.1 [38.8, 45.4]
2010: 42.8 [39.3, 46.2]
2011: 42.4 [39.1, 45.7]
2012: 40.3 [37.1, 43.5]
2013: 44.2 [41.1, 47.4]
2014: 42.8 [39.6, 46.1]
2015: 40.5 [37.4, 43.6]
2016: 43.2 [40.0, 46.3]
2017: 40.3 [36.7, 43.9]

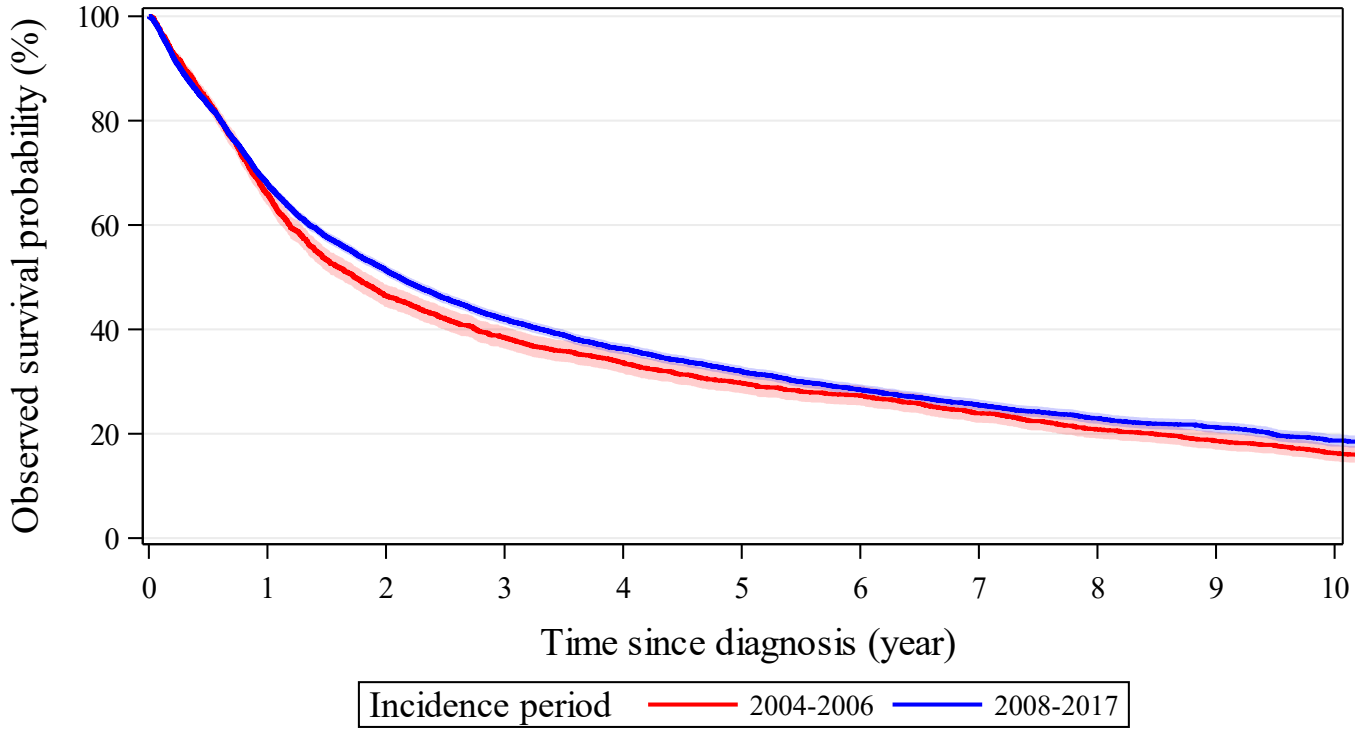
D



Year: Med. ST [95%CI]
2004: 1.8 [1.5, 2.1]
2005: 1.7 [1.5, 2.0]
2006: 1.6 [1.4, 2.0]
2007: 1.8 [1.6, 2.1]
2008: 2.0 [1.7, 2.2]
2009: 2.1 [1.8, 2.5]
2010: 2.3 [2.0, 2.6]
2011: 2.2 [2.0, 2.5]
2012: 1.9 [1.7, 2.2]
2013: 2.2 [1.9, 2.6]
2014: 2.2 [2.0, 2.5]
2015: 2.0 [1.8, 2.2]
2016: 2.1 [1.9, 2.5]
2017: 2.0 [1.7, 2.4]

*Med. ST: median survival time; 3-y OS: 3-year observed survival; * the error bars represent the 95%CI. ** When the upper error is not plotted, the upper limit could not be determined with the available follow-up data. Source: BCR.*

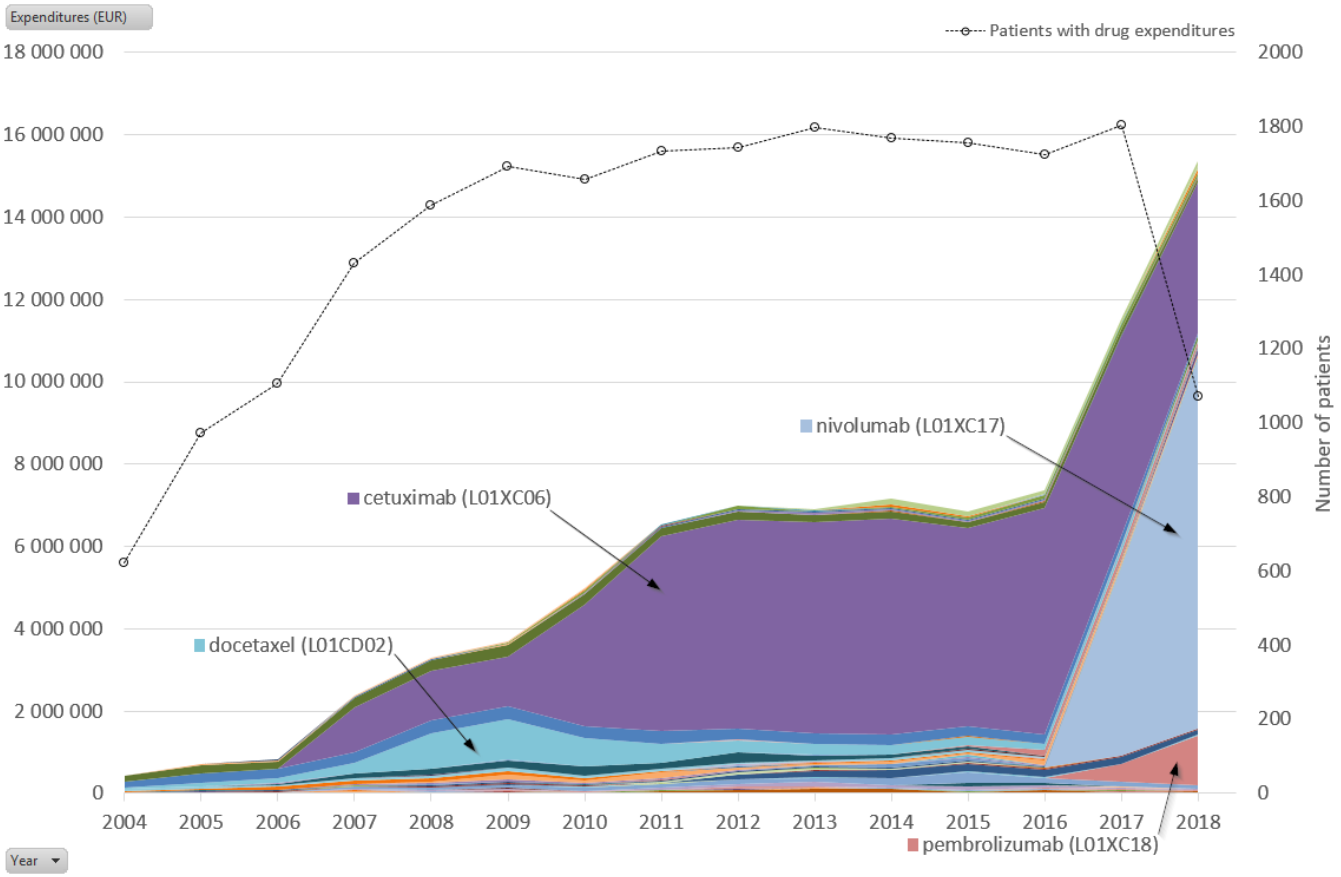
Figure 4 – Head and neck cancers (2004-2017), combined stage IV (observed survival): Kaplan-Meier graph 2004-2006 vs 2008-2017



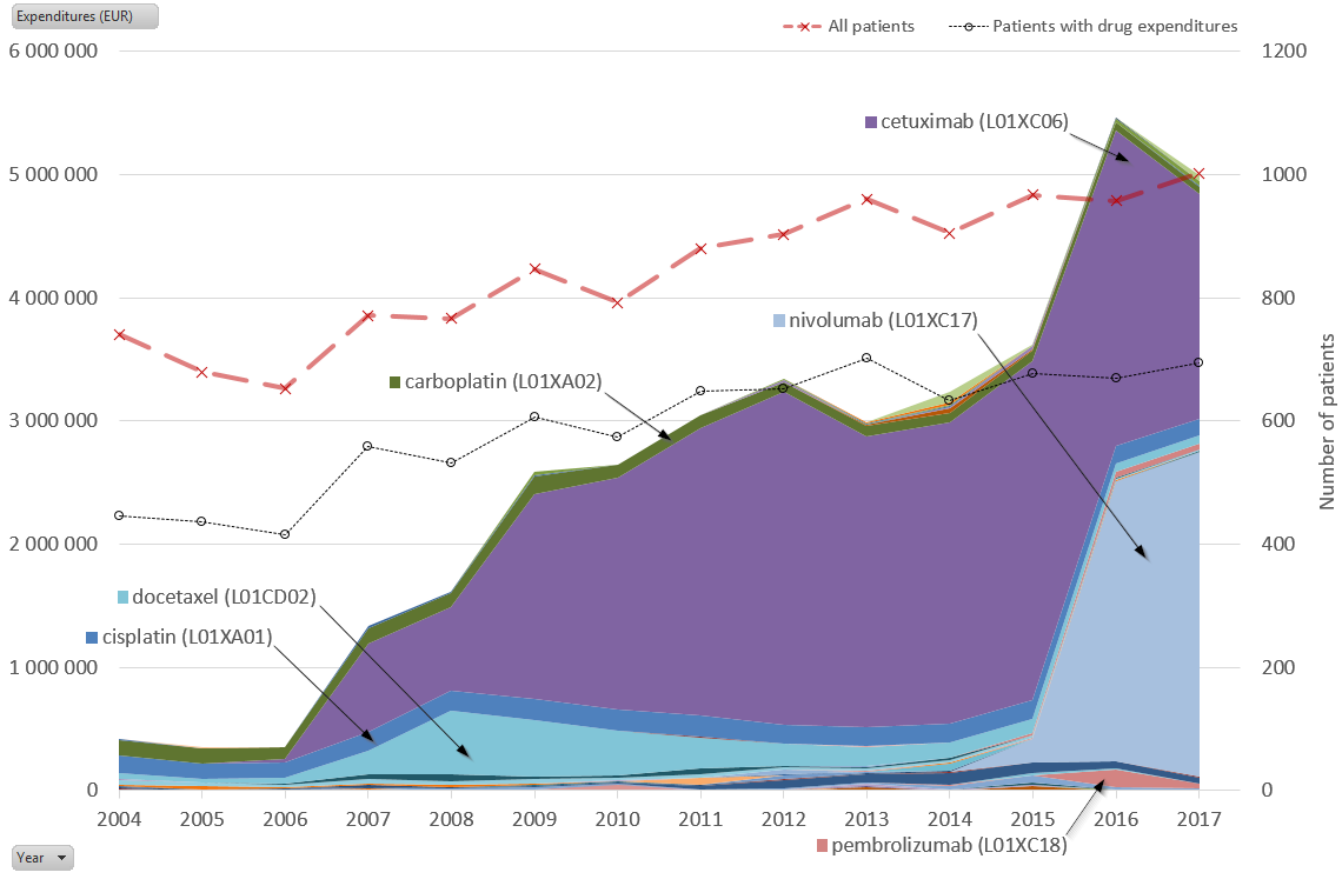
Source: BCR.

Table 19 – Head and neck cancers: drug expenditures

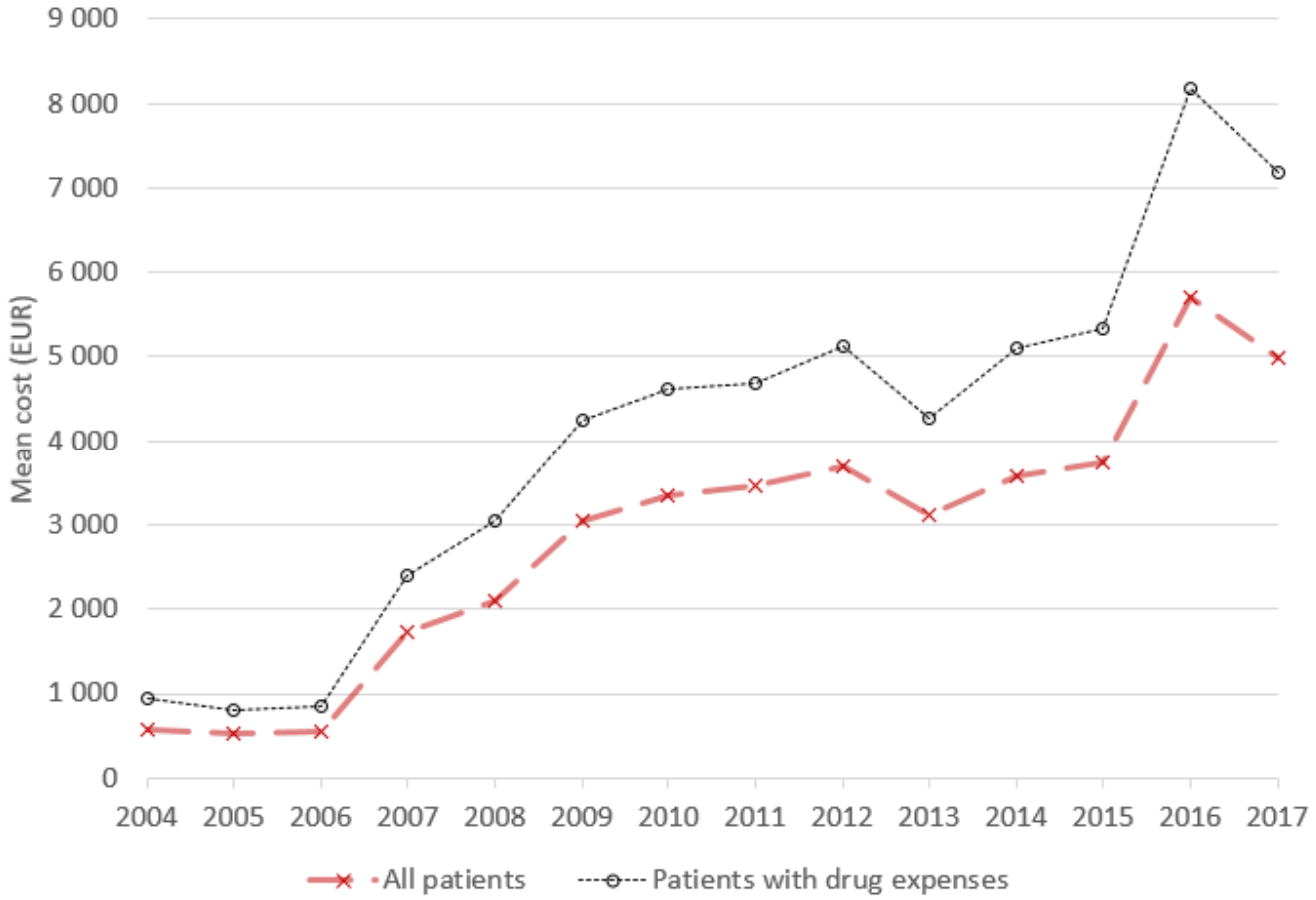
A) Oncological drug expenses per calendar year (all stages)



B) Expenses for the first two years after incidence, per incidence year (stage IV)



C) Mean cost per patient for the first two years after incidence, per incidence year (stage IV)



Source: BCR-IMA.

4.4.2.2 *Drug uptake for a selection of drugs during the first 5 years after diagnosis*

Cetuximab is reimbursed since 2006. Before incidence year 2007, uptake during the first five years after diagnosis ranged between 0.5 to 2% (Table 20). Uptake substantially rose from incidence year 2007 and peaked at the value of 29% in the incidence year 2011-2012. Its uptake decreased from the incidence year 2012 onwards and reached 17% in 2017 but this decrease should be interpreted cautiously since the follow-up period is less than 5 years for the more recent incidence years.

Table 20 – 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. $ IMA data were only available up to the second trimester of 2019 and might have a delay of two years. Five-year follow-up data are thus not 100% complete from incidence year 2012 onwards (see part 3.1.3). Source: BCR-IMA.

4.4.3 *Medical literature: efficacy*

Systemic reviews indicate that overall, adding cetuximab (and no other anti-EGFR drug) to standard therapy improves overall survival of patients with a SCC tumour treated with radiotherapy or chemotherapy.[151] Nevertheless, a significant higher rate of secondary adverse events is reported when cetuximab is added to standard therapy.[151] For patients presenting recurrent or metastatic SCC, a survival benefit is observed when anti-EGFR drugs are administered simultaneously with chemotherapy in comparison to chemotherapy alone. Also for patients with a stage III or IV SCC of the H&N who are treated with radiotherapy, the addition of anti-EGFR therapy to radiotherapy improves overall survival compared to radiotherapy alone. However, if the combination of radiotherapy and anti-EGFR therapy is compared to concurrent chemoradiation, no clear survival benefit is seen.[151, 152]

Chan et al. performed a systematic review in the subgroup of people with oral cavity and oropharyngeal tumours and reported specifically for cetuximab. Compared to concurrent chemoradiation, no survival benefit was seen for radiotherapy combined with cetuximab.[152]

Reference + search date	Intervention and comparator + indication	OS	Quality of life	Other outcomes
Tian 2018[151] Search date: 28 July 2016	Patients with SCC of the H&N Intervention: standard therapy + cetuximab Comparator: standard therapy	HR 0.83 (95%CI 0.73-0.94)		Serious adverse events: RR 1.05 (95%CI 1.01-1.10)
Tian 2018[151] Search date: 28 July 2016	Patients with recurrent or metastatic SCC of the H&N Intervention: chemotherapy + anti-EGFR therapy (majority of studies with cetuximab) Comparator: chemotherapy	HR 0.86 (95%CI 0.78-0.95)		
Tian 2018[151] Search date: 28 July 2016	Patients with stage III/IV SCC of the H&N treated with radiotherapy Intervention: anti-EGFR therapy + radiotherapy Comparator: radiotherapy (+/- chemotherapy)	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)		
Chan 2015[152] Search date: 3 February 2015	Patients with cancer of the oral cavity or the oropharynx Intervention: anti-EGFR monoclonal antibodies (cetuximab or nimotuzumab) Comparator: radiotherapy alone or radiotherapy + chemotherapy	anti-EGFR therapy + radiotherapy versus radiotherapy alone: HR 0.73 (95%CI 0.58-0.91) Cetuximab + radiotherapy versus chemoradiation HR 0.95 (95%CI 0.74-1.23)		

4.4.3.1 Discussion

Although for adding cetuximab to radiotherapy and for adding cetuximab to chemotherapy in patients with advanced head and neck cancer a survival benefit is seen in clinical trials, our observational data show no positive evolution of survival over time. This may partially be explained by a limited uptake (maximum 29%). Abolute survival gains may also be limited.

Findings in other countries

Studies of survival trends of HNC patients in nationwide population-based settings are limited.

- In a population based sample of 6 291 patients with HNC in Germany, survival was analysed from 1996 to 2011. The 5-year and 10-year overall survival for the entire cohort was 49.1% and 34.1%, respectively. The use of cetuximab increased over time, mainly during the last year of the observation period. Specifically, in stage III-IV HNC patients, 5-year overall survival showed a significant increasing trend and was 34.9% in 1996-2000, 38% in 2001-2005 and 44.3% in 2006-2011.[153]
- In Denmark, data from the Nationwide Cancer Registry on 34 606 HNC patients were analysed between 1980 to 2014. For all HNC patients, the relative survival at 5 years rose significantly from 49.0% (95%CI 47-51) in 1980-1984 to 62.4% (95%CI 61-63.8) in 2010-2014. This study included all histological types of tumours (including thyroid cancer) and squamous cell carcinoma accounted for 69% (23 894 people) of the total cohort.[154]
- In Italy, data from national cancer registry showed that the five-year age-standardized relative survival significantly improved between 1988 and 2012 in the patients with squamous cell carcinoma cancers arising from HPV-related sites (tonsil-oropharynx, base of the tongue) and the oral cavity. Rates increased from 24.1% for the 1988-1992 period to 45.3% for the 2008-2012 period. Conversely, it remained rather unchanged in the patients with laryngeal/hypopharyngeal HNC.[155]
- In Australia, data from 1301 metastatic HNC patients treated in four medical centres were analysed in four decades-periods between 1980 and 2017. Between 1990-1999 and 2000-2009, a significant reduction in overall survival was observed, when compared to the baseline cohort treated between 1980-1989. Adjusted hazard ratio were 0.56 (95%CI 0.33-0.96) for 1990-1999, 0.55 (95%CI 0.33-0.92) for 2000-2009 and 0.50 (0.29-0.87) for 2010-2017, respectively.[156]
- In the US, statistically significant improvement in survival was observed, with the overall 5-year relative survival probability, from 54.7% in 1992-1996 to 65.9% in 2002-2006. In metastatic stages, 5-year relative survival increased across different tumour localisations, from 20.2% to 29.5% (oral cavity), 24.7% to 35.2% (tongue) and from 23.5% to 41.5% (tonsil)oropharynx). However, immunotherapy was not yet approved during this studied period.[157] In another study, locoregionally advanced HNC, improvements of survival has been observed principally in oropharyngeal cancer. In a comparison of three time periods in US, 5-year overall survival significantly improved from 42.3% (1993-1998) to 72.5% (1999-2003), and 78.4% (2004-2010) in patients with oropharyngeal tumours. Conversely, a non-significant trend (adjusted p= 0.51) was reported for non-oropharyngeal HNC: five-year overall survival was 51.0% (1993-1998), 58.8% (1999-2003), and 66.3% (2004-2010), respectively.[158]

Limitations

- In this report, survival data did not differentiate between HPV(+) and HPV(-) tumours, who have a different prognosis.[159] However, taking into account this feature could give more insight of oncology drugs on specific subgroups for several reasons:
  - The prevalence of HPV-associated oropharyngeal tumour is relatively high and reaches up to 30% of oropharyngeal squamous cell carcinoma.[160]
  - It is predominantly found in young patients without severe comorbidities and associates with a better outcome.[159, 161]

- Cetuximab along with radiotherapy led to an inferior survival in comparison with cisplatine-radiotherapy regimen in locoregionally advanced HPV-positive oropharyngeal carcinoma.[162]

- The survival gain with cetiximab is rather limited to a few months. Besides,there are no data in the systematic reviews on quality of life of patients receiving cetuximab-based regimens and those receiving chemo-radiotherapy.
- Although adding cetuximab to radiotherapy improves survival compared to radiotherapy alone, it does not result in improved survival if compared to concurrent chemoradiation with cisplatin, which is the current standard of care. Cetuximab should thus only be used if a contraindication for cisplatin is present (see reimbursement criteria in Appendix). We don't have data on the appropriate use of cetuximab.
- Cetuximab is currently less used and indicated in recurrent/metastatic disease. Pembrolizumab is now the treatment used in the majority of patients. However, our analyse did not select immune check-point inhibitors because their uptake were too recent.
- Finally, our survival analysis did not discriminate between the several categories of stage IV (metastatic stage IVc from IVa-b).

4.4.4 Economic literature: cost-effectiveness

For more information about the economic evaluations in the identified HTA reports, we refer to the Appendix.

Confidential prices

Two HTA reports assessing the effectiveness and cost-effectiveness of cetuximab in patients with squamous-cell carcinoma of the head and neck (SCCHN) were identified. In the oldest report (TA145 (2008)),[163] including patients with locally advanced SCCHN for which chemoradiotherapy is not considered an appropriate option, no reference was made to confidential discounts. In the more recent published report (TA473 (2017)),[164] including patients with recurrent or metastatic SCCHN, the analysis was restricted to cancer starting in the oral cavity and (revised) confidential discounts were negotiated.

Quality of life

In both identified studies, there are major limitations in the measurement of QoL and inclusion of utilities in the economic evaluations.

In TA473, no generic utility instrument is used in the underlying trial. In this HTA report, "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."[164]

In TA145, the authors mention QoL is measured in the trial: "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."[165] However, at the moment of their assessment, no such information was available: "The published paper makes no reference to a HRQoL questionnaire, although details of

HRQoL assessment are provided in the clinical trial protocol.[166] To date any HRQoL findings from the Bonner et al study remain unpublished.[167"165] Instead, a very indirect way to include utilities was used by the manufacturer: "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 system[168] 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'.[169"165] The ERG had several concerns about this approach. First, "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."[165] "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."[165] … "this implies that the adverse events are utility independent of one another. This is a strong assumption, and it is possible that having two or more adverse events at the same time could lead to a lower utility score than that of the adverse events with the lowest utility taken separately."[165] Furthermore, "it appears that they have actually identified the adverse events that differ between cetuximab plus radiotherapy and radiotherapy plus cisplatin. This would not account for adverse events that may differ between cetuximab plus radiotherapy and radiotherapy alone, which is the comparison in the model. As a result, relevant adverse events may have been excluded."[165]

Uncertainty & influential parameters

In TA473, the main uncertainty was related to the modelled overall survival gains for the subgroup analyses that were performed. "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."[164] Furthermore, "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."[164]

In TA145, "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."[163] Furthermore, "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."[163] Nevertheless, the authors of the HTA report also note that "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."[165]

Results

The ICERs in the identified HTA reports are as follows (see more details in appendix):

- **Cetuximab**
  - Patients with recurrent or metastatic squamous cell cancer of the head and neck. In the Cancer Drugs Fund reconsideration, the analysis included only the oral cavity cancer subgroup:[164]

    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"

    "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."

    "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."[164]
  - Patients with locally advanced squamous-cell carcinoma of the head and neck (LA SCCHN) for which chemoradiotherapy is not considered an appropriate option:[163]

    "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."[165]

    Results per Karnofsky performance-status scores:

    - 100%: £13 151 per QALY gained
    - 90%: £4 467 per QALY gained
    - 80%: £58 200 per QALY gained
    - Less than 70%: £37 000 per QALY gained

    In case of TA473 (2017), cetuximab was recommended for a subgroup after a negotiated confidential discount reduced the ICER to a level that was considered cost-effective: "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."[164]

    In case of the TA145 (2008), no confidential price discounts were taken into account. As a consequence, results were more transparent and ICERs were presented in general and per Karnofsky performance-status score. "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."[163] As a result, "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. "[163]

4.4.5 Summary

Observational data

- Observational data indicate that overall survival of stage IV head and neck cancer patients did not change substantially over time between 2004 and 2017. Three-year observed survival maintained the same level and was 39.0% (95%CI 35.4-42.5) for patients diagnosed in 2004 and 40.3% (95%CI 36.7-43.9) for those diagnosed in 2017. Median survival was 1.8 years (95%CI 1.5-2.1) in incidence year 2004 and 2.0 years (95%CI 1.7-2.4) in incidence year 2017.
- For all stages of head and neck cancer, oncological drug expenditures sharply increased from less than €500 000 in 2004 to more than €15 million in 2018.
- Drug expenditures for stage IV head and neck cancer during the first two years after diagnosis, increased overtime, from €420 000 for incidence year 2004 to about €5 million in incidence year 2017.
    - This rise was largely due to the uptake of cetuximab from incidence year 2007 and later from nivolumab.
    - The number of patients with stage IV head and neck cancer, for which oncology drug expenditures were identified, went up from 447 in incidence year 2004 to 695 in incidence year 2017.
    - Mean cost per patient during the first two years after diagnosis was less than €1 000 for incidence year 2004 and more than €7 000 per patient for incidence year 2017.
- For stage IV HNC patients, five-year uptake of cetuximab grew significantly from incidence year 2007 and peaked at the value of 29% in the incidence year 2011-2012.

Medical literature

- In patients with recurrent or metastatic head and neck squamous cell carcinoma, anti-EGFR drugs along with chemotherapy improves survival when compared to chemotherapy alone.
- For patients with a stage III or IV SCC of the H&N who are treated with radiotherapy, the addition of anti-EGFR therapy to radiotherapy improves overall survival compared to monotherapy radiotherapy. However, if the combination of radiotherapy and anti-EGFR therapy is compared to concurrent chemoradiation, no clear survival benefit is seen.
- Cetuximab causes adverse secondary effects, more frequently than standard therapy.

Economic literature

- In the 2008 assessment of cetuximab, no confidential price discounts were taken into account. In the 2017 assessment, the assessment was made taking into account (revised) confidential discounts.
- Measuring QoL with a generic instrument was not present in the underlying RCT in both of the identified HTA reports. In TA473 (2017), the Evidence Review Group (ERG) considered that the data from the EXTREME trial did not allow for reliable utility estimates for the 2 treatment arms. In TA145, there were also several concerns with the followed approach to estimate utility values.
- The main uncertainty in both assessments is related to the modelled overall survival gains for the subgroup analyses that were performed. In TA473, confidentiality of analyses and results made it difficult to interpret the influence of this uncertainty on results and conclusions. In TA145, this was less a problem since altering the method of extrapolation would be unlikely to cause the ICER to

increase to above £20 000. The ERG stressed that it would require large changes in parameter values to result in cetuximab plus radiotherapy not being cost-effective.

- The decision-making ICERs were transparently reported in TA145 but remained confidential in TA473. In the initial analysis of TA473, including a discount in a revised patient access scheme, the intervention was not considered cost-effective since the most plausible ICER was above the range that would normally be considered cost effective if the end-of-life criteria apply. In a subsequent negotiated commercial access agreement, the ICER was reduced 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.

4.5 Melanoma

4.5.1 Introduction

Melanoma is the most aggressive skin cancer and is part of the ten most frequent cancers in Belgium. It ranks fourth in women and sixth in men. In 2018, 3 489 cases were newly diagnosed.[33]Although most patients are diagnosed at an early stage and have a somewhat favourable prognosis, metastatic melanoma is associated with poor outcomes.

Until 2010, conventional treatment for patients with metastatic melanoma included the conventional chemotherapeutic alkylating agent dacarbazine and the immunostimulatory cytokine, interleukin-2. However, the level of evidence supporting such therapies was low and no substantial benefit on overall survival was clearly demonstrated. In addition, the use of interleukin 2 was hampered by marked toxicity. In the last decade, new immunomodulating agents and targeted therapies focusing on specific molecules involved in the control of immunosuppressive pathways were developed and provided promising results.[170]

In 2010, the immune checkpoint inhibitor ipilimumab, an anti-CTLA4 (cytotoxic T lymphocyte antigen 4) monoclonal antibody, was the first treatment proposed to enhance the immunologic antitumor effect. It blocks the negative regulator of lymphocyte activation CTLA4 and promotes an anti-tumour immune response through the proliferation of activated lymphocytes. It is reimbursed in Belgium since 2012.[171]

Later, programmed cell death protein 1 (PD-1) and its ligand (PD-L1) have also been recognized as key-point targets to hamper tumour growth and promote lymphocytes activation.[172] In Belgium, monoclonal anti-PD-1 antibodies nivolumab, and pembrolizumab have been approved in 2016 among the first-line treatment option for patients with metastatic melanoma.

Besides, melanoma could display activating mutations of the BRAF (V600E) or RAS oncogenes giving rise to increased cell proliferation through modifications of the common RAS/RAF/MEK kinase pathway. It is estimated that 65% of melanoma display the BRAF mutation and 20% the NRAS mutation.[173] Targeted therapy consists in inhibiting the mutated BRAF or MEK protein kinases. It is reimbursed from 2013 in Belgium.

Currently, the standard of care treatments for unresectable stage III/IV are PD-1 and CTLA4 blockade by immune checkpoint inhibitors.[174] BRAF (vemurafenib, dabrafenib, encorafenib) and MEK (cobimetinib, trametinib, binimetinib) inhibitors are added for mutated melanoma.

Table 21 shows the list of selected drugs for metastatic melanoma.

Table 21 – Drugs selected for Melanoma

Drug	Year#	Trade Name$	Company$	Mechanism of action
Nivolumab	2016	Opdivo	Bristol-Myers Squibb	monoclonal antibody (HuMAb), which binds to the programmed death-1 (PD-1) receptor
Pembrolizumab	2016	Keytruda	MSD	Monoclonal antibody which binds to the programmed cell death-1 (PD-1) receptor
Ipilimumab	2012	Yervoy	Bristol-Myers Squibb	CTLA-4 immune checkpoint inhibitor
Vemurafenib	2013	Zelboraf	Roche	inhibitor of BRAF serine-threonine kinase
Dabrafenib	2014	Tafinlar	Novartis	inhibitor of RAF kinases (BRAF inhibitor)
Trametinib	2017	Mekinist	Novartis	inhibitor of RAF kinases (MEK inhibitor)

$ from the originator; #year of start reimbursement first indication in Belgium

4.5.2 Observational data

4.5.2.1 Patient characteristics, survival and expenditures

The general composition of the whole melanoma population has changed over the incidence periods. Stage I melanoma accounts for 72.3% of reported cases in the incidence period 2014-2017 whereas it accounted for 54.2% and 59.3% in the previous incidence periods (see Appendix). While stage IV melanoma accounted for 2.7% in the incidence period 2004-2007, it represents now 1.5%. Overall reported cases of stage IV melanoma has remained relatively stable over the incidence periods (Table 22A). The percentage of male patients is noticeably higher in the last incidence period (62.2%). The proportion of elderly people over 80 years has gradually increased over time accounting for 10.8% in the 2004-2008,18.5% in 2009-2013 and 27.8% in 2014-2017, respectively (Table 22A).

Melanoma with an unknown localisation of the primary tumour receive no TNM staging (stage NA – not applicable). For this report, those cases are considered as predominantly metastatic cases, but are reported separately. The characteristics of the patients with a stage NA tumour did not change significantly over time (see Appendix).

For stage IV patients, we do not observe a clear positive trend in the observed survival over the years (Table 22B&C). The variation in observed survival over the years (e.g. a 3-year OS of 40.0%, 23.1% and 46.4% in 2014, 2015 and 2016, respectively) is probably linked to the small patient population. Also in the median survival we observe a large variation over the years. While the most positive observation with a median survival of 2.6 years is observed in 2016, this was again only 1.4 years in 2017 (see Table 22D). Additional analysis comparing the period before and after the introduction of innovative drugs (2004-2010 vs 2012-2017) shows at most a slight improvement of overall survival, but confidence intervals are overlapping (Figure 5). 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 (Table 23B). The 3-years observed survival was the lowest in 2012 (23.9%) and steadily growing up to 53.7% in 2017 (Table 23C). Also the median survival

increased from less than 1.5 years before 2013 to more than 3 years in 2017 (Table 23D). The clear survival benefit is confirmed in the additional analysis comparing 2004-2010 with 2012-2017 (Figure 6).

For the general melanoma population, yearly oncology drug expenditures were almost non-existing before 2011 (Table 24A). Since then, yearly expenses steadily increased and reached about €49 million in 2018. This growth is attributable to the reimbursement of new drugs that came to market (targeted therapy and later immunotherapy). For patients diagnosed with stage IV melanoma, the number of patients treated with oncology drugs increases from 23 in 2010 to 33 in 2016 (Table 24B). The oncology drug expenditures increase more rapidly from almost non-existing before 2010 to more than €3 million in 2016. This increase is largely due to a price effect. The mean cost for oncology drug expenditures per stage IV melanoma patient the first two year after diagnosis sharply increased and reached almost €100 000 in 2016 (Table 24C).

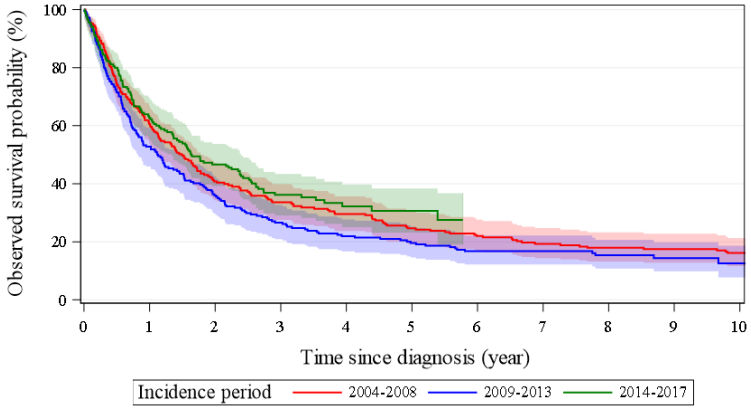
In a similar trend as for the stage NA group, yearly expenditures rose steadily from almost no expenditures before 2010 to reach almost €6 million in 2017 for NA stage patients (Table 25B). The number of patients with oncology drug expenditures considerably increased from 18 in 2011 to 58 in 2017. Next to this volume effect, there is also a large price effect: the mean cost for oncology drug expenditures per stage NA melanoma patient the first two year after diagnosis considerably grew: from non-existing before 2010 to more than €100 000 per patient in 2017 (Table 25C).

Table 22 – Melanoma (2004-2017), combined stage IV (observed survival): A) Patient characteristics; B) Kaplan-Meier graph per incidence period; C) Time trend with incidence year*; D) Median survival time* **

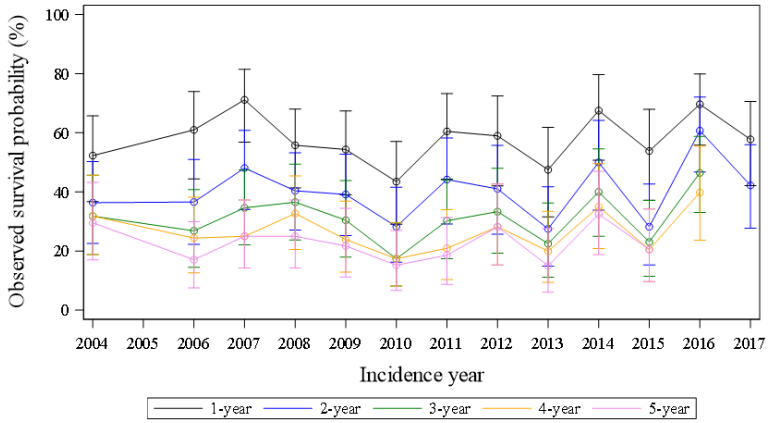
A

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

B

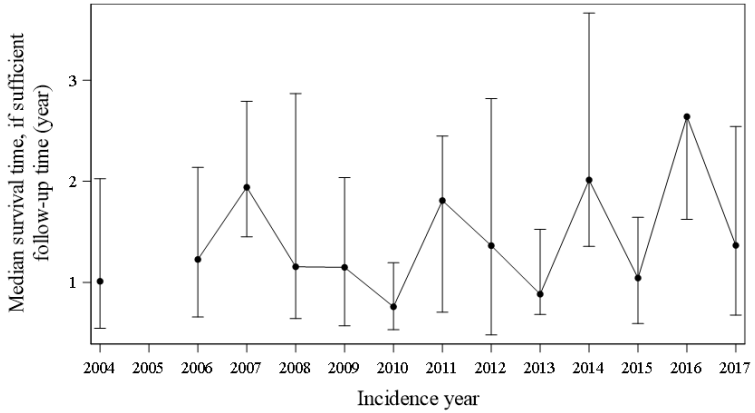


C



Year: 3-y OS [95%CI]
2004: 31.8 [18.8, 45.6]
2005: N<35
2006: 26.8 [14.5, 40.8]
2007: 34.6 [22.1, 47.4]
2008: 36.5 [23.8, 49.4]
2009: 30.4 [18.0, 43.9]
2010: 17.4 [8.1, 29.5]
2011: 30.2 [17.4, 44.1]
2012: 33.3 [19.3, 48.0]
2013: 22.5 [11.2, 36.3]
2014: 40.0 [25.0, 54.6]
2015: 23.1 [11.4, 37.1]
2016: 46.4 [33.1, 58.8]
2017: no FU

D



Year: Med. ST [95%CI]
2004: 1.0 [0.5, 2.0]
2005: N<35
2006: 1.2 [0.7, 2.1]
2007: 1.9 [1.5, 2.8]
2008: 1.2 [0.6, 2.9]
2009: 1.1 [0.6, 2.0]
2010: 0.8 [0.5, 1.2]
2011: 1.8 [0.7, 2.4]
2012: 1.4 [0.5, 2.8]
2013: 0.9 [0.7, 1.5]
2014: 2.0 [1.4, 3.7]
2015: 1.0 [0.6, 1.6]
2016: 2.6 [1.6, NA]
2017: 1.4 [0.7, 2.5]

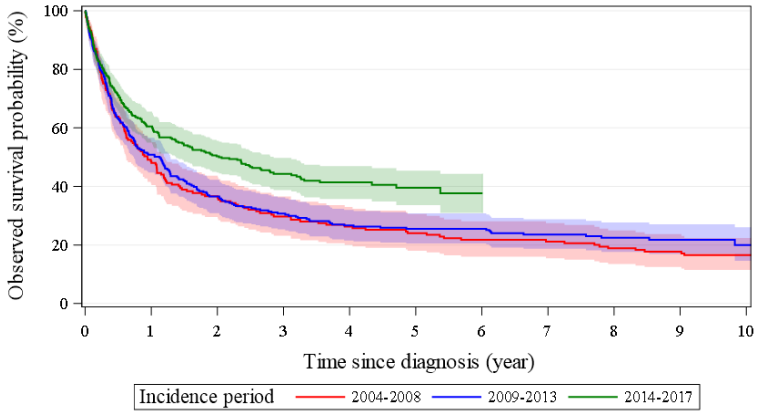
*Med. ST: median survival time; 3-y OS: 3-year observed survival; * the error bars represent the 95%CI. ** When the upper error is not plotted, the upper limit could not be determined with the available follow-up data. Survival results based on small number of persons initially at risk (N<35) can be too variable to be practically meaningful and are therefore not reported. Source: BCR.*

Table 23 – Melanoma (2004-2017), combined stage NA (observed survival): A) Patient characteristics; B) Kaplan-Meier graph per incidence period; C) Time trend with incidence year*; D) Median survival time* **

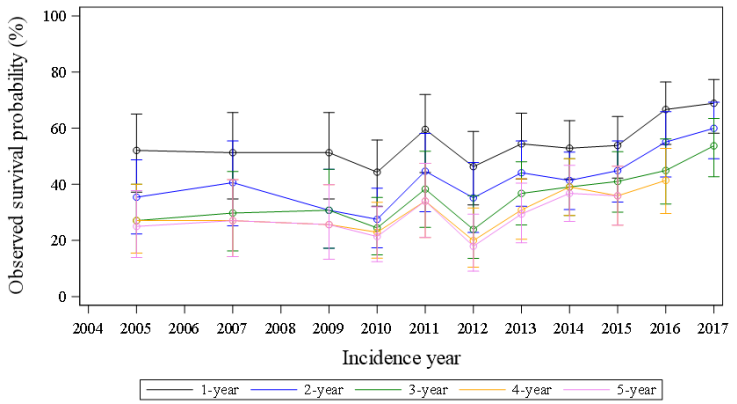
A

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

B

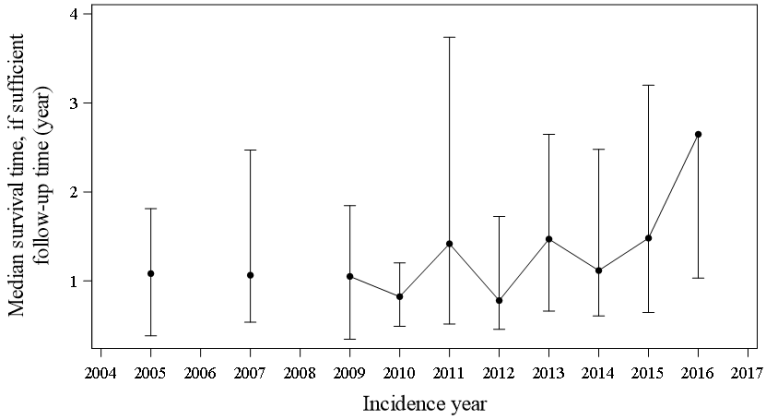


C



Year: 3-y OS [95%CI]
2004: N<35
2005: 27.1 [15.5, 40.0]
2006: N<35
2007: 29.8 [16.3, 44.5]
2008: N<35
2009: 30.8 [17.3, 45.4]
2010: 24.5 [14.9, 35.3]
2011: 38.3 [24.6, 51.8]
2012: 23.9 [13.6, 35.9]
2013: 36.8 [25.5, 48.1]
2014: 39.1 [28.9, 49.1]
2015: 41.0 [30.1, 51.6]
2016: 44.9 [33.0, 56.1]
2017: 53.7 [42.7, 63.5]

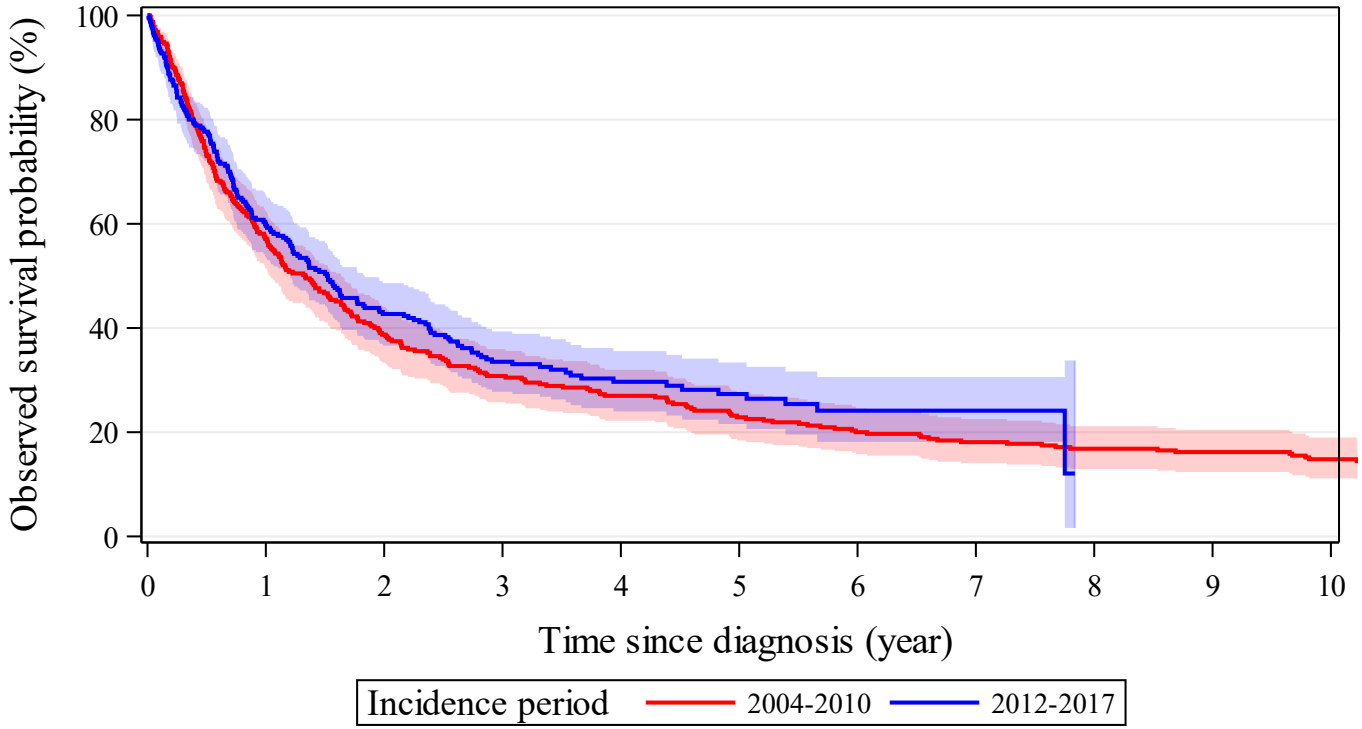
D



Year: Med. ST [95%CI]
2004: N<35
2005: 1.1 [0.4, 1.8]
2006: N<35
2007: 1.1 [0.5, 2.5]
2008: N<35
2009: 1.1 [0.3, 1.8]
2010: 0.8 [0.5, 1.2]
2011: 1.4 [0.5, 3.7]
2012: 0.8 [0.5, 1.7]
2013: 1.5 [0.7, 2.6]
2014: 1.1 [0.6, 2.5]
2015: 1.5 [0.6, 3.2]
2016: 2.6 [1.0, NA]
2017: >3

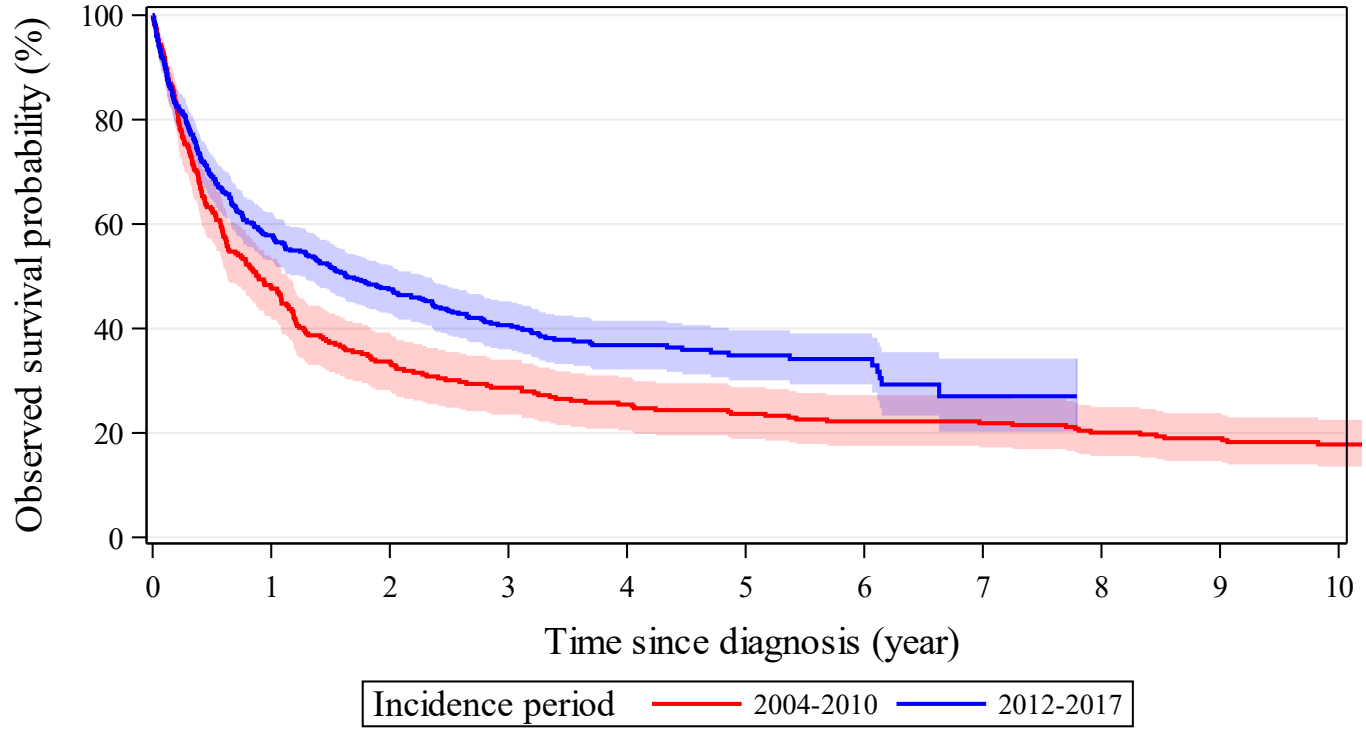
*Med. ST: median survival time; 3-y OS: 3-year observed survival; * the error bars represent the 95%CI. ** When the upper error is not plotted, the upper limit could not be determined with the available follow-up data. Survival results based on small number of persons initially at risk (N<35) can be too variable to be practically meaningful and are therefore not reported. Source: BCR.*

Figure 5 – Melanoma (2004-2017), combined stage IV (observed survival): Kaplan-Meier graph 2004-2010 vs 2012-2017



Source: BCR.

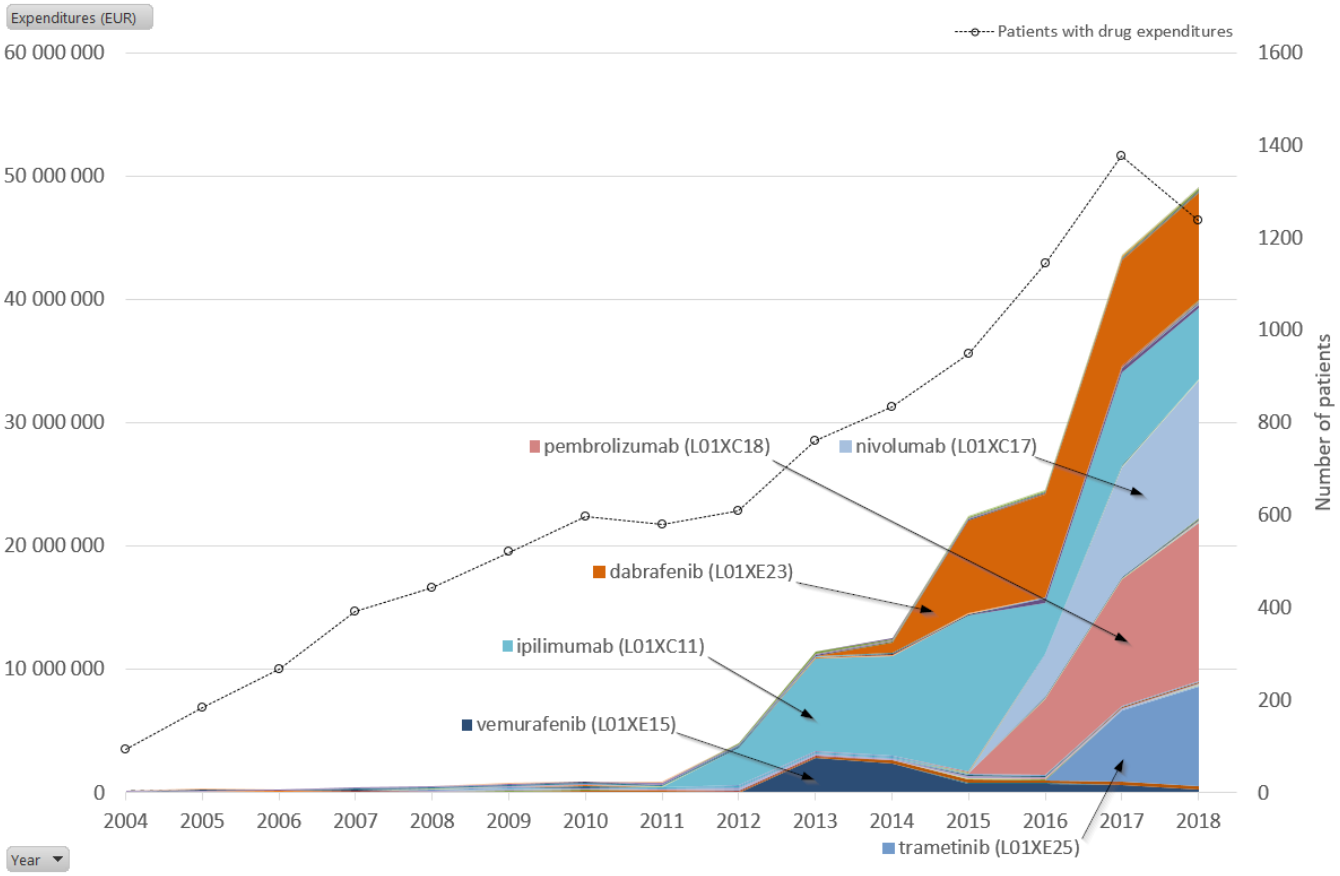
Figure 6 – Melanoma (2004-2017), combined stage NA (observed survival): Kaplan-Meier graph 2004-2010 vs 2012-2017



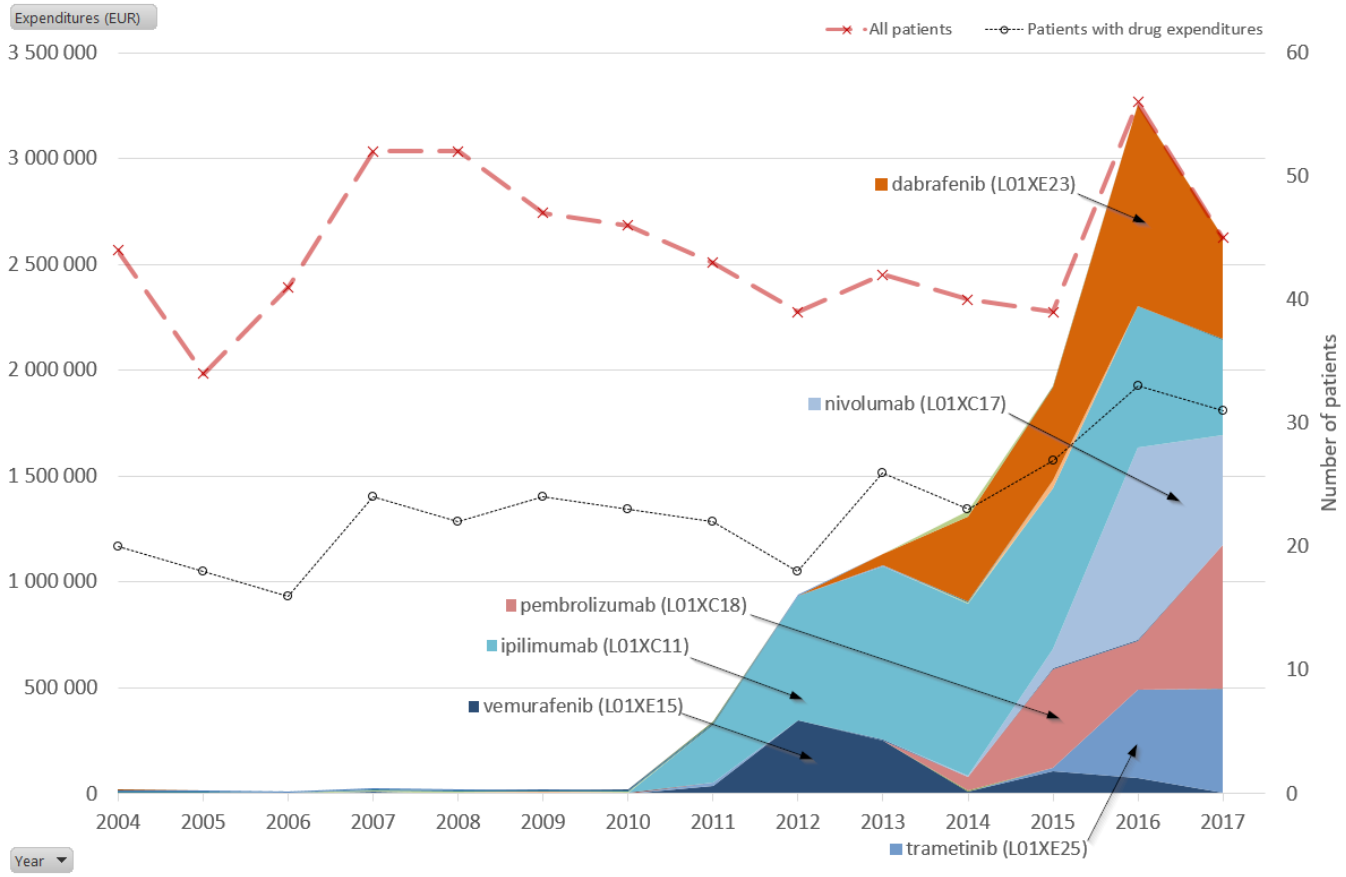
Source: BCR.

Table 24 – Melanoma stage IV: drug expenditures

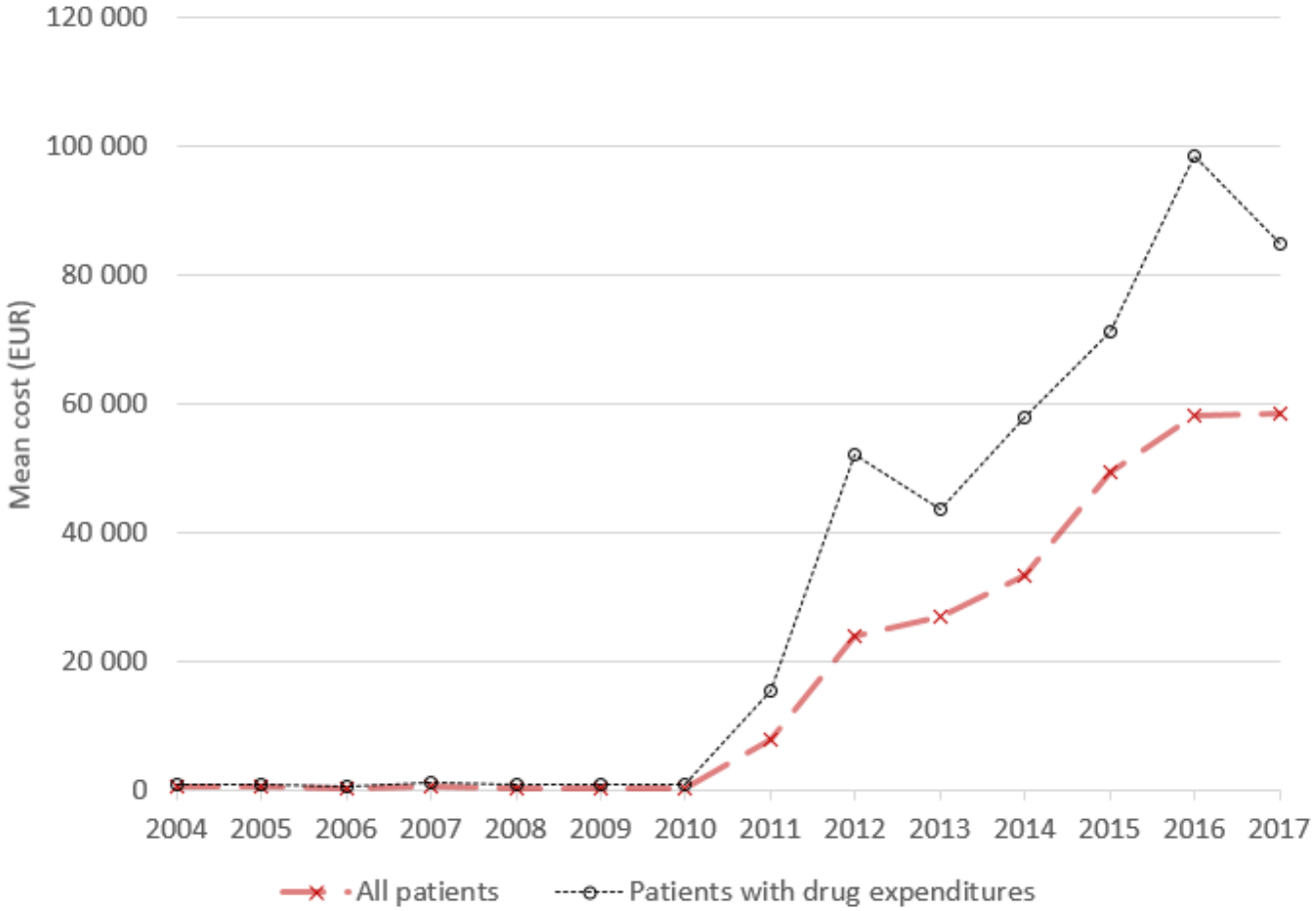
A) Oncological drug expenses per calendar year (all stages)



B) Expenses for the first two years after incidence per incidence year (stage IV)



C) Mean cost per patient for the first two years after incidence per incidence year (stage IV)



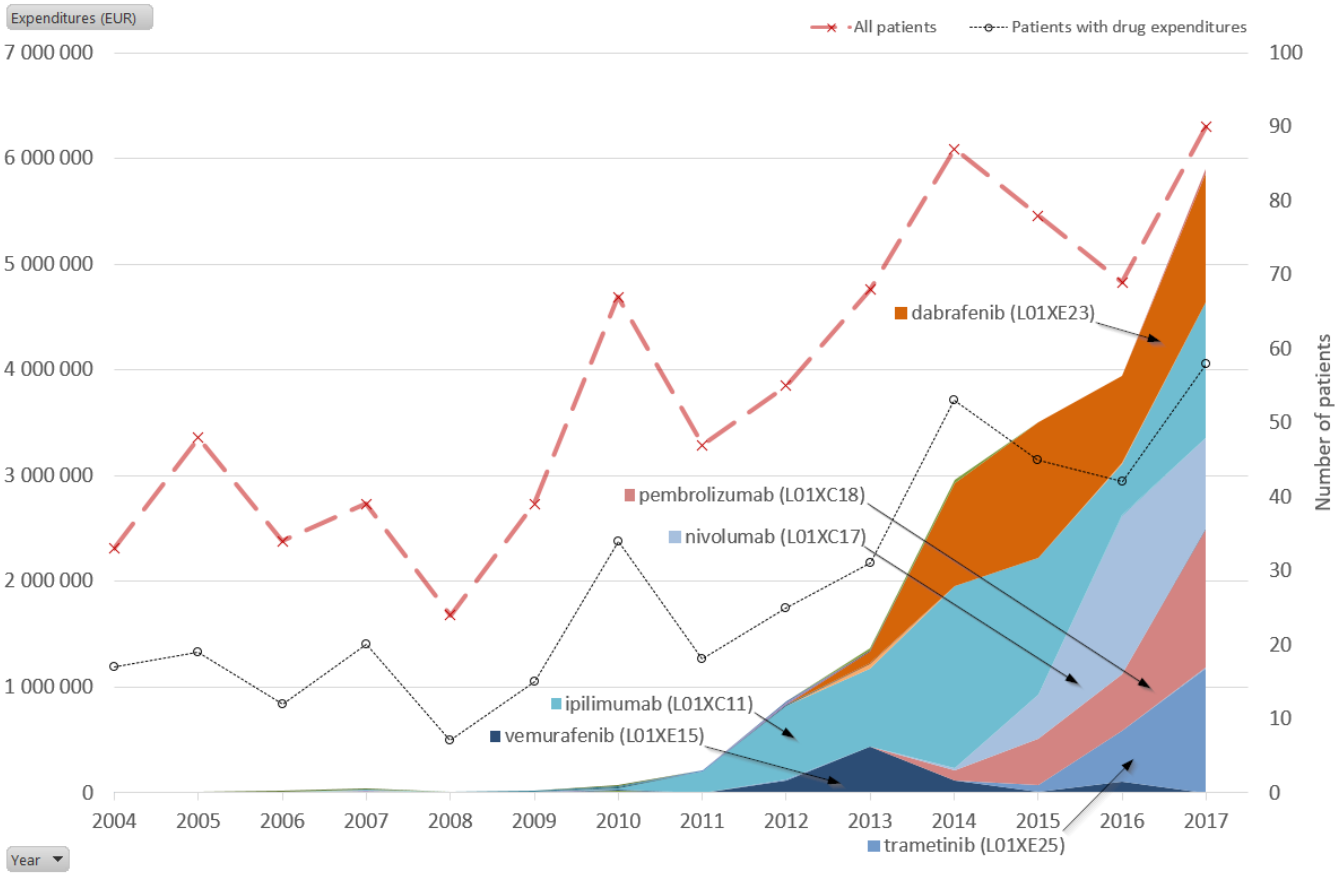
Source: BCR-IMA.

Table 25 – Melanoma stage NA: drug expenditures

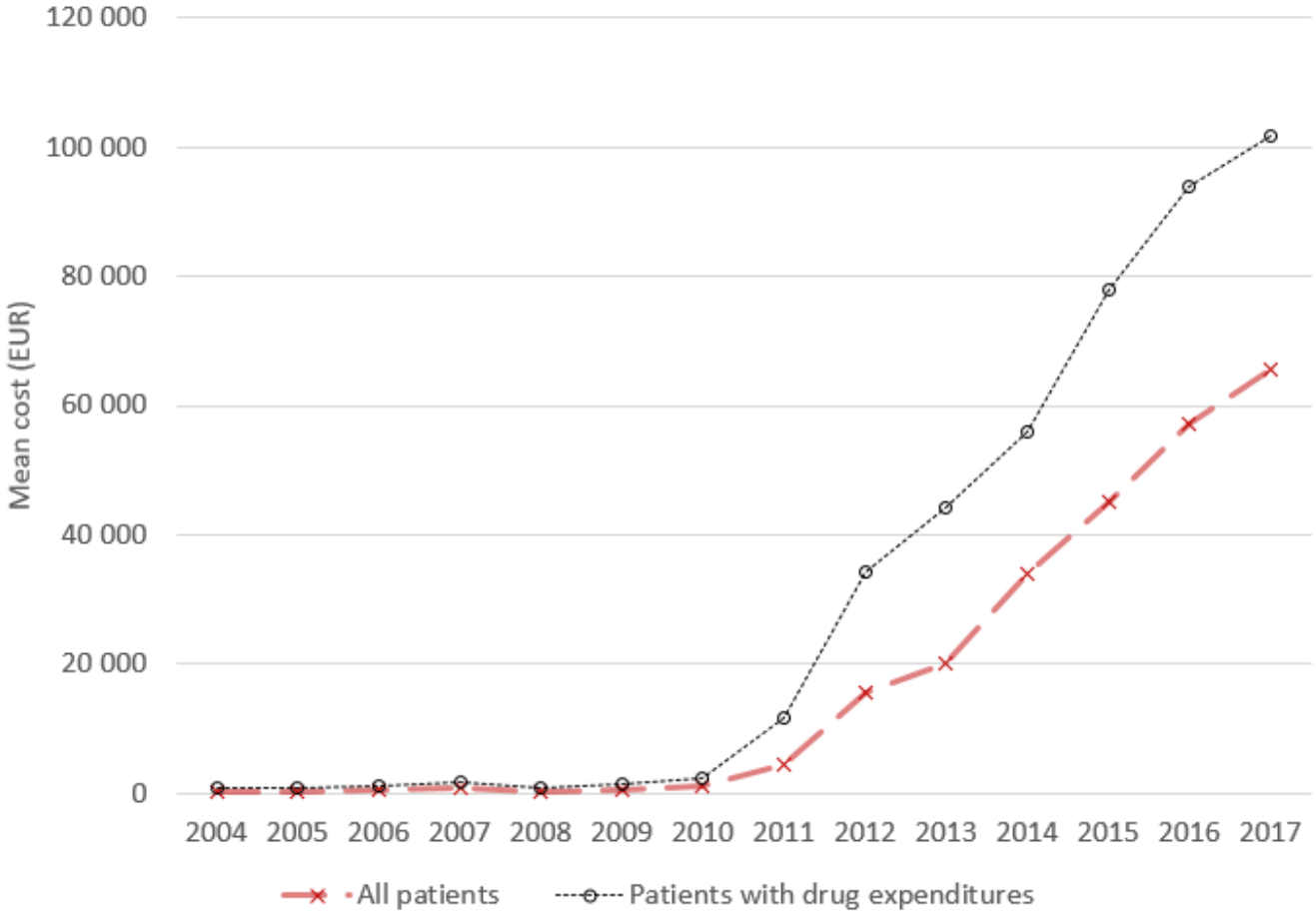
A) Oncological drug expenses per calendar year (all stages)

see Table 3

B) Expenses for the first two years after incidence per incidence year (stage NA)



C) Mean cost per patient for the first two years after incidence per incidence year (stage NA)



Source: BCR-IMA.

4.5.2.2 *Drug uptake for a selection of drugs during the first 5 years after diagnosis*

Among BRAF and MEK inhibitors, vemurafenib started to be used in 2011. Its uptake in patients with stage IV melanoma went up to reach 21.4% per incidence year in 2013 and decreased afterwards in favour of both other inhibitors (dabrafenib, trametinib). Associated with less side effects, the uptake of dabrafenib rose substantially in patients diagnosed in 2014 to reach 22.5% and fell slightly to 17.8% in 2017 (5 year follow-up not complete for the last incidence years). The uptake of trametinib went up from incidence year 2014 and came to 20% in incidence year 2017 (Table 26). This growth may be explained by the delayed reimbursement for trametinib compared with dabrafenib and the phase 3 trial demonstrating, in 2015, that combining both BRAF along with MEK inhibitory drugs improved the overall survival.[175] Prescription of ipilimumab has begun for patients diagnosed in 2007 and reached 33.3% in the incidence year 2013. Its uptake decreased from the incidence year 2014 onwards and reached 22.2% in 2017. Uptakes of nivolumab and pembrolizumab are substantially increasing from the incidence year 2013 onwards with an uptake in 2017 of 31.1% and 26.7% for nivolumab and pembrolizumab, respectively. Although no superiority between both drug has been demonstrated[176], the uptake of nivolumab has decreased somewhat in the last recorded incidence year while the use of pembrolizumab is still increasing. Regarding metastatic patients without TNM classification (stage NA), we observed the same trend for the targeted therapy characterized by the use of vemurafenib that peaked at 17.6% in incidence year 2013. It was followed by a marked decline whereas the use of both other same-class molecules went up to proportions quite similar as grade IV patients: dabrafenib reached 25.6% in 2015 and trametinib reached 18.9% in 2017 (Table 27). The uptake of ipilimumab grew considerably to peak at 28.7% in incidence year 2014 and decreased afterwards. Anti-PD-1 antibodies uptakes has been rising from the 2013 cohort onwards: nivolumab reached its highest value of 29.0% in incidence year 2016 while it was 22.2% in the 2017 cohort for pembrolizumab.

Table 26 – Proportion of patients who received at least one dose during 5-year period after diagnosis (stage IV Melanoma)

Drug/incidence year (N)	2004 (44)	2005 (34)	2006 (41)	2007 (52)	2008 (52)	2009 (47)	2010 (46)	2011 (43)	2012$ (39)	2013 (42)	2014 (40)	2015 (39)	2016 (56)	2017 (45)
Vemurafenib						4.3%		11.6%*	15.4%	21.4%	2.5%	7.7%	3.6%	2.2%
Dabrafenib									5.1%	9.5%	22.5%	23.1%	17.9%	17.8%
Trametinib									2.6%		7.5%	7.7%	17.9%	20.0%
Ipilimumab				1.9%	5.8%	2.1%	6.5%	16.3%	23.1%	33.3%	32.5%	30.8%	16.1%	22.2%
Nivolumab										4.8%	12.5%	7.7%	37.5%	31.1%
Pembrolizumab										2.4%	12.5%	12.8%	14.3%	26.7%

** Numbers in yellow indicate the first calendar year of reimbursement. For example, vemurafenib was first reimbursed in 2013. The columns in this table indicate the incidence year. For example, for incidence year 2011, 11.6% of patients received reimbursed vemurafenib during the 5 years after the year of diagnosis. $ IMA data were only available up to the second trimester of 2019 and might have a delay of two years. Five-year follow-up data are thus not 100% complete from incidence year 2012 onwards (see part 3.1.3). Source: BCR-IMA.*

Table 27 – Proportion of patients who received at least one dose during 5-year period after diagnosis (stage NA Melanoma)

Drug/incidence year (N)	2004 (33)	2005 (48)	2006 (34)	2007 (39)	2008 (24)	2009 (39)	2010 (67)	2011 (47)	2012$ (55)	2013 (68)	2014 (87)	2015 (78)	2016 (69)	2017 (90)
Vemurafenib									5.5%*	17.6%	5.7%	1.3%	2.9%	
Dabrafenib									3.6%	7.4%	16.1%	25.6%	20.3%	18.9%
Trametinib									1.8%	1.5%	3.4%	9.0%	11.6%	18.9%
Ipilimumab							3.0%	6.4%	21.8%	17.6%	28.7%	23.1%	18.8%	22.2%
Nivolumab											4.6%	10.3%	29.0%	26.7%
Pembrolizumab								2.1%		5.9%	9.2%	12.8%	17.4%	22.2%

** Numbers in yellow indicate the first calendar year of reimbursement. For example, vemurafinib was first reimbursed in 2013. The columns in this table indicate the incidence year. For example, for incidence year 2012, 5.5% of patients received reimbursed vemurafinib during the 5 years after diagnosis. $ IMA data were only available up to the second trimester of 2019 and might have a delay of two years. Five-year follow-up data are thus not 100% complete from incidence year 2012 onwards (see part 3.1.3). Source: BCR-IMA.*

4.5.3 Medical literature: efficacy

Systematic reviews in the medical literature reveal that BRAF inhibitors significantly improve overall survival when compared with conventional chemotherapy, while MEK inhibitors alone do not.[170] BRAF inhibitors are not associated with more toxicity than chemotherapy unlike MEK inhibitors that induce higher toxicity rates. The combination of both inhibitors in BRAF-mutated melanoma provides a significant benefit in terms of overall survival when compared with a single BRAF inhibitor. Moreover, the association of both inhibitors do not increase the toxicity.

In 2010, ipilimumab showed a survival benefit in patients with previously treated metastatic melanoma.[171] It was also demonstrated that ipilimumab along with chemotherapy (dacarbazine) improved overall survival in previously untreated metastatic melanoma patients. That was nonetheless associated with increased rates of grade 3 toxicity.[170, 177] If compared with chemotherapy alone (dacarbazine), a treatment including the single use of ipilimumab significantly improves overall survival in previously untreated patients. It may induce less severe toxicity.[178]

When comparing anti-PD1 monoclonal versus anti-CTLA4 antibodies, anti-PD1 monoclonal antibodies show an advantage in terms of survival and may also induce less grade 3 toxicity.[170] Besides, conjointly use anti-PD1 monoclonal and anti-CTLA4 antibodies provides a better progression-free survival (overall survival not determined) in comparison with anti-CLA4 monoclonal antibodies alone and without adding more toxicity.

4.5.3.1 *BRAF and MEK inhibitors melanoma*

Reference + search date	Intervention and comparator + indication	OS	Quality of life	Other outcomes
Pasquali 2018[170] Search date: 4 October 2017	People with unresectable lymph node metastasis (stage IIIC) or distant metastatic (stage IV) cutaneous melanoma Intervention: BRAF inhibitors Comparator: chemotherapy	HR 0.40 (95%CI 0.28-0.57)	Single agent dabrafenib was found superior to dacarbazine chemotherapy in improving quality of life	grade ≥ 3 toxicity RR 1.27 (95%CI 0.48-3.33)
Pasquali 2018[170] Search date: 4 October 2017	People with unresectable lymph node metastasis (stage IIIC) or distant metastatic (stage IV) cutaneous melanoma Intervention: MEK inhibitors Comparator: chemotherapy	HR 0.85 (95%CI 0.58-1.25)		grade ≥ 3 toxicity RR 1.61 (95%CI 1.08-2.41)
Pasquali 2018[170] Search date: 4 October 2017	People with unresectable lymph node metastasis (stage IIIC) or distant metastatic (stage IV) cutaneous melanoma Intervention: BRAF inhibitors with MEK inhibitors Comparator: BRAF inhibitors without MEK inhibitors	HR 0.70 (95%CI 0.59-0.82)	Global health dimension scores from baseline were better in the combination therapy group	grade ≥ 3 toxicity RR 1.01 (95%CI 0.85-1.20)
An 2019[179] Search date: March 2017	Adult patients with advanced melanoma (TNM stage III-IV) Network meta-analysis including PD-1/L1 blockade, CTLA-4 blockade, BRAF plus MEK inhibitors and combinations; +/- chemotherapy	Results network-meta-analysis: BRAF and MEK inhibitors had a survival advantage compared with all other treatments except PD-1/L1 blockade (HR 0.85 95%CI 0.59-1.21)		

4.5.3.2 *Immunotherapy in melanoma*

Reference + search date	Intervention and comparator + indication	OS	Quality of life	Other outcomes
Pasquali 2018[170] Search date: 4 October 2017	People with unresectable lymph node metastasis (stage IIIC) or distant metastatic (stage IV) cutaneous melanoma Intervention: Anti-CTLA4 monoclonal antibodies + chemotherapy Comparator: chemotherapy	Ipilimumab 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	grade ≥ 3 toxicity RR 1.69 (95%CI 1.19-2.42)
Pasquali 2018[170] Search date: 4 October 2017	People with unresectable lymph node metastasis (stage IIIC) or distant metastatic (stage IV) cutaneous melanoma Intervention: Anti-PD1 monoclonal antibodies Comparator: chemotherapy	HR 0.42 (95%CI 0.37-0.48)	From KEYNOTE-002 trial: participants treated with pembrolizumab consistently reported less detoriation in individual function and symptoms scales when compared to 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	grade ≥ 3 toxicity RR 0.55 (95%CI 0.31-0.97)

Reference + search date	Intervention and comparator + indication	OS	Quality of life	Other outcomes
Pasquali 2018[170] Search date: 4 October 2017	People with unresectable lymph node metastasis (stage IIIC) or distant metastatic (stage IV) cutaneous melanoma Intervention: Anti-PD1 monoclonal antibodies Comparator: anti-CTLA4 monoclonal antibodies	HR 0.63 (95%CI 0.60-0.66)		grade ≥ 3 toxicity RR 0.70 (95%CI 0.54-0.91)
Li 2019[180] Search date: 30 May 2018	Advanced or metastatic melanoma Intervention: PD-1 inhibitors + ipilimumab Comparator: monotherapy PD-1 inhibitor or ipilimumab	HR 0.58 (95%CI 0.50-0.67)		

4.5.3.3 Discussion

Contrary to what would be expected from RCT results, observational data do not show a substantial better survival for stage IV patients in the 2014-2017 cohort compared to the 2004-2008 cohort. Changes in patient characteristics (e.g. higher proportion of elderly patients in the 2014-2017 cohort) and small patient numbers may explain our observations. Furthermore, uptake of new drugs remained modest during the study period, with no drug having an uptake of more than 30%, although the combined uptake of new drugs is high as well as the increase in expenditures for these drugs. Nevertheless, for patients in the category 'stage NA', an improved survival is seen after the introduction of new drugs is seen, as expected based on trial results.

Findings in other countries

In Denmark, it appeared that fifty-five percent of the real-world patients did not meet at least one of the eligibility criteria of the clinical trials.[181] Overall survival of patients diagnosed in 2012, 2014 and 2016 were compared. For "trial-like patients" (patients who would have been eligible for the pivotal clinical trials), median survival was 16.5 months for patients diagnosed in 2012, 18.8 months for patients diagnosed in 2014 and not reached at the time of database lock (1 November 2018) for patients diagnosed in 2016 . The HR for death was 0.59 (95%CI 0.42-0.85) for 2016 versus 2014 and 0.45 (95%CI 0.30-0.648) for 2016 versus 2012. For "trial-excluded" patients, the median survival was 6.9 months in 2016, 5.2 months in 2014 and 4.2 months in 2012. Uptake of new treatment modalities was higher compared to Belgium, with 81% of patients being treated with anti-CTLA-4 antibodies as first-line treatment in 2014 and 77% of patients diagnosed in 2016 receiving an anto-PD-1 drug as first-line treatment. In 2012, 51% of patients was treated with Interleukin-2 and 28% participated in a clinical trial which may have improved survival compared with standard treatments available at the time.[182]

In France, overall survival of all new patients receiving a systemic treatment for metastatic melanoma in four time periods was compared, based on when the first treatment line was initiated. Dates for availability of new drug categories were used to define the cut-offs between cohorts. Median overall survival was 8.5 months (95%CI 7.9-9.0) for cohort 1 (Jan 2010-Dec 2011), 8.6 months (95%CI 7.9-9.1) after BRAF inhibitors became available (cohort 2; Jan 2012-Oct-2013), 12.5 months (95%CI 11.4-13.5) after ipilimumab became available (cohort 3; Nov 2013-May 2015) and 18.0 months (95%CI 16.8-19.6) for the last cohort when also combination therapy of MEK and BRAF inhibitors and anti-PD-1 antibodies were available.[183]

In the Netherlands, median survival of metastatic melanoma was 6.3 months in the period 2004-2008, 5.9 months in 2009-2013 and 11.4 months in 2014-2018. In 2018, 45% of patients were treated with immunotherapy and 23% with targeted therapy.[184] In a more detailed analysis for the period 2013-2017, Van Zeijl et al. assessed the evolution of survival over time of patients with unresectable stage IIIC or IV melanoma. The percentage of patients treated with systemic therapy increased from 76% in 2013 to 89% in 2017. Median overall survival increased from 11.7 months (95%CI 10.4-13.5) in 2013 to 18.9 months (95%CI 17.1-23.2) in 2017. The 3-year overall survival probabilities were 27% (95%CI 23-31) in 2013 and 33% (95%CI 29-37) in 2017.[185]

Limitations

- It is unclear why no improved survival over time is seen in stage IV melanoma patients in Belgium, in contrast to patients who were not assigned a TNM stage (stage NA) and patients with metastatic melanoma in other countries. A possible explanation could be the changes in patient characteristics with more male and elderly patients in the last time period 2014-2017 compared to earlier years.
- For the group of patients with a BRAF carrying tumour, no separate survival curves could be obtained based on available data, to assess a possible impact of the introduction of BRAF and MEK inhibitors.
- In addition, as seen in clinical studies, the survival benefit of immunotherapy seems to be limited to a minority of patients who achieve a long term response and survival and unfortunately, still many patients have a poor prognosis in spite of treatment with the new treatment options. Ipilimumab provides benefits only in a limited proportion of patients of about 11%.[171] This can account for the inability to detect a potential survival benefit. Furthermore, the use of immunotherapy may change over time, with a shift towards first-line treatment and better patient selection based on more knowledge regarding negative predictive factors such as high levels of CRP or LDH, which may signpost futile treatment.[186] These changes may lead to improved (cost-)effectiveness of immunotherapy in melanoma in the future.

4.5.4 Economic literature: cost-effectiveness

For more information about the economic evaluations in the identified HTA reports, we refer to the Appendix.

Confidential prices

In all NICE evaluations, there are confidential price discounts for the intervention and/or the included comparators.

In some results, the confidential discount is included and only the ICER is presented.[187-190] In cases where there are also confidential discounts for comparators or follow-up treatments, the company's results could not be used for decision-making and exact ICERs including all discounts could not be presented.[191-195]

Quality of life

The Norwegian study identified 17 trials reporting HRQoL. Unfortunately, only three used the EQ-5D questionnaire and one of these studies did not present any results for the EQ-5D outcome parameters.[196] This review also showed that when available, the quality of evidence was often poor with e.g. no information on the uncertainty associated with the results.[196] The Expert Review Committee of the Canadian study also noted the QoL reporting was limited. They 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*."[197] The authors of the Norwegian study mention that important differences between the interventions regarding patients health related quality of life may not have been captured in their analysis.[196] This might result in both over- or underestimation of an intervention's impact on QoL.

Also in the NICE evaluations, it is observed that in several studies, researchers of the underlying trials did not measure QoL with a generic utility instrument.[187, 188, 190] In such cases, researchers have to map information from disease-specific instruments or use information from other sources, entailing extra uncertainty in their economic evaluation. For an evaluation of nivolumab and ipilimumab, no underlying full HTA report

could be identified and no details related to QoL were provided in the technology appraisal guidance.[193]

In other studies, utility estimates are collected in the underlying trial with the EQ-5D questionnaire.[189, 191, 192, 194, 195, 198, 199] However, results for this outcome in the included treatment arms are often not transparently reported. Transparent reporting would mean that the results are presented separately for both treatment arms, at all points in time where this outcome is measured. These results for this patient-reported outcome should already be presented in the clinical section of the submission. However, it is noticed that in several evaluations, EQ-5D data are not reported by the company in the clinical section of the submission.[200, 201] Making numerical data for HRQoL confidential in the economic part[201, 202] is also not very transparent. General descriptions such as "it is notable that the mean EQ-5D evolves in a similar manner in both arms"[202] or "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"[194] are rather relatively vague. Transparent reporting is not only a problem for the results measured with a generic utility instruments. Also for other QoL measures, results seem not always to be reported transparently. For example, in TA269, the researchers of the underlying HTA report state "it is recognised that quality of life data [measured with the FACT-M questionnaire], although collected, are not available from the BRIM 3 trial."[203]

Furthermore, the results of the EQ-5D are never used directly to model the impact on QoL for the different treatment arms. With 'directly', we mean 'using the utilities as measured at different points in time in these separate treatment arms of the underlying trial'. Impact on QoL is usually modelled by assuming a utility for the different health states (PFS and progressed disease), e.g. using regression analysis to estimate utility values for the health states in the model.[194] Exceptionally, in evaluations of pembrolizumab, this is modelled in function of time to death.[191, 194, 199]

Uncertainty & influential parameters

In several analyses, no head-to-head comparison of the alternatives was available. This is the case in analyses of ipilimumab,[188, 197] nivolumab,[192] and dabrafenib.[204] Of course, this also leads to uncertainty about the impact on OS and QoL.

In the economic evaluations, the greatest uncertainty is present about the impact on OS and/or the modelling/extrapolation of OS,[187, 188, 191, 192, 194-196, 198, 199, 203] or the modelling of progression-free,[204] post-progression[193] or relapse-free survival.[189] Often, this is related to the immaturity of data. For example, in a recent evaluation of pembrolizumab, "*the ERG did not perform any exploratory analyses because the data from the underlying trial was too immature. The ERG noted that in the company's ICER, only 1% of the total discounted QALYs came from the actual trial data.*"[198] This was also the case in an assessment of nivolumab, where "*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.*"[192] Or another example of dabrafenib where "*the follow up in COMBI-AD was too short for firm conclusions other than that a delay in recurrence was achieved. Extended follow up from this trial is required together with monitoring for post treatment unanticipated and anticipated effects of therapy.*"[202] "The ERG notes that immature data can lead to spurious projections of OS, especially in cancer studies."[205]

A large part of the calculated incremental benefits relies on the extrapolation assumptions. This is shown in the three identified analyses of pembrolizumab: 1) in completely resected stage III melanoma: "Over 99% of the QALY gain predicted by the company model for pembrolizumab comes from projections rather than actual trial data."[205] ; 2) in advanced (unresectable or metastatic) melanoma that had not been previously treated with ipilimumab: "87.5% of the health gain with pembrolizumab occurred after 12 months."[191] ; and 3) in patients with unresectable or metastatic melanoma previously treated with ipilimumab and whose disease had progressed within 24 weeks of the last dose: "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."[200] Similarly for an assessment of dabrafenib, "*The ERG noted that the majority of the estimated QALY gain in the company's model arises from the estimated life-years after disease progression (… 93% for the comparison with vemurafenib). It also noted that the estimated mean survival in the company's model is much larger than is normally observed in clinical trials or in registry data.*"[204] The latter observation underlines the importance of checking the modeled result with e.g. what is observed in trials or real-world registries. Another important recommendation is to use the available trial data as much as possible. As noted in an evaluation of trametinib, "the ERG did not consider that the company had appropriately extrapolated long-term OS. It considered that it was preferable to use all of the available trial data, rather than extrapolation, over a period for which data exists."[195]

Other important variables for which the ICERs were sensitive are the modelled utility parameters,[188, 191, 196] and the treatment duration and thus related treatment costs.[191, 194, 196]

Of course, one of the most influential factors of the ICER is the price (and thus also the discount) of the intervention. In an assessment of pembrolizumab, "*direct treatment costs (drug acquisition and administration) are the most influential costs in the model (for example, over 90% of the overall cost saving of pembrolizumab compared to ipilimumab is attributable to differences in direct treatment costs). This means that, in reality, the only influential variables are treatment costs and length of time on treatment. Treatment costs have already been agreed with the Department of Health, and are therefore fixed, and survival benefit is uncertain.*"[206] In another assessment of this drug, "*nearly all (99.1%) of the overall incremental cost is attributable to differences in direct treatment costs (drug acquisition and administration). This means that only variations in the assumed NHS price of pembrolizumab can have any meaningful effect on the estimated incremental cost per patient.*"[200]

Results

The above mentioned price negotiations and uncertainties have their impact on the transparency and reliability/uncertainty of the results from the underlying economic evaluations. There is no single assessment where the authors conclude an intervention being cost-effective if the official list prices are used. In all dossiers, confidential prices are negotiated.

The ICERs are as follows (see more details in appendix):

- **Nivolumab, pembrolizumab, ipilimumab, vemurafenib, dabrafenib, trametinib (& cobimetinib)**
  - Metastatic and/or unresectable malignant melanoma (with list prices):[196]

    "Generally, all the interventions have very high incremental cost-effectiveness ratios." "None of the interventions are cost-effective at the maximum pharmacy retail prices."

    "We believe that drug price reductions in the region of 63 to 84 percent,[t] depending on drug, would be necessary for the interventions to represent cost-effective use of resources in the Norwegian setting."[196]
- **Ipilimumab**
  - Previously untreated unresectable or metastatic melanoma (with list prices):[197]

[t] "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."[196]



- BRAF V600 Mutation-Negative Disease: ipilimumab vs dacarbazine: ICER between CAD165 389 and CAD197 382 per QALY.
- BRAF V600 Mutation-Positive Disease: ipilimumab vs vemurafenib: ICER between CAD9 231 and CAD216 773 per QALY.

"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."

- Untreated advanced (unresectable or metastatic) melanoma (including confidential discounts):[187]

  "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."

- Previously treated (with interleukin-2, dacarbazine, temozolomide or other chemotherapies) advanced (unresectable or metastatic) melanoma (including the patient access scheme):[188]

  "The manufacturer's ICER of £42 200 per QALY gained and the ERG's updated preferred estimate of £58 600 per QALY gained" for ipilimumab plus gp100 compared with gp100 alone.

- **Pembrolizumab**
  - Completely resected stage III melanoma at high risk of recurrence (including commercial arrangments, also for subsequent treatments):[198, 205]

    "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."

    "The ERG considers that the company's estimated ICERs per QALY gained are unreliable." "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."

  - Advanced (unresectable or metastatic) melanoma that had not been previously treated with ipilimumab (including commercial arrangments, also for comparators):[191]

    "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."

  - Unresectable or metastatic melanoma previously treated with ipilimumab and whose disease had progressed within 24 weeks of the last dose (including PAS):[199]

    "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."

- **Nivolumab and ipilimumab**
  - Advanced melanoma (mixed population of BRAF mutation-positive and mutation-negative advanced melanoma) (with list prices and with discounts):[193]

    Comparing nivolumab plus ipilimumab with ipilimumab alone: "£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."

- **Nivolumab**
  - Completely resected melanoma in adults with lymph node involvement or metastatic disease (including commercial arrangments for the intervention but not for comparators):[192]

    "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."
  - Previously untreated advanced (unresectable, metastatic) melanoma (results with all discounts are confidential):[194]

    "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." "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"
- **Dabrafenib & trametinib**
  - BRAF V600 mutation-positive patients who when at stage III had their disease resected (including discounts):[189]

    Dabrafenib with trametinib compared with routine surveillance: "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."
- **Dabrafenib**
  - Previously untreated patients with unresectable or metastatic BRAF V600 mutation-positive melanoma (including discounts for intervention and comparator):[204]

    "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. 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."
- **Vemurafenib**
  - Locally advanced or metastatic BRAF V600 mutation-positive malignant melanoma (including discounts):[190]

    Vemurafenib compared with dacarbazine: "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."
- **Trametinib**
  - Unresectable or metastatic BRAF V600 mutation-positive melanoma (results are kept confidential):[195]

    "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." No information on incremental costs and ICERs is presented in the report.

In the Norwegian study, none of the interventions was cost-effective at the maximum pharmacy retail prices.[196] According to this study, very high price discounts, in the region of 63 to 84 percent, were necessary for the interventions to represent cost-effective use of resources in the Norwegian setting.[196] This is also the case for the Canadian study: without price discounts, the intervention under consideration is not considerd cost-effective.[197]

In many cases, there was high uncertainty around the calculated ICERs. In most assessments,[188, 192, 197, 204] this was because no results from a head-to-head trial were available. For example, in TA321, "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."[204] In this case "the ERG concluded that any estimated ICERs generated by this indirect comparison would be unreliable and likely to be misleading."[204] In TA553,[198, 205] the high uncertainty was because data from the underlying trial was too immature with only 1% of the total discounted QALYs coming from the actual trial data.

In four assessments, ICERs are presented, but incremental costs and benefits remain confidential.[187-190] In TA396, incremental benefits are presented, but transparent information on incremental costs or ICERs is lacking.[195] In five assessments, exact ICERs, including discounts for all interventions, are not presented since they are considered as commercial in confidence.[191-194, 198] Confidential discounts are negotiated for the intervention under consideration. The situation becomes even more complex since there are also confidential discounts included for the comparators (e.g. TA366[191] or TA384[194]) or confidential discounts for the subsequent treatments included in the model (e.g. TA553[198] or TA558[192]). In such cases, the exact ICERs are confidential and could not be reported.

When confidential discounts are also present for comparators or subsequent treatments, it is difficult for companies and independent researchers to calculate ICERs relevant for decision making. For example, in TA558, "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."[192] Or in TA366, "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."[191]

If there was a positive recommendation for reimbursement, this was always under the condition that discounts would be provided. Higher ICERs were accepted when end-of-life criteria were fulfilled.[187, 188, 190, 191, 199] In these cases, instead of applying a £20 000 - £30 000 per QALY threshold, NICE considers whether the most plausible ICERs are less than £50 000 per QALY gained. Due to limited data (indirect comparison and/or immature data), the ICERs in TA553[198] and TA558[192] were very uncertain. The intervention could, therefore, not be recommended for routine use. In these cases, use within the Cancer Drugs Fund was recommended as an option.[192, 198]

4.5.5 Summary

Observational data

- Observational data show that overall survival has not clearly changed for stage IV melanoma between 2004 and 2017 but an improved overall survival is seen for metastatic melanoma that is reported as 'stage not applicable' in the third incidence period (2014-2017). Median survival for that group of patients increases from less than or equal to 1.5 years to 2.6 years for patients diagnosed in 2016 and more than 3 years for patients diagnosed in 2017.
- For melanoma, all stages; yearly oncology drug expenditures increased from less than €1 million before 2012 to about €49 million in 2017.

- For melanoma stage IV, yearly oncology drug expenditures increased over the years from almost non-existing before 2011 to about €3.3 million in 2016.
  - The number of patients with stage IV melanoma with oncology drug expenditures did not substantially change over the years: 20 in 2004, 23 in 2010 and 33 in 2016.
  - The mean cost per stage IV melanoma patient with drug expenses for the first two years after incidence increased from about €1 000 before 2010 to almost €100 000 in 2016.
- For melanoma stage NA, yearly oncology drug expenditures increased over the years from almost non-existing before 2011 to almost €6 million in 2017.
  - The number of patients with stage NA melanoma with oncology drug expenditures increased over the years: 17 in 2004, 34 in 2010 and 58 in 2017.
  - The mean cost per stage NA melanoma patient with drug expenses for the first two years after incidence increased from less than €2 000 per patient before 2010 to more than €100 000 in 2017.
- Uptake of BRAF targeted drugs for stage IV patients started in 2011 with a maximum uptake of approximately 21% for patients diagnosed in 2013 for vemurafenib and about 23% in for patients diagnosed in 2014 for dabrafenib. Uptake of the MEK-inhibitor trametinib started in 2014 with a maximum uptake of 20% for patients diagnosed in 2017. For patients who were reported with stage NA, a similar pattern with a slightly lower uptake was seen.
- For melanoma stage IV, uptake of the anti-CLA4 monoclonal antibody ipilimumab was below 10% for the incidence years 2007-2010, then increased to a maximum uptake of 33.3% for patients diagnosed in 2013. Uptake of other immunotherapy, anti-PD1 drugs nivolumab and pembrolizumab, started in 2013 (< 10%), increasing to an uptake of 31.1% and 26.7% for patients diagnosed in 2017, respectively. Again, for patients who were reported with stage NA, a similar pattern with in general a slightly lower uptake was seen.

Medical literature

- BRAF and MEK inhibitors (vemurafinib, dabrafenib, trametinib)
  - Data available in the medical literature show a survival benefit for BRAF inhibitors in mutated melanoma compared to traditional chemotherapy.
  - Combination therapy with BRAF and MEK inhibitors further improve overall survival compared to BRAF monotherapy in mutated tumours.
- Immunotherapy (ipilimumab, nivolumab, pembrolizumab)
  - In unselected tumours, ipilimumab improves overall survival if added to chemotherapy compared to chemotherapy alone.
  - Anti-PD1 monoclonal antibodies result in better overall survival compared to anti-CTLA4 monoclonal antibodies; combination of both further improves survival.

Economic literature

- In all identified NICE evaluations, there are confidential price discounts for the intervention and/or the included comparators. In five cases, there were also confidential discounts for comparators or follow-up treatments. In such cases, the company's results could not be used for decision-making and exact ICERs including all discounts could not be presented.
- Canadian experts 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*."[197]
  - The Norwegian study identified 17 trials reporting HRQoL. Only three used the EQ-5D questionnaire. When available, the quality of evidence was often poor (e.g. no information on the uncertainty associated with the results).



  - In seven of the identified NICE evaluations, utility estimates were collected in the underlying trial with the EQ-5D questionnaire. However, transparent reporting of the outcomes is problematic. Examples show such data are not always reported by the company in the clinical section of the submission. In other examples, HRQoL data remain confidential or general descriptions are provided making it difficult to include these estimates and the surrounding uncertainty in economic evaluations.
  - Impact on QoL is usually modelled by assuming a utility for the different health states. None of the identified evaluations includes utilities per treatment arm as measured during the follow-up period in the trial.
- In the economic evaluations, the greatest uncertainty is present about the impact on OS and/or the modelling/extrapolation of OS. In four cases, this is related to the lack of a head-to-head comparison. Researchers also note the use of immature data. In one case, the Evidence Review Group even notes that only 1% of the total discounted QALYs came from the actual trial data.
- The method used to model/extrapolate survival is very influential. It is noted that it is preferable to use all of the available trial data, rather than extrapolation, over a period for which data exists.
- Next to OS estimates, other important variables influencing ICER estimates are the modelled utility parameters and treatment costs (and thus also variables such as treatment duration and applied discounts).
- There is no single assessment where the authors conclude an intervention being cost-effective if the official list prices are used.
- As a result of the confidential discounts, exact ICERs used for decision making are not transparently reported. In most analysis, a general description is provided stating that the ICER remained under a certain ICER threshold.

- The lowest ICERs were noted in evaluations where the compared was one of the relative expensive treatments selected in our overview (e.g. TA400 comparing nivolumab plus ipilimumab with ipilimumab alone or TA384 including ipilimumab, vemurafenib and dabrafenib as comparator). Only in the evaluation of dabrafenib with trametinib compared with routine surveillance, the calculated ICERs were also relatively low.
- In two analyses, the ERG decided not to do any exploratory analyses because the data from the underlying trial were too immature (TA553) or because of the indirect treatment comparison (TA321), making the generated ICERs unreliable.

4.6 Mesothelioma

4.6.1 Introduction

Mesothelioma is an uncommon aggressive malignancy arising from the mesothelial cells of the pleura and generally appearing after a long latency exposure to asbestos.[207] Its incidence has risen over the last decades.[208] In 2018, 291 mesothelioma cancers were newly diagnosed in Belgium.[33] It carries a poor prognosis since patients commonly present at diagnosis with advanced unresectable disease.[209, 210] Stage III corresponds to a locally advanced tumour with the invasion of lymph nodes and adjacent structures, while stage IV concurs with the presence of distant metastasis.[211]

Mesothelioma displays a range of histological subtypes that are divided into epithelioid, biphasic, and sarcomatoid. The epithelioid subtype has a less poor prognosis than other subtypes.[210, 212]

Surgical treatment is an option for a small minority of patients with resectable tumour and is proposed in a multimodal approach therapy. Its efficacy remains nevertheless much debated because of a lack of high-quality evidence.[213]

To date, the combination of pemetrexed and platinum-based chemotherapy is the standard first-line systemic therapy.[207] Pemetrexed is an antifolate drug inhibiting DNA synthesis and preventing tumour growth.[214]

More recently, immunotherapy drugs have shown promising results, and they may be added to the treatment schedules of mesothelioma in the near future.[215]

Table 28 presents the selected drugs for mesothelioma.

Table 28 – Selected drugs for Mesothelioma

Drug	Year#	Trade Name	Company$	Mechanism of action
Pemetrexed*	2006	Alimta	Elli Lilly	Pemetrexed is a multi-targeted anti-cancer antifolate agent that exerts its action by disrupting crucial folate-dependent metabolic processes essential for cell replication.

**Generic available $ of the originator; # year of start reimbursement first indication in Belgium*

4.6.2 Observational data

4.6.2.1 Patient characteristics, survival and expenditures

Overall reported cases of stage III/IV/X mesothelioma has risen over the three incidence periods[u] with an increasing percentage of older patients (>80 years). Mesothelioma predominantly affects men (>80%) and occurs after 60 years for a large majority (Table 9A). No clear improvement in observed survival (Table 29B) and relative survival (Appendix) is noticeable over the three incidence periods. The 3-year observed survival probability remained globally unchanged and was 16.9% (95%CI 9.0-27.0) for patients diagnosed in 2004 and 19.5% (95%CI 12.2-28.1) for whom diagnosis was made in 2017 (Table 29C). Its maximum value was 21.7% (95%CI 14.8-29.4) in the incidence year 2011 and minimum 5.3% (95%CI 2.2-10.5) in incidence year 2013. Five-year overall survival is less than 10% for all reported incidence years (Appendix). Likewise, the median survival time did not display any meaningful change over the incidence periods. It was 1.2 years (95%CI 0.8-1.6) in incidence year 2004 and remained at 1.2 years (95%CI 0.9-1.5) in 2017 (Table 29D).

[u] Remark: the 3rd incidence period (2014-2017) covers 4 years, while the first two incidence periods cover 5 years.

In the region of Flanders, a broader follow-up period from 2000 to 2017 was available. Given that pemetrexed is reimbursed since 2006, more data also including the period before its reimbursement can allow a better appraisal of its possible impact on survival. An increase of cases was observed over the 17 years-follow-up with an increase of 80+ patients (Table 30A). No positive trend in survival is observed over the follow-up time (Table 30B). For patients diagnosed between 2000 and 2003, 3-years observed survival was not reported due to a small number of persons initially at risk (less than 35). In incidence year 2004, 3-year observed survival was 20.0% (95%CI 9.4-33.5) and widely fluctuated afterwards. Its minimal value was 5.3% (95%CI 1.7-11.9) in 2013. It reached its maximum value of 25.6% (95%CI 15.1-37.4) in 2017 (Table 30C). Median survival has not changed over time. It was not reported for incidence years 2000 to 2003 and was 1.5 years (95%CI 0.8-2.1) for patients diagnosed in 2004. In incidence year 2017, it was 1.2 years (95%CI 0.8-1.8) (Table 30D).

For all stages mesothelioma patients, yearly oncology drug expenditures were almost non-existing before 2005 and increased from about €50 000 in incidence year 2004 to more than €2 million in 2017. This rise is attributable to the uptake of pemetrexed and a raise in the number of patients for whom oncological drugs are prescribed (Table 31A).

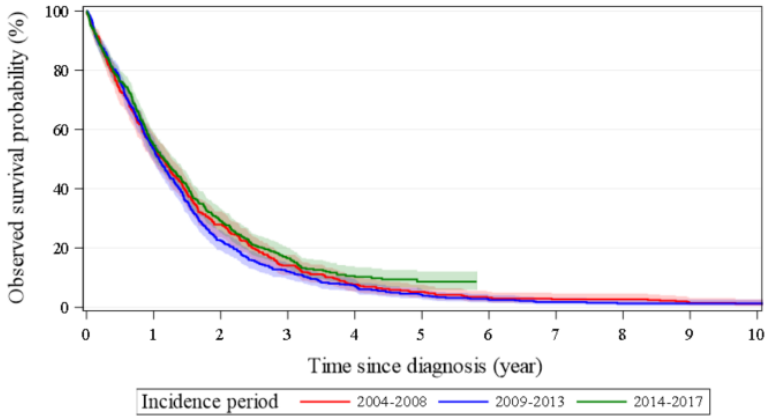
For stage III/IV/X mesothelioma patients, a similar trend was observed. Oncology drug expenditures during the first two years after diagnosis substantially rose from about €100 000 in 2004 to reach about €1.6 million in 2015 and decreased to about €1.1 million in 2017. The increase was due to a price effect related to the introduction of pemetrexed and a rise in the number of patients treated with oncological drugs (41 in incidence year 2004 to 100 in 2015). The decrease in 2017 was due to a smaller group of patients (n=68) with drug expenses (Table 31B). In incidence year 2004, the mean cost per patient the first two years after diagnosis was about €2 500 and considerably grew from 2005 onwards to be above €20 000 in 2007. It decreased afterwards but remained above €15 000 up till 2017 (Table 31C).

Table 29 – Mesothelioma (2004-2017), combined stage III/IV/X (observed survival): A) Patient characteristics; B) Kaplan-Meier graph per incidence period; C) Time trend with incidence year*; D) Median survival time* **

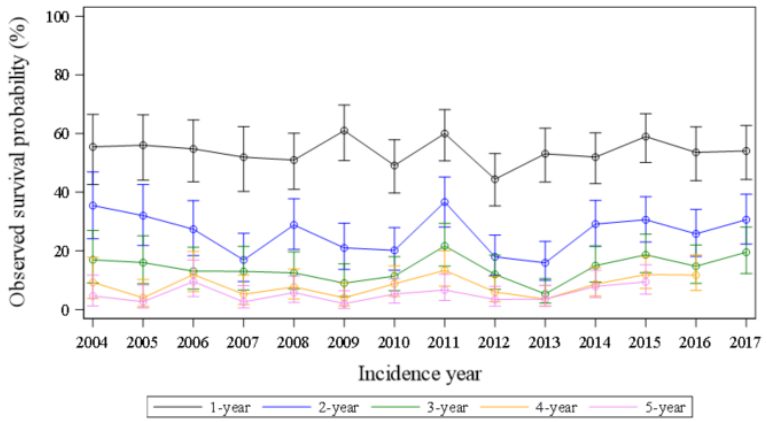
A

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

B

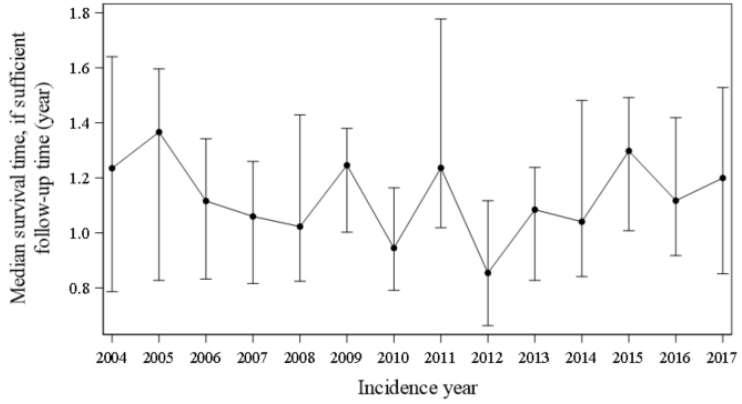


C



Year: 3-y OS [95%CI]
2004: 16.9 [9.0, 27.0]
2005: 16.0 [8.8, 25.1]
2006: 13.1 [7.0, 21.2]
2007: 13.0 [6.7, 21.5]
2008: 12.5 [7.0, 19.6]
2009: 9.0 [4.4, 15.6]
2010: 11.4 [6.4, 18.0]
2011: 21.7 [14.8, 29.4]
2012: 12.0 [6.9, 18.6]
2013: 5.3 [2.2, 10.5]
2014: 15.0 [9.4, 21.7]
2015: 18.7 [12.6, 25.7]
2016: 14.7 [8.9, 22.0]
2017: 19.5 [12.2, 28.1]

D



Year: Med. ST [95%CI]
2004: 1.2 [0.8, 1.6]
2005: 1.4 [0.8, 1.6]
2006: 1.1 [0.8, 1.3]
2007: 1.1 [0.8, 1.3]
2008: 1.0 [0.8, 1.4]
2009: 1.2 [1.0, 1.4]
2010: 0.9 [0.8, 1.2]
2011: 1.2 [1.0, 1.8]
2012: 0.9 [0.7, 1.1]
2013: 1.1 [0.8, 1.2]
2014: 1.0 [0.8, 1.5]
2015: 1.3 [1.0, 1.5]
2016: 1.1 [0.9, 1.4]
2017: 1.2 [0.9, 1.5]

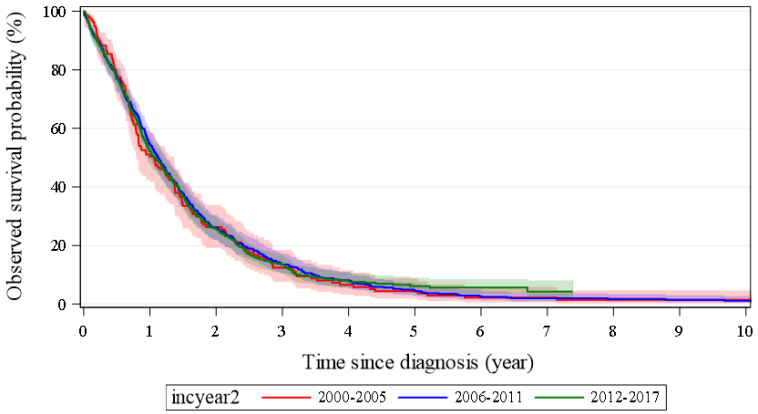
*Med. ST: median survival time; 3-y OS: 3-year observed survival; * the error bars represent the 95%CI. ** When the upper error is not plotted, the upper limit could not be determined with the available follow-up data. Source: BCR.*

Table 30 – Mesothelioma Flanders (2000-2017), combined stage III/IV/X (observed survival): A) Patient characteristics; B) Kaplan-Meier graph per incidence period; C) Time trend with incidence year*; D) Median survival time* **

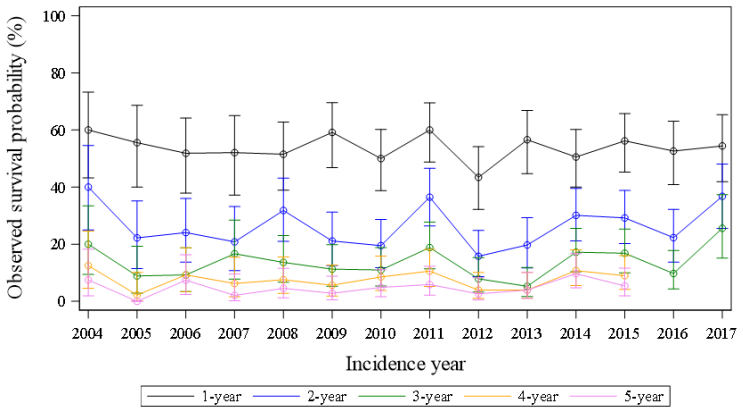
A

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

B

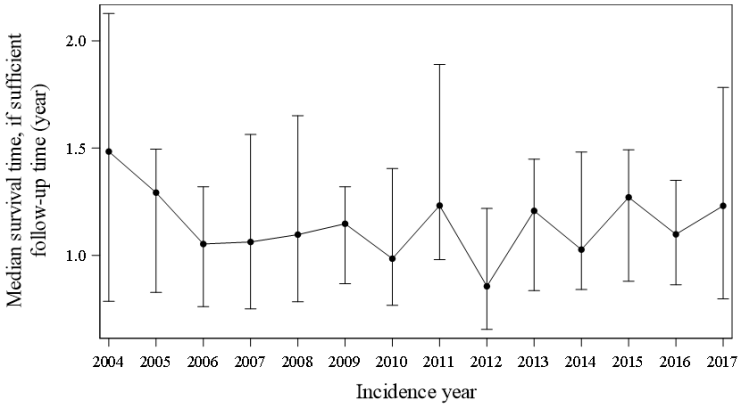


C



Year: 3-y OS [95%CI]
2000-2003: N<35***
2004: 20.0 [9.4, 33.5]
2005: 8.9 [2.8, 19.3]
2006: 9.3 [3.4, 18.7]
2007: 16.7 [7.8, 28.4]
2008: 13.6 [6.7, 23.0]
2009: 11.3 [5.3, 19.8]
2010: 11.0 [5.4, 18.8]
2011: 18.8 [11.4, 27.7]
2012: 7.9 [3.2, 15.3]
2013: 5.3 [1.7, 11.9]
2014: 17.2 [10.4, 25.5]
2015: 16.9 [10.0, 25.3]
2016: 9.8 [4.3, 17.8]
2017: 25.6 [15.1, 37.4]

D

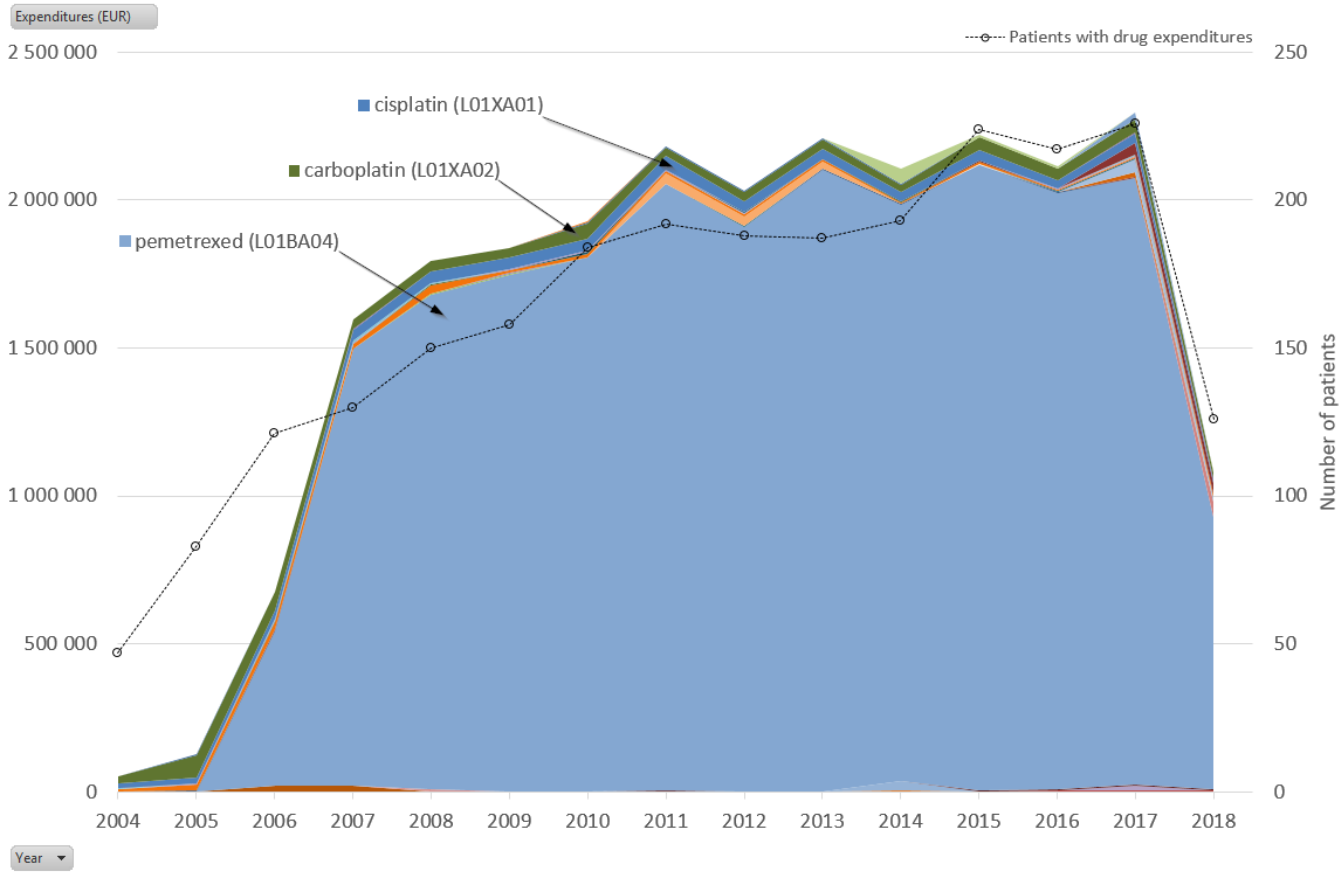


Year: Med. ST [95%CI]
2000-2003: N<35
2004: 1.5 [0.8, 2.1]
2005: 1.3 [0.8, 1.5]
2006: 1.1 [0.8, 1.3]
2007: 1.1 [0.8, 1.6]
2008: 1.1 [0.8, 1.7]
2009: 1.1 [0.9, 1.3]
2010: 1.0 [0.8, 1.4]
2011: 1.2 [1.0, 1.9]
2012: 0.9 [0.7, 1.2]
2013: 1.2 [0.8, 1.4]
2014: 1.0 [0.8, 1.5]
2015: 1.3 [0.9, 1.5]
2016: 1.1 [0.9, 1.3]
2017: 1.2 [0.8, 1.8]

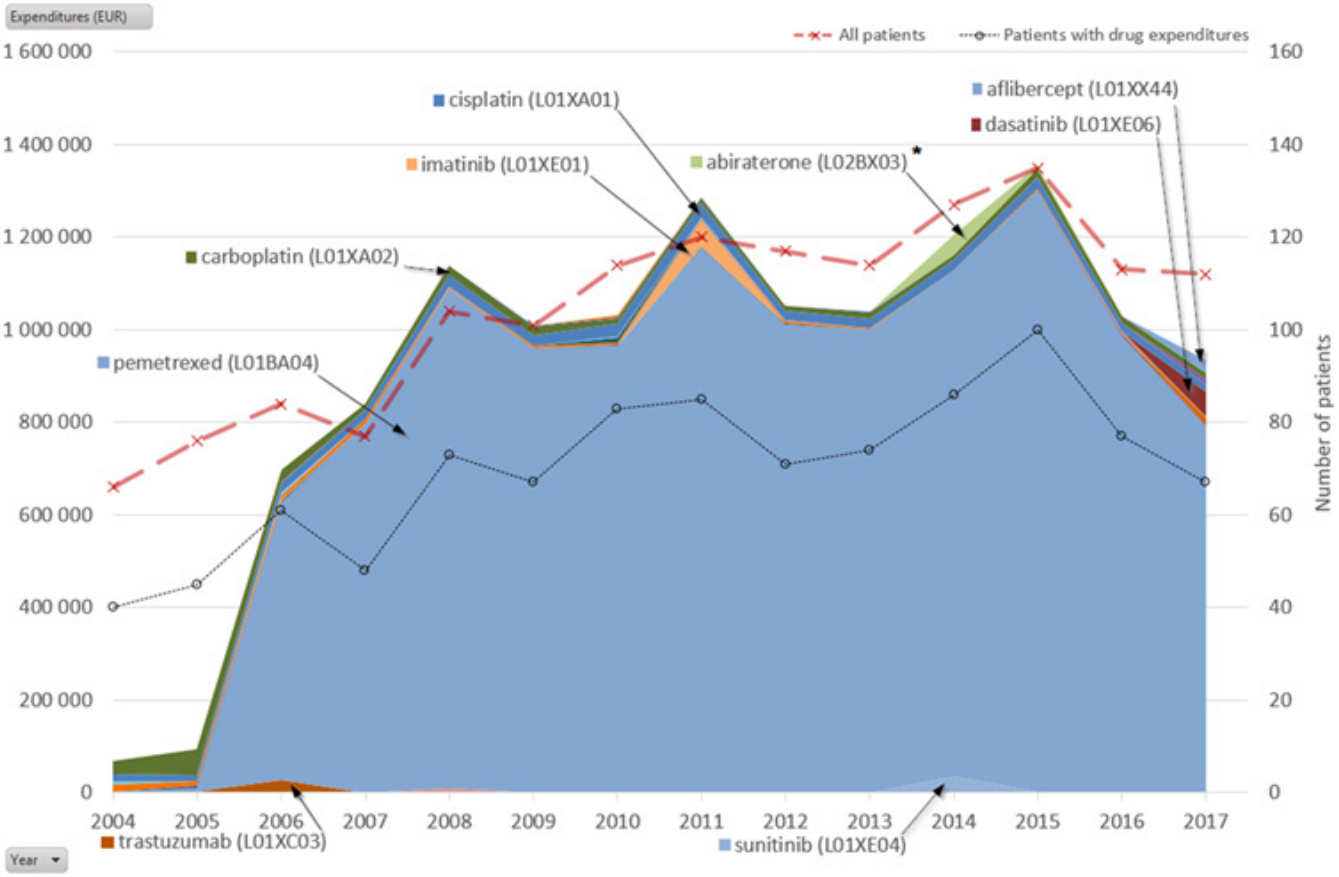
*Med. ST: median survival time; 3-y OS: 3-year observed survival; * the error bars represent the 95%CI. ** When the upper error is not plotted, the upper limit could not be determined with the available follow-up data. *** Survival results based on small number of persons initially at risk (N<35) can be too variable to be practically meaningful and are therefore not reported. Source: BCR.*

Table 31 – Mesothelioma cancer: drug expenditures

A) Oncological drug expenses per calendar year (all stages)

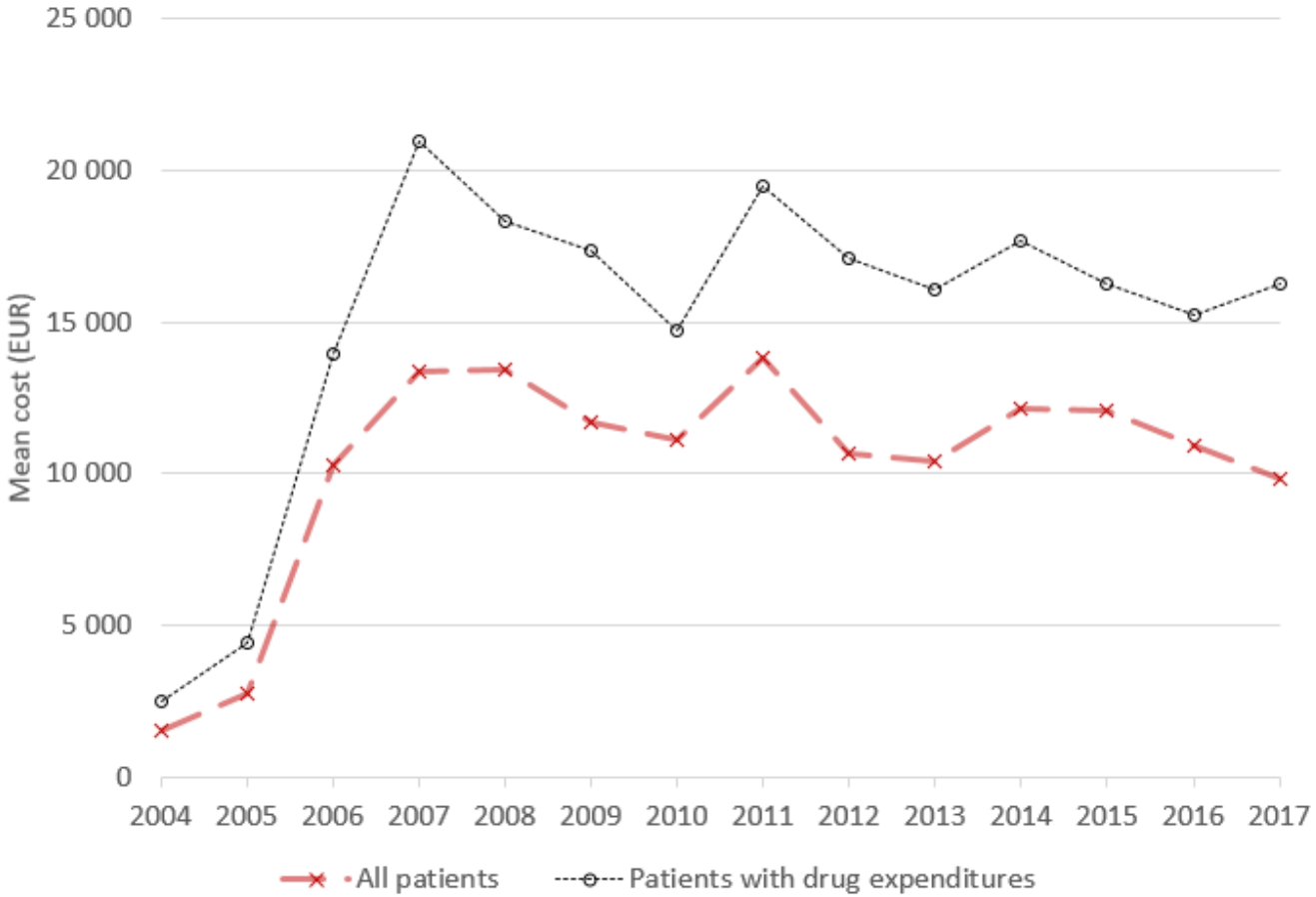


B) Expenses for the first two years after incidence per incidence year (stage III/IV/X)



** Remark: one of the external experts noted that drugs not prescribed in mesothelioma (e.g. abiraterone) appear on the graph. This is because these patients can also have other cancers. In this case, it was checked and confirmed that this indeed concerns patients with another cancer (in this case this was prostate cancer).*

C) Mean cost per patient for the first two years after incidence per incidence year (stage III/IV/X)



Source: BCR-IMA.

4.6.2.2 *Drug uptake for a selection of drugs during the first 5 years after diagnosis*

Pemetrexed is reimbursed since 2006. Its uptake during the first five years after diagnosis was below 20% for patients diagnosed in 2004 and 2005. It sharply increased from 2006 onwards and peaked at 71.2% in incidence year 2008. Since then, it remained fairly constant. Its uptake decreased at the level of 56.3% in 2017, but this decrease should be interpreted cautiously since the follow-up period is less than 5 years for incidence year 2017.

Table 32 – 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. $ IMA data were only available up to the second trimester of 2019 and might have a delay of two years. Five-year follow-up data are thus not 100% complete from incidence year 2012 onwards (see part 3.1.3). Source: BCR-IMA.*

4.6.3 *Medical literature: efficacy*

One systematic review included a single international randomized and controlled trial on 448 patients who had not been previously treated with chemotherapy. It revealed that median survival was longer in the group of patients who received pemetrexed plus cisplatin than those who were treated with cisplatin alone. Pemetrexed provided a benefit on median survival that accounted for approximately three months. The incidence of grade 3/4 adverse events was higher in patients who received pemetrexed plus cisplatin than in those treated with cisplatin alone. However, patients treated with pemetrexed-based regimen demonstrated significantly greater improvement in global quality of life.

Reference + search date	Intervention and comparator + indication	OS	Quality of life	Other outcomes
Green 2007[216] Search date: October 2005	Chemotherapy naïve patients with unresectable malignant pleural mesothelioma. Intervention: Pemetrexed disodium and cisplatin combination, supplemented with folic acid and vitamin B12. Comparator: cisplatin, supportive care, other commonly used alternatives	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 improvement in global QoL (p=0.0012)."	"The incidence of grade 3/4 adverse events was statistically significantly more frequent in patients receiving pemetrexed plus cisplatin than those receiving cisplatin alone."

4.6.3.1 Discussion

In spite of a proven efficacy in terms of survival seen in RCTs and a quick and high uptake up to 69%, the introduction of pemetrexed for patients with advanced pleural mesothelioma was not associated with an improved survival in our observational data. The survival benefit of approximately 4 months seen in clinical trials may be too limited to make a meaningful difference in clinical practice.

Findings in other countries

In a population-based study based on cancer registry data in The Netherlands, the impact of new oncological drugs was assessed. Survival probabilities of 4 731 patients diagnosed for mesothelioma were compared in two time-periods (1995-1998 and 2005-2006). The use of chemotherapy increased over time (8% in 1995-1998 versus 36% in 2005-2006). Antifolate-therapy combined with platinum-based chemotherapy was used in 62% of patients in 2003-2004 and in 85% of them in 2005-2006. Median survival of patients with mesothelioma (pleural and peritoneal) increased over time, from 7.1 months in the first period to 9.2 months in the second one.[217]

In Germany, data from the Centre for Cancer Registry on survival of patients with thoracic (pleural and pericardial) mesothelioma were analysed between 2000 and 2014. Age-standardized 5-year relative survival was 9.9% for the whole period. However, they reported a statistically significant 5-year relative survival improvement from 9.1 % in the period 2002-2007 to 11% in 2008-2013. Data were compared with survival of patients in the US (Surveillance Epidemiology and End Results-18 database) in the same period. In the US, 5-year relative survival remained rather stable at the levels of 8.3% in 2002-2007 and 8.6% in 2008-2013. Details on treatment schedules were not reported.[218]

In Slovenia, data from the Cancer Registry were compared between two periods from 1974 to 2003 and from 2004 to 2008, in order to assess the impact of new chemotherapy regimens. Chemotherapy was used in 17.2% and 80.7% of patients during the first and second period, respectively. Cisplatin and gemcitabine were reported, but only 5 among the 444 patients received pemetrexed plus platinum. Median survival significantly differed between both periods, from 7.4 months (95%CI 5.9-23.8) in 1974-2003 to 12.6 months (95%CI 10.7-14.5) in 2004-2008.[219]

In Canada, the national cancer registry analysed the survival of 30 individual cancers between periods from 1992 to 1994 and 2012 to 2014 and estimated the net survival. The estimated 5-year net survival was 7% for mesothelioma and no improvement was observed between both study periods.[220]

In Australia, survival data from the Australian Mesothelioma Registry showed on 1 362 patients diagnosed from 1960 to 2005 an improvement of median survival up to 301 days (IQR 134-611) for the period 2000-2005 whereas it was 238 (IQR 108–502) in the decade 1990-1999 and 221 (IQR 97–504) in the decade 1980-1989 and less than 200 days in the both previous decades Pleural localization accounted for 92% of the cohort.[221]

Limitations

- Data of high-quality for evidence in the medical literature is limited. EMPHACIS study was the sole randomized controlled clinical trial comparing pemetrexed versus standard therapy. EMPHACIS included patients with good performance status (Karnofsky ≥70).[222] No data on the use of petrexemed in patients with poor performance status at diagnosis is available.
- Even if quality of life has been reported to be better in patients receiving pemetrexed, more detailed analysis of quality of life is required.
- Although the randomised controlled trial reported statistically significant results, the absolute survival gain appears to be limited to a few months.
- Although it remains controversial whether radical surgery lead to better results in term of survival, it is used in highly selected patients.[207] We did not have data on the use of surgery in our analysis.
- In our analyses, we did not consider other drugs such as raltitrexed or bevacizumab (in combination with pemetrexed and chemotherapy,

not reimbursed in Belgium).[223, 224] However, uptake of e.g. raltitrexed is low (see Table 31).

4.6.4 *Economic literature: cost-effectiveness*

For more information about the economic evaluation in the identified HTA report, we refer to Appendix.

Confidential prices

In the identified HTA report, no reference is made to confidential price agreements.

Quality of life

In the underlying EMPHACIS trial reported in TA135, quality of life was evaluated with a disease-specific questionnaire (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.”[225] Unfortunately, no generic utility instrument was used. As a result, for the economic evaluation, “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.”[225] “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.”[225] “The Committee agreed that the economic analyses may have underestimated the overall quality of life benefits of pemetrexed in people with [malignant pleural mesothelioma] MPM.”[225]

Uncertainty & influential parameters

Two models with a different comparator were set up. Model 1 compared pemetrexed plus cisplatin with cisplatin alone. Model 2 compared pemetrexed plus cisplatin with standard care. Unfortunately, for the second model, no head-to-head comparison was available. “The Committee noted the high degree of uncertainty surrounding the assumptions underpinning the model and observed that the survival estimates had been taken from relatively small, non-comparative and observational studies.” The 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.”[225] In the underlying HTA report, it was also noted that “such trials also need to include an assessment of appropriate QoL data to inform subsequent economic evaluations better.”[226]”The Committee concluded that it could not base its decision on the indirect comparison model.”[225]

In the first model, “A wide-ranging sensitivity analysis was undertaken, in which survival and drug costs were found to be the key parameters.”[226]

Results

The ICERs are as follows (see more details in appendix):

- **Pemetrexed**
  - Malignant pleural mesothelioma (list prices):[225]

    The Assessment Group's analysis resulted in the following ICERs:

    - fully supplemented population: £60 600 per QALY gained
    - fully supplemented patients with advanced disease: £49 100 per QALY gained
    - fully supplemented patients with good performance status: £50 400 per QALY gained
    - fully supplemented patients with advanced disease and good performance status: £37 700 per QALY gained

- fully supplemented patients with advanced disease and good performance status + smaller 100-mg vial of pemetrexed: £34 500 per QALY gained.

"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."[225] Furthermore, "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."[225] In first instance, "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."[225] However, "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."[225] "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."[225]

4.6.5 Summary

Observational data

- Observational data reveal that overall survival of patients with stage III/IV/X mesothelioma did not considerably modify over time periods between 2004 and 2017. Three-year observed survival globally maintained the same level and was 16.9% (95%CI 9.0-27.0) for patients diagnosed in 2004 and 19.5% (95%CI 12.2-28.1) for those diagnosed in 2017. Median survival was 1.2 years (95%CI 0.8-1.6) in incidence year 2004 and 1.2 years (95%CI 0.9-1.5) in incidence year 2017.
- For all stages of mesothelioma, oncological drug expenditures sharply increased from less than €50 000 in 2004 to more than €2 million in 2017.
- Drug expenditures for stage III/IV/X mesothelioma during the first two years after diagnosis, increased over time, from approximately €100 000 for incidence year 2004 to peak at €1.6 million in incidence year 2015 and reach about €1.1 million in incidence year 2017.
    - This rise was largely due to the uptake of petrexemed from incidence year 2006 onwards.
    - The number of patients with stage III/IV/X mesothelioma, with drug expenses for the first two years after incidence, went up from 41 in incidence year 2004 to a peak of 100 in 2015 and 68 in 2017.
    - Mean cost per patient during the first two years after diagnosis was €2 500 for incidence year 2004 and increased from 2005 onwards to remain above €15 000 up till incidence year 2017.

Medical literature

- One randomized controlled clinical trial showed that in chemotherapy-naïve patients with unresectable mesothelioma, pemetrexed combined with cisplatin provided a survival benefit and quality of life in comparison with cisplatine alone. However, grade 3/4 adverse events are more frequent.

Economic literature

- We identified one HTA report with an economic evaluation of pemetrexed for the treatment of patients with malignant pleural mesothelioma. The manufacturer set up two models with different comparators. The first model compared pemetrexed plus cisplatin with cisplatin alone. The second model compared pemetrexed plus cisplatin versus other chemotherapy treatments and active symptom control. The latter model was not considered further by the researchers due to a lack of a direct RCT comparison.
- In the underlying trial comparing pemetrexed plus cisplatin with cisplatin alone, no generic utility instrument was applied. For the economic evaluation, utility scores were taken from an ongoing observational study in patients with non-small-cell lung cancer who completed the EQ-5D questionnaire. This is linked to high uncertainty and the economic analysis may have underestimated the overall QoL benefits.
- Next to the uncertainty on QoL estimates, the impact on survival and drug costs were key parameters in the economic evaluation.
- In the identified HTA, the range of ICERs for pemetrexed plus cisplatin versus cisplatin alone produced by the manufacturer and the Assessment Group were higher than is normally considered acceptable. However, the ICER was better for several subgroups including patients with a good performance status. Above that, other arguments (e.g. lower numbers of treatment cycles in clinical practice) were cited and the Committee also noted that malignant pleural mesothelioma (MPM) is a rare and aggressive malignancy caused by occupational exposure to asbestos and was mindful that this disease has a very poor prognosis. In the end, the Committee concluded the intervention could be recommended as an option for the treatment of MPM in advanced disease and who have a WHO performance status of 0 or 1, in whom surgical resection is not considered appropriate.

4.7 Multiple myeloma

4.7.1 Introduction

Multiple myeloma (MM) is a haematological tumour characterized by an uncontrolled proliferation of monoclonal plasma cells mainly occurring in the elderly with a median age at diagnosis of 70 years.[227] It accounts for the second most frequent haematological malignancy and is expected to rise gradually during the upcoming decades.[228] In 2018, 1009 patients were diagnosed with multiple myeloma in Belgium. From 2004, incidence of multiple myeloma is slightly increasing for men and reached 4.65/100 000 in 2018 while women had a rather stable reported incidence of 3.11/100 000 (http://kankerregister.org/). MM is usually preceded by an asymptomatic premalignant proliferation of plasma cells called monoclonal gammopathy of undetermined significance (MGUS), which further progresses to symptomatic disease. Overt multiple myeloma is generally associated with substantial morbidity. Its manifestations encompass renal failure, hypercalcemia, anaemia, bone damages and increased risk of infection.

Proteasome inhibitors (PIs) include the first generation agent bortezomib and the second generation drugs – carfilzomib and ixazomib. The proteasome activity plays a key-role in myeloma cells. Its upregulation has been described and leads to a reduction of anti-proliferation proteins enabling tumor growth. PIs bind to their molecular target on the proteasome and directly inhibit proliferation and induce apoptosis of myelomatous cells. Thalidomide and its analogues, lenalidomide and pomalidomide are immunomodulatory agents that target both MM cells and their microenvironment. They are able to enhance the immunity

response against myeloma through immunomodulatory, anti-angiogenic, anti-inflammatory and anti-proliferative properties.

To date, chemotherapy followed by autologous stem cell transplantation (ASCT) is the standard of care for young patients and fit elderly. However, the majority of new diagnosed MM patients are elderly patients unsuitable for an ASCT. Frequently presenting with pre-existing frailty and comorbidities, such patients require a different approach that consider the side effects of proposed therapies. The combination of melphalan and prednisone (MP) was the former standard treatment for patients who were not eligible for transplantation. The most recent Belgian guideline published in 2018, recommends the combination of bortezomib, melphalan and prednisone (VMP) or lenalidomide with low-dose dexamethasone (Rd) as standard of care in this group of patients. Bortezomib-lenalidomide-dexamethasone (VRd), daratumab-lenalidomide-dexamethasone and daratumab-bortezumib-melphalan-prednisone are also possible options.[227]

Bortezomib and Lenalidomide are also used in the treatment schemes of transplant eligible patients.[229]

For relapsed and refractory multiple myeloma, the combination of lenalidomide and dexamethasone became the backbone of treatment in 2007 (2008 in Belgium). Several studies have evaluated the addition of a third drug to this combination, for example cafilzomib, ixazomib, daratumib and elotuzomab, with at least benefits in response rate and progression-free survival. The combination pomalidomide-dexamethasone is tested in a heavily pretreated population.[230]

Drugs selected for multiple myeloma are listed in Table 33.

Table 33 – selected drugs for multiple myeloma

Drug	Year#	Trade Name	Company$	Mechanism of action
Lenalidomide	2008	Revlimid	Celgene	Lenalidomide binds directly to cereblon, a component of a cullin ring E3 ubiquitin ligase enzyme complex
Bortezomib*	2005	Velcade	Janssen-Cilag	Bortezomib is a proteasome inhibitor
Pomalidomide	2014	Imnovid	Celgene	Pomalidomide binds directly to the protein cereblon (CRBN), which is part of an E3 ligase complex t
Daratumumab	2017	Darzalex	Janssen-Cilag	an IgG1κhuman monoclonal antibody (mAb) that binds to the CD38 protein expressed at a high level on the surface of multiple myeloma tumour cells

$ of the originator; # year of start reimbursement first indication in Belgium,
** generic/biological available*

4.7.2 Observational data

4.7.2.1 Patient characteristics, survival and expenditures

The number of reported cases of multiple myeloma has increased over the three incidence periods[v] (Table 34A). Observed survival has remained stable between 2004 and 2013 while it tends to be higher in the last incidence period 2014-2017 (Table 34B). The 3-years observed survival probability displays an increase from 56.4 (95%CI 52.6-60) in 2004 to 67.4 (95%CI 63.9-70.5] in 2017 (Table 34C). In the same way, the median survival time has risen from 3.7 years (95%CI 3.3-4.2) in 2004 to 5 years (95%CI 4.4-NA] in 2015 (median survival not yet reached for incidence years 2016 and 2017) (Table 34D).

Table 3 indicates that oncology drug expenditures have largely grown. Before 2005, yearly drug expenses were virtually non-existent. Expenditures consistently went up ever since, to reach €90 million in 2018 (Table 34A).

This substantial increase is mainly attributable to the reimbursement of bortezomib, lenalodomid and later to pomalidomide and daratumumab. The number of patients treated with oncology drugs noticeably increased from less than 400 in 2004 to almost 2 000 in 2017 (data for 2018 are not yet complete). The oncology drug expenditures during the first two years after diagnosis more rapidly increase from €2.5 million for patients diagnosed in 2004 to reach nearly €41 million for those diagnosed in 2018 (Table 35B). While there is also an increase in patients being treated with oncology drugs, this sharp increase mainly matches up to the uptake of bortezomib and lenalidomide in combination with a price-effect. The mean cost per patient with drug expenses for the first two years after incidence sharply rose from less than €10 000 before 2006 to nearly €60 000 in 2018 (Table 35C).

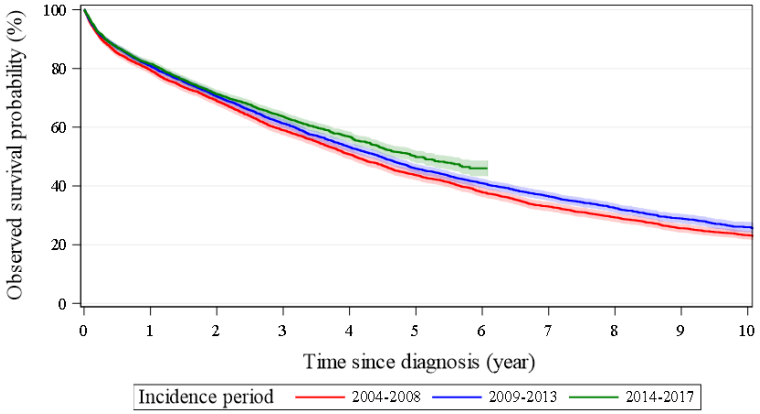
[v] We remark that the third incidence period (2014-2017) only covers four years, while this is five years for the first two incidence periods (2004-2008 & 2009-2013). Taking this into account, the number of patients diagnosed with multiple myeloma increases over time.

Table 34 – Multiple myeloma (2004-2017) (observed survival): A) Patient characteristics; B) Kaplan-Meier graph per incidence period; C) Time trend with incidence year*; D) Median survival time* **

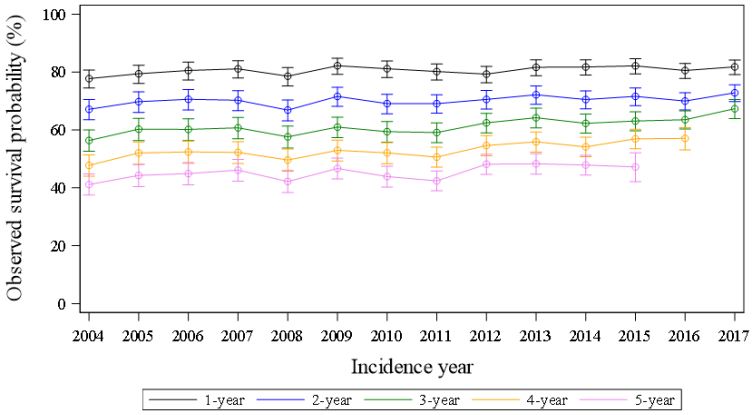
A

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

B

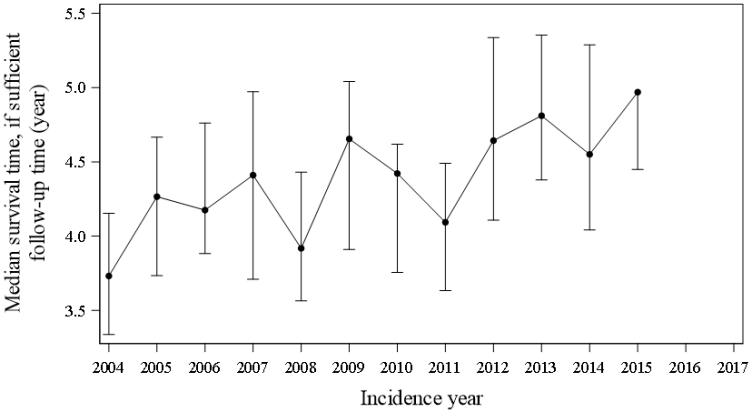


C



Year: 3-y OS [95%CI]
2004: 56.4 [52.6, 60.0]
2005: 60.3 [56.4, 64.0]
2006: 60.2 [56.3, 63.9]
2007: 60.7 [56.9, 64.3]
2008: 57.6 [53.7, 61.3]
2009: 61.0 [57.4, 64.4]
2010: 59.4 [55.7, 62.9]
2011: 59.1 [55.6, 62.4]
2012: 62.5 [59.0, 65.8]
2013: 64.2 [60.7, 67.5]
2014: 62.3 [58.9, 65.5]
2015: 63.1 [59.7, 66.3]
2016: 63.5 [60.3, 66.6]
2017: 67.4 [63.9, 70.5]

D

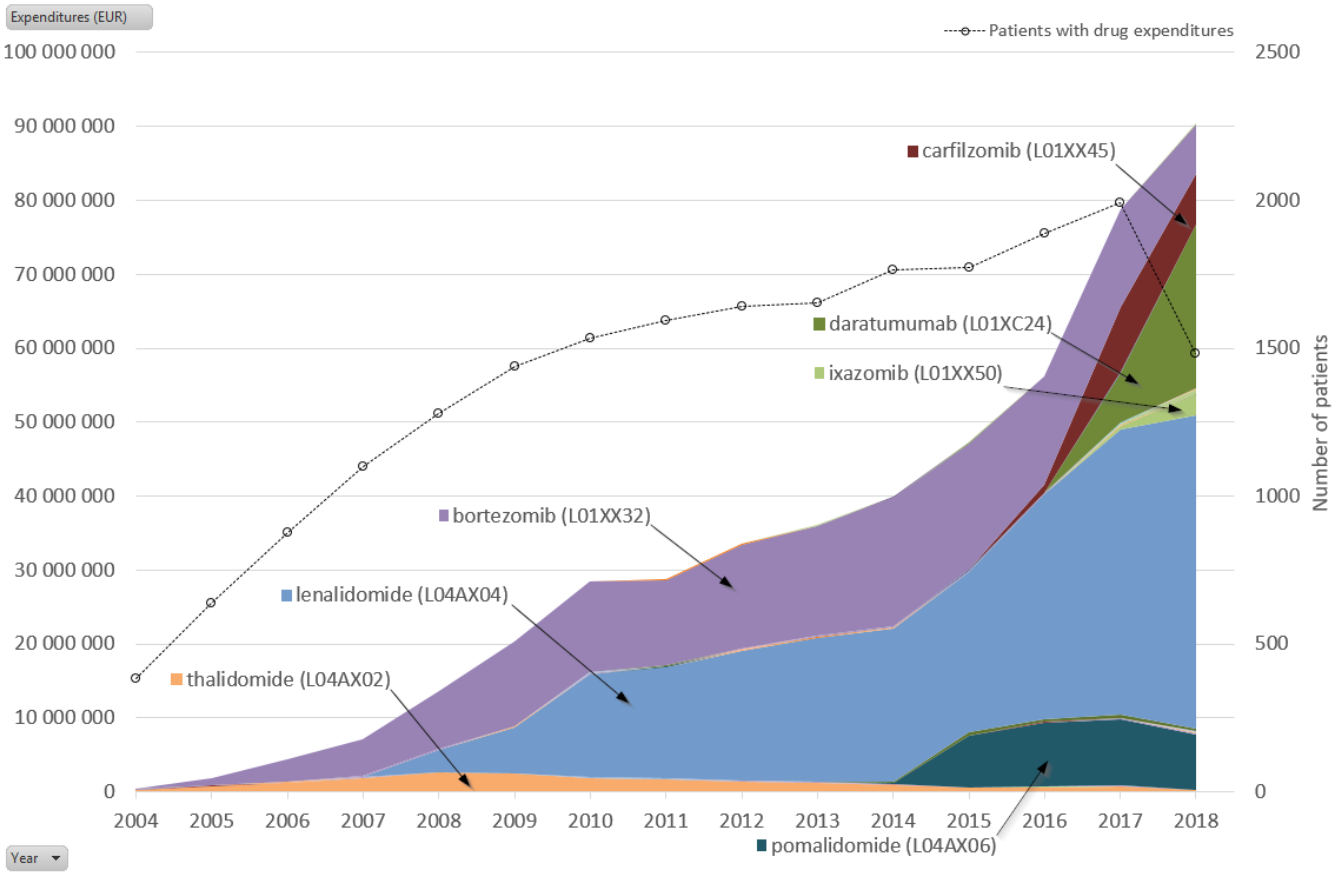


Year: Med. ST [95%CI]
2004: 3.7 [3.3, 4.2]
2005: 4.3 [3.7, 4.7]
2006: 4.2 [3.9, 4.8]
2007: 4.4 [3.7, 5.0]
2008: 3.9 [3.6, 4.4]
2009: 4.7 [3.9, 5.0]
2010: 4.4 [3.8, 4.6]
2011: 4.1 [3.6, 4.5]
2012: 4.6 [4.1, 5.3]
2013: 4.8 [4.4, 5.4]
2014: 4.6 [4.0, 5.3]
2015: 5.0 [4.4, NA]
2016: >4
2017: >3

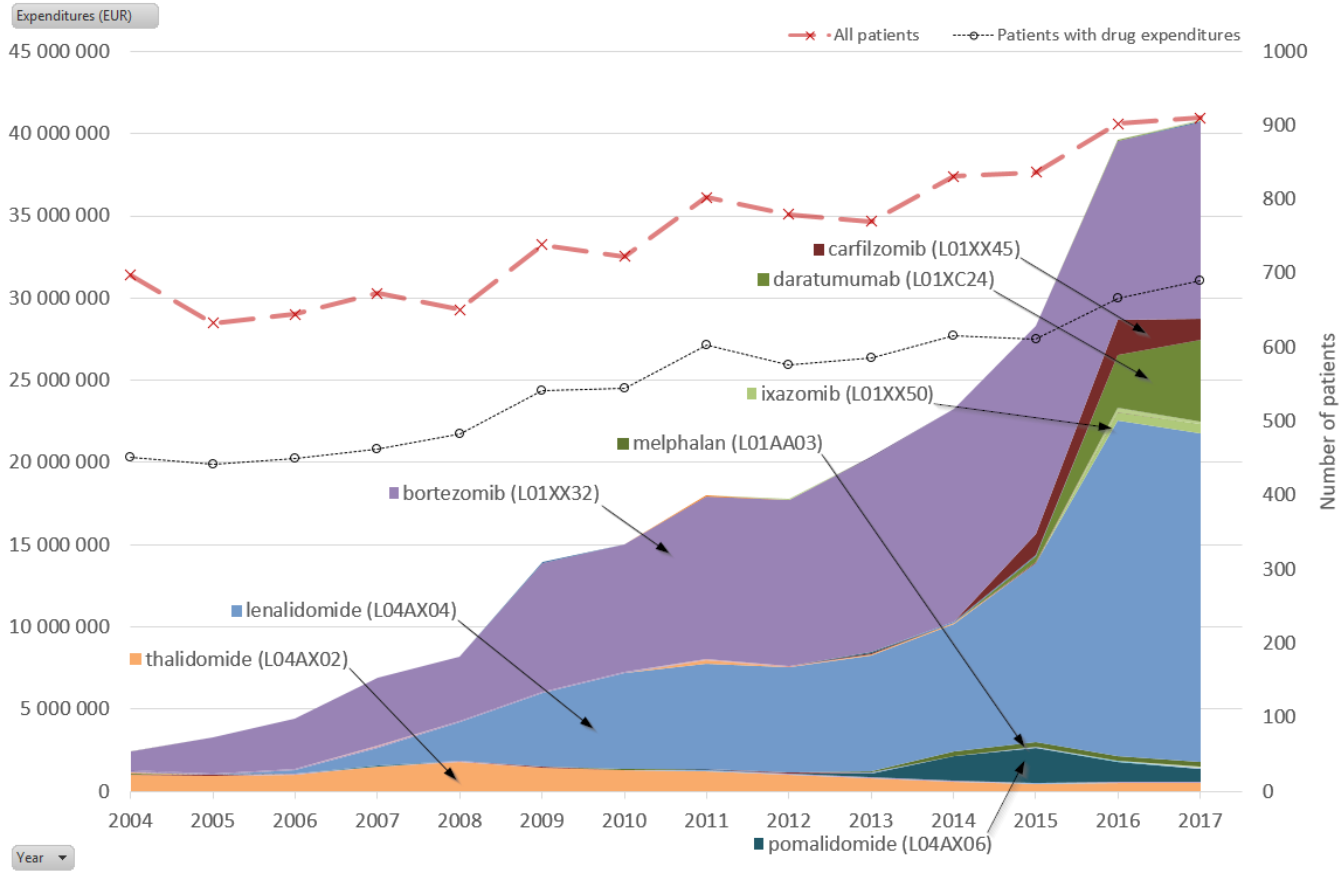
*Med. ST: median survival time; 3-y OS: 3-year observed survival; * the error bars represent the 95%CI. ** When the upper error is not plotted, the upper limit could not be determined with the available follow-up data. Source: BCR.*

Table 35 – Multiple myeloma: drug expenditures

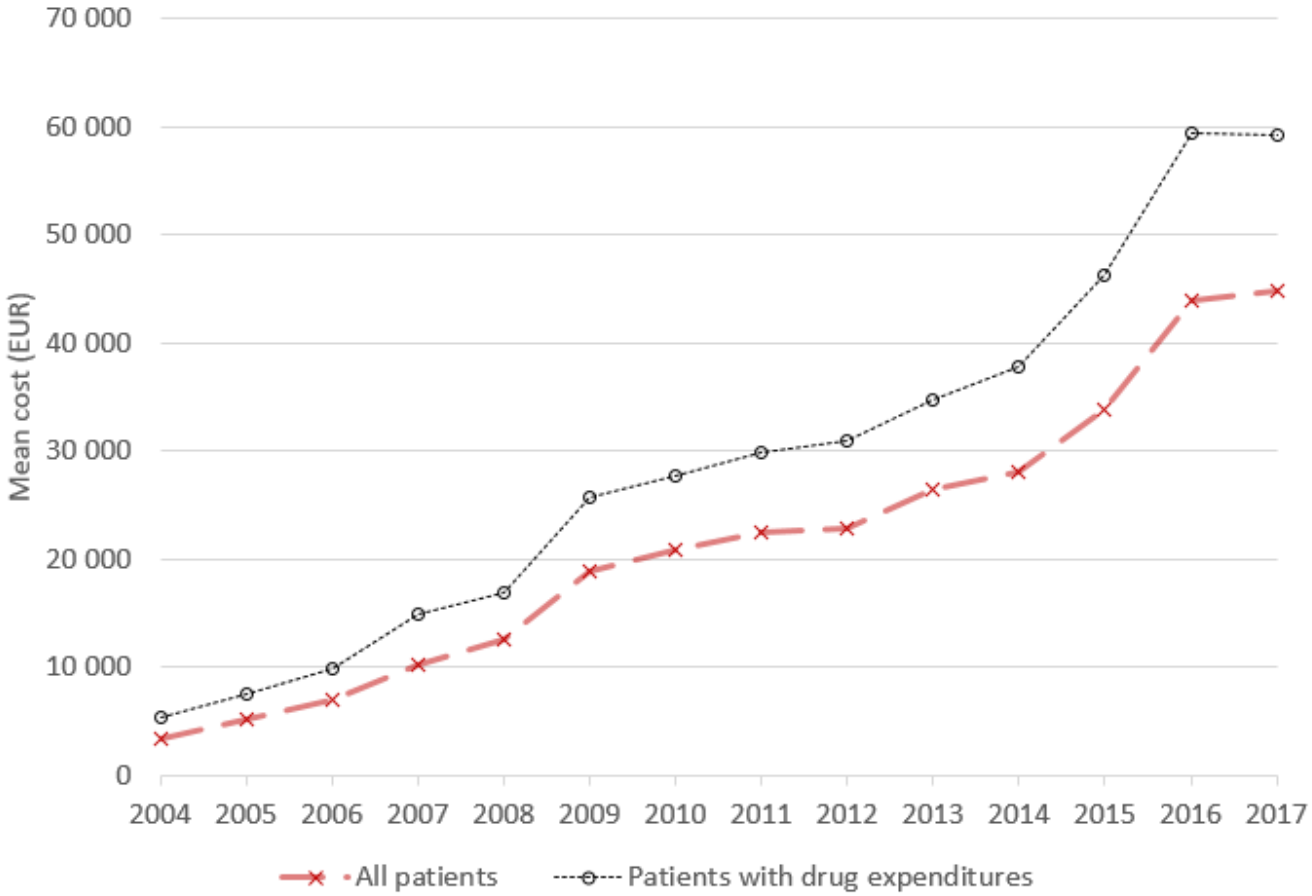
A) Oncological drug expenses per year



B) Expenses for the first two years after incidence



C) Mean cost per patient for the first two years after incidence



Source: BCR-IMA.

4.7.2.2 *Drug uptake for a selection of drugs during the first 5 years after diagnosis*

Bortezomib is reimbursed in Belgium since 2005 for recurrent multiple myeloma. Twenty-nine percent of patients who were diagnosed in 2004 received bortezomib during the first five years after diagnosis. Uptake increased further to 67% of patients diagnosed in 2014-2015. Lenalidomide is reimbursed since 2008. Uptake was 8.2% in patients diagnosed in 2004 and increased over the years to 49% in patients diagnosed in 2017.

Pomalidomide and daratumumab are reimbursed since 2014 and 2017 respectively for recurrent and refractory multiple myeloma. Maximum uptake was 13% for pomalidomide and 11% for daratumumab. We remark, however, that the 5-year follow-up period is not yet complete for the last years in Table 36.

Table 36 – 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. $ IMA data were only available up to the second trimester of 2019 and might have a delay of two years. Five-year follow-up data are thus not 100% complete from incidence year 2012 onwards (see part 3.1.3). Source: BCR-IMA.*

4.7.3 *Medical literature: efficacy*

Many combinations of drugs are available for patients with multiple myeloma who are not eligible for ASCT and for recurrent and refractory multiple myeloma. Combinations have been evaluated in clinical trials with different comparators and have not always been directly compared. Therefore, for many comparisons, results can only be obtained using network meta-analysis.[231] We discuss further impact on OS and QoL for the most relevant comparisons of the selected drugs.

Frontline treatment of patients who are not eligible for ASCT improved in terms of overall survival with the lenalidomide-dexamethasone (RD) combination compared to melphalan-prednisone (MP) combination and possibly compared with thalidomide-melphalan-prednisone (TMP) (results non-conclusive). Quality of life improved with RD compared to treatment with TMP. The triplet bortezomib-lenalidomide-dexamtasone (VRD) may further improve overall survival compared with RD but results remain inconclusive (see part 4.7.3.1).[231]

In patients who are eligible for stem-cell transplantation, induction therapy that includes thalidomide, bortezomib or lenalidomide appear to perform better than therapeutic protocols relying on antracyclic backbones (see part 4.7.3.2).

For patient with recurrent or refractory multiple myeloma, pomalidomide with low dose dexamethasone improves overall survival[232] and QoL[233] compared to high dose dexamethasone (see part 4.7.3.3).[232] The addition

of daratumumab to lenalidomide and dexamethasone also may improve overall survival at 12 months in the group of recurrent multiple myeloma, however the difference was not statistically significant. The results for the triplet daratumumab-bortezomib-dexamethasone were unclear due to early cross-over after the interim analysis.[234]

4.7.3.1 Multiple Myeloma: First-line treatment in adult patients ineligible for stem-cell transplantation

Reference + search date	Intervention and comparator + indication	OS	Quality of life	Other outcomes
Piechotta 2019[231] search date 14 February 2019	Adults with newly diagnosed multiple myeloma Interventions: melphalan (M) prednisone (P) bortezomib (V) lenalidomide (R) thalidomide (T) Dexamethasone (D), Prednisone (P) Melphalan (M), cyclophosphamide (C) continuous (c) = first-line treatment followed by maintenance therapy, continuous first-line therapy, or continuous first-line therapy until a plateau phase (response) was reached (results from network meta-analysis, not from direct comparisons)	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) VRDc vs RD HR 0.79 (95%CI 0.42-1.48) VRDc vs RDc HR 0.71 (95%CI 0.44-1.15)	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.	SAEs RD vs VRDc RR 0.73 (95%CI 0.59-0.89) RDc vs VRDc RR 0.90 (95%CI 0.75-1.09)
Piechotta 2019[231] search date 14 February 2019	Adults with newly diagnosed multiple myeloma comparator: bortezomib (V) + dexamethasone (D) Intervention: bortezomib (V) + lenalidomide (R) + dexamethasone (D)	median OS VD: 60.22 months (95%CI 37.06 - NE) median OS VRD: 69.22 months (95%CI 59.7-NE) HR: 0.77 (95%CI 0.35-1.70)		

**Selected results for treatment regimens recommended by guidelines of the Belgian Society of Hematology[227] the ESMO guideline 2017[235] NMA: Network meta-analysis.*

4.7.3.2 *Multiple myeloma: first-line treatment in adult patients eligible for stem-cell transplant*

Reference + search date	Intervention and comparator + indication	OS	Quality of life	Other outcomes
Sekine 2019[236] search date: 1 May 2018	newly diagnosed transplant-eligible MM patients, induction treatment	"Overall, therapeutic protocols including T, V and/or R performed better than those relying on antracyclic backbones"		

4.7.3.3 *Multiple myeloma: treatment of relapsed or refractory disease*

Reference + search date	Intervention and comparator + indication	OS	Quality of life	Other outcomes
*Sparano 2018[233] Search date: May 2017	Patients with relapsed/refractory multiple myeloma Intervention: bortezomib Comparator: dexamethasone		"This study showed that bortezomib was associated with higher AEs but better HRQoL."	
*Sparano 2018[233] Search date: May 2017	Patients with relapsed/refractory multiple myeloma Intervention:Pomalidomide + low dose dexamethasone Comparator: high dose dexamethasone		"Better results were reached with pomalidomide, …, statistically and clinically significant differences were found in most scales of the PRO instruments."	
Chen 2017[232] search date: 20 September 2016 &Miguel 2013[237]	Patients with relapsed/refractory multiple myeloma Intervention: Pomalidomide + low dose dexamethasone Comparator: high dose dexamethasone	HR 0.74 (95%CI 0.56-0.97) 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		
Dhakal 2020[234] Search date: 1 July 2018 Palumbo 2016[238]	Patients with multiple myeloma who had received at least one previous line of therapy. (relapsed or refractory disease) Intervention: daratumumab + bortezomib + dexamethasone Comparator: bortezomib + dexamethasone	Not reported (early unblinding and cross-over after interim analysis)		Progression-free survival HR 0.39 (95%CI 0.28-0.53) Patients free of disease after 12 months 65.4% (95%CI 56.1-74.8) vs 28.8% (95%CI 17.8-39.8)

Dhakal 2020[234] Search date: 1 July 2018 Dimopoulos 2016[239]	Patients with multiple myeloma who had received at least one previous line of therapy. (relapsed or refractory disease) Intervention: daratumumab + lenalidomide + dexamethasone Comparator: lenalidomide + dexamethasone	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)	Progression-free survival HR 0.37 (95%CI 0.27-0.52) Patients free of disease after 12 months 85.7% (95%CI 80.9-89.4) vs 63.2% (95%CI 57.1-68.8)

**No critical appraisal performed but included as no recent SR on patient-reported outcomes was identified. &Only phase III RCT identified in SR by Chen et al.*

4.7.3.4 Discussion

Uptake of lenalidomide and bortezomib raised over time to 49% and 67% respectively, which seems to be associated with a slightly improved survival for patients diagnosed during the last incidence period 2014-2017. For first line treatment with lenalidomide, indeed a survival benefit is seen in RCTs compared to chemotherapy, while for bortezomib the results of RCTs remained inconclusive. For pomalidomide and daratumumab, RCTs showed a positive effect on overall survival, but uptake remained below 15%.

Findings in other countries

In a population-based study based on cancer registry data in Norway, a linear increase in relative survival was seen from the period 1982-1987 until 2013-2017 for patients younger than 65 years old. For patients aged 65-79 years, an improvement in relative survival was seen from 2002 onwards. For patients older than 80 years at diagnosed, relative survival started improving from 2008 onwards. Start of reimbursement and uptake of lenalidomide, bortezomib, pomalidomide and daratumumab seems quite similar to Belgium.[240]

In Taiwan, an improvement in the median overall survival was seen in what they call the post-novel agent period (2013-2015), compared to the pre-novel agent period (2007-2009) and transition period (2010-2012). Median overall survival increased from 2.10 years for patients diagnosed in 2007-2009 to 3.12 years for patients diagnosed in 2013-2015. From 2007 to 2015, the percentage of patients receiving first-line therapy with novel agents increased from 0.4% to 89.4%.[241]

In a study performed in Japan and the United States, a decline in mortality from multiple myeloma was seen, despite an increasing incidence. The change in mortality trend appeared to coincide with the introduction of new agents (2002 in the US, 2005 in Japan).[242]

Limitations

- The benefit of lenalidomide and bortezomib treatment for patients with recurrent or refractory disease compared to the old standard is not covered in recent systematic reviews.
- For comparison of the efficacy of different treatment schedules, often a network meta-analysis is performed as no trials with a direct comparison are available.
- Based on available data, we could not obtain separate survival curves for patients who are eligible or non-eligible for ASCT.
- As Sparano et al. conclude in their systematic review on patient-reported outcomes in relapsed/refractory multiple myeloma, published comparative data on quality of life in multiple myeloma is very scarce.[233]
- As median survival of multiple myeloma is more than 4 years and patients are often treated several times for recurrence, probably not all treatment lines are covered in the uptake data available, which include only the first five years after diagnosis (and even less for the most recent years). Furthermore, longer-time follow-up may reveal

further improvement of (median) survival for patients diagnosed in 2016-2017.

4.7.4 Economic literature: cost-effectiveness

For more information about the economic evaluations in the identified HTA reports, we refer to the Appendix.

Confidential prices

In most evaluations (7 out of 9) there were confidential price discounts for the interventions (i.e. lenalidomide, pomalinomide, bortezomib and daratumumab);[243-249] and also for the comparators in five of them.[245-249] All ICERs in those evaluations were calculated including the confidential price reductions.

In the two evaluations of bortezomib for untreated multiple myeloma there was no price reduction, neither for the comparators. Results based on published list prices were used by the decision makers.[250, 251]

Quality of life

In all TAs, the outcome measure in the economic evaluations are QALYs. In virtually all cases however, utilities were not measured from direct head-to-head trials comparing the interventions under consideration and alongside which a generic HRQoL instrument was administered. This is because either there was no (appropriate[249]) underlying head-to-head trial,[246-249, 251] or because such trial existed but did not measure HRQoL with a generic utility instrument.[243, 244, 250] Instead, utilities were obtained from the following sources:

- A cost-utility analysis of intensive chemotherapy in patients with untreated multiple myeloma (van Agthoven et al., 2004[252]) whose source for EQ-5D utility measures is an unpublished PhD thesis.[243, 244, 247, 251]
- A published set of disease-specific HRQoL data in patients with untreated multiple myeloma (EORTC QLQ-C30 instrument) mapped to generic EQ-5D utility data.[250]
- EQ-5D data collected from one arm of the FIRST RCT for the intervention, and disease-specific EORTC data mapped to generic EQ-5D data for the comparator.[248]
- EORTC health-related quality-of-life data collected from ENDAVOUR that were mapped to EQ-5D utilities.[249]
- Utility data from an ongoing observational study providing early access to daratumumab.[246] In this TA, there was no information on the methods used to derive the data.

In an assessment of daratumumab, even though EQ-5D data were collected form the underlying head-to-head CASTOR trial, the committee stated that these data were not appropriate as “the difference between the modelled utility of people before and after disease progression was implausibly small because quality of life would be expected to decrease more after disease progression”.[249] The committee concluded that the ERG utility values from the ENDEAVOR trial appeared more plausible even tough they were not derived from EQ-5D data and even though this trial did not directly compare the interventions of interest.

In one TA there was a head-to-head trial, the MM-003 trial comparing pomalidomide versus conventional chemotherapy, from which EQ-5D utilities were obtained. The utilities derived from this trial were however used to describe the disease health states instead of modelling per treatment arm.[245]

QoL was always modelled per health state,[243, 244, 246, 247, 249-251] except in a recent TA of lenalidomide (i.e. lenalidomide plus dexamethasone versus bortezomib plus melphalan plus prednisone) that modelled QoL per treatment arm.[248] In this TA however, the utility values for each treatment arm were not obtained from a head-to-head trial but were extracted from different sources (cfr. Supra).[248]

Uncertainty and influential parameters

In half of the TAs, there was no head-to-head trial directly comparing the interventions under consideration,[245-248, 251] and evidence came from indirect treatment comparisons which generated uncertainty in the results (OS, QALYs and ICERs).[w] In one of those evaluations, NICE was further concerned about the paucity of trials included in a network analysis comparing lenalidomide to bortezomib which added to the uncertainty.[248]

In the other half of the TAs, there was a RCT available to provide direct comparative evidence about different interventions.[243-245, 249, 250] In some cases however, uncertainties in the results still emerged. This was the case in a TA comparing bortezomib to high-dose dexamethasone based on the APEX trial:[243] "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."[243] A similar problem of treatment crossover also occurred in the MM-003 trial comparing pomalidomide with high-dose chemotherapy.[245]

In most evaluations the main uncertainty relates to the estimation of the treatment effect, and more specifically to the magnitude of the overall survival gain as there was no head-to-head comparison of the interventions considered. This was the case for the assessments of lenadidomide,[247, 248] pomalidomide (versus bendamustine and versus panobinostat)[245] and bortezomib.[251] Uncertainty in the treatment effect was also related to the modelling of OS, such as the impact of the method used to calibrate the OS curve from the trial population in the economic model,[244] or to adjust for treatment crossover in the course of the trial.[243, 245] In all those evaluations, OS was identified as the parameter with the strongest influence on the cost-effectiveness results.

Another source of uncertainty in the estimation of the overall survival gain is the immaturity of the data. This was the case in the two recent (2018 and 2019) assessments of daratumumab because of the short median follow-up of the underlying trials at the time of the assessment and because median OS for daratumumab patients had not yet been reached during this follow-up (median follow-up was 27 months for the CASTOR trial,[249] and 31.3 months in the MMY2002 and GEN501 single-arm trials[246]). In both assessments, there was further high uncertainty in the plausibility of the extrapolation methods to model OS in the long-term. For example in TA573, the committee states that "to model the average life expectancy of people having treatment in the model, it was necessary to extrapolate trial data from CASTOR (a short-term trial, with immature data) for more than 10-times the length of the actual trial follow-up."[249] Because of this, the committee appreciated that any extrapolation would be associated with high uncertainty.

Another parameter associated with great uncertainty is QoL. The committee considered indeed that the utility values obtained from the van Agthoven et al. (2014) study[252] and used in four evaluations, lacked supporting evidence and were uncertain.[243, 244, 247, 251] Further in TA129,[243] the population considered in the evaluation differed from the one considered in van Agthoven et al.,[252] i.e. patients with relapsed MM in the TA versus newly diagnosed patients with MM in van Agthoven.

Methodological issues about the calculation of ICERs may also generate uncertainty. This was a concern in an evaluation of pomalidomide where different datasets were used in each comparison (versus conventional chemotherapy, versus bendamustine and versus panobinostat) making a fully incremental analysis not possible.[245] Though the ERG recommended to run a full incremental analyses based on a pooling of the pomalidomide datasets, the committee preferred to base its appraisal on the one-to-one

[w] In NICE TA427, pomalidomide is compared with three different comparators. Direct evidence form head-to-head trial was available for one comparison (pomalidomide versus high-dose chemotherapy). For the other two comparisons (versus bendamustine and versus panobinostat) there was no such direct evidence.[245]

comparisons with pomalidomide and justified its choice as follows: “However, the committee noted that this [the ERG proposal] would mean losing the head-to-head trial data compared with conventional chemotherapy, and some of the trial arm comparability for pomalidomide compared with bendamustine. The committee understood the ERG's approach but did not consider that it was more appropriate than the company's approach.”[245]

Drug costs are reported as being a main driver of cost-effectiveness in an assessment of bortezomib.[251] Such parameter is however clearly a key parameter in almost all technology assessments of relatively expensive treatments.

Results

The ICERs supporting the committee’s conclusions are (see more details in appendix):

- **Lenalidomide**
  - Patients with untreated MM who cannot have a stem cell transplant or first-line thalidomide (including PAS in intervention and comparator):[248]

    £26 713 per QALY gained for lenalidomide plus dexamethasone compared with bortezomib plus melphalan plus prednisone (Conclusion: cost-effective).
  - Patients with MM who had one previous therapy with bortezomib and who cannot have a stem cell transplant or first-line thalidomide (including PAS in intervention and comparator):[247]

    over £30 000 per QALY gained for lenalidomide plus dexamethasone compared with melphalan plus prednisolone (Conclusion: not cost-effective but recommended as unmet need).
  - Patients with MM who had two or more previous therapies (including PAS in intervention):[244]

    £43 800 per QALY gained for lenalidomide compared with high-dose dexamethasone; £41 300 per QALY gained when thalidomide is one of the previous therapies received (Conclusion: cost-effective with EOL criteria).
- **Pomalidomide plus low-dose dexamethasone**
  - Patients with MM who received three or more previous treatments, including both lenalidomide and bortezomib (including PAS in intervention):[245]
    - £48 673 per QALY gained versus conventional chemotherapy (Conclusion: cost-effective with EOL criteria),
    - £45 082 per QALY gained versus bendamustine with thalidomide and dexamethasone (Conclusion: cost-effective with EOL criteria),
    - Versus panobinostat with bortezomib and dexamethasone: the ICER was not reported because of a confidential PAS for panobinostat. The committee noted however 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” (Conclusion: cost-effective).
- **Bortezomib**
  - Patients with untreated MM, who are eligible for high-dose chemotherapy with stem cell transplantation (no PAS):[251]
    - £17 800 to £22 700 per QALY gained for bortezomib plus thalidomide and dexamethasone versus thalidomide and dexamethasone (Conclusion: cost-effective);
    - £20 600 to £24 300 per QALY gained for bortezomib and dexamethasone versus cyclophosphamide, thalidomide and dexamethasone (Conclusion: cost-effective).
  - Patients with untreated MM, who are not eligible for high-dose chemotherapy with stem cell transplantation (no PAS):[250]



- £19 000 per QALY gained for bortezomib plus melphalan and prednisone versus melphalan and prednisone (Conclusion: cost-effective);
- £320 000 per QALY gained versus thalidomide, melphalan and prednisone (Conclusion: not cost-effective).

- Patients at first relapse of MM (including confidential response-based rebate scheme in intervention):[243]

  £20 700 per QALY gained for bortezomib monotherapy versus high-dose dexamethasone (Conclusion: cost-effective).

- **Daratumumab**
  - As monotherapy for adults with relapsed and refractory multiple myeloma (including commercial access agreements in the intervention and confidential discounts in the comparators):[246]
    - daratumumab versus pomalidomide plus dexamethasone: the ICERs varied considerably;
    - daratumumab versus panobinostat plus bortezomib and dexamethasone: the ICERs varied considerably.

    "The degree of uncertainty in the current evidence is too high to be able to identify the most plausible ICERs".[246]

    Conclusion: not recommended but considered for use in CDF
  - As combination therapy for patients with relapsed multiple myeloma who have received at least one prior treatment (including confidential PAS and CAA for the intervention and the comparators)[249]
    - £40 000 to £50 000 per QALY gained for daratumumab plus bortezomib and dexamethasone versus bortezomib plus dexamethasone;
    - above £50 000 per QALY gained for daratumumab plus bortezomib and dexamethasone versus carfilzomib plus dexamethasone.

Conclusion: not cost-effective but recommended for use in CDF

With a few exceptions,[245, 246, 249] the ICERs backing up the committee's conclusions were explicitly reported, both when those ICERs were based on list prices (such as in two assessments of bortezomib in which there is no price discount[250, 251]) and when those ICERs were based on confidential price discounts. This latter is the case for the evaluations of lenalidomide,[244, 247, 248] pomalidomide[245] and in another evaluation of bortezomib.[243] In two of those evaluations, the most recent ones (2019), the ICERs also included a price discount for the comparators.[247, 248]

The ICER was kept confidential in an evaluation of pomalidomide because of a confidential patient access scheme for its comparator, panobinostat.[245] This was also the case for the evaluation of daratumumab versus carfilzomib or bortezomib for which ranges were reported instead of exact ICERs: "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."[249] In another assessment of daratumumab, ICERs could not be reported due to high uncertainties: "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."[246]

Information about the incremental costs and effects was barely reported in the documents reviewed. Such information was however available in an assessment of lenalidomide whose discounted price was commercial in confidence.[244] At that time (2009) a complex PAS was agreed on lenalidomide such that elicitation of its discounted price via the incremental costs is not straightforward.

In general, the committee assessments for therapies against MM were favourable and most of the interventions evaluated were considered as a good use of NHS resources in the various indications explored (i.e. for lenalidomide, bortezomib and pomalidomide). One exception is when bortezomib is administered first-line to MM patients who are not eligible to stem cell transplantation but in whom thalidomide is suitable, which

generated an incremental cost over £300 000 per QALY gained and which was therefore not recommended in this indication.[250]

In its other indications, bortezomib was the only cancer drug for which the committee concluded that it was cost-effective at its official list price. For this drug, ICERs below £25 000 per QALY gained were reported for the following comparisons and indications: bortezomib plus thalidomide plus dexamethasone compared to thalidomide plus dexamethasone, and bortezomib plus dexamethasone compared to cyclophosphamide plus thalidomide plus dexamethasone both for the first-line treatment of MM patients eligible to stem cell transplantation;[251] bortezomib plus melphalan plus prednisone compared to melphalan plus prednisone for the first-line treatment of MM patients who are not eligible to stem cell transplantation and in whom thalidomide is unsuitable;[250] and bortezomib monotherapy versus high-dose dexamethasone for patients at first relapse of MM.[243]

For the other drugs, confidential price reductions were negotiated and resulting ICERs were usually within the accepted UK range of £20 000 to £30 000 QALYs gained, e.g. for lenalidomide administered first-line and for pomalidomide.[245, 248] In some cases however, even including these price discounts, decision-making ICERs were as high as £40 000 to £50 000 per QALY gained which is above the range normally considered by the appraisal committees to represent a cost effective use of NHS resources. However ICERs exceeding the NICE cost-effectiveness threshold of £30 000 per QALY gained may be considered as an effective use of NHS resources provided that the patients have a short life expectancy (<2 years) and that the new treatment extends life by at least three months compared with current NHS treatment and applies to small patient populations. Such “end-of-life” criteria were met in the appraisals of lenalidomide[244] and pomalidomide.[245] against relapsed/refractory MM, which led to the positive recommendation of both drugs in this indication. For example, the committee stated that: “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.”[245]

In another assessment of lenalidomide used second-line resulting in an uncertain ICER above £30 000 per QALY gained, the committee further departed from its standard threshold and recommended the new treatment on the grounds a.o. that it represented an unmet need and that it would be administered to few patients: “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: 1) the unmet need for an alternative treatment option to cytotoxic chemotherapy for people who had 1 previous treatment, which included bortezomib, 2) that lenalidomide is a cost-effective first-line treatment for people who cannot have thalidomide in a separate parallel appraisal, 3) 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, and 4) 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.”[247]

Finally, for daratumumab, due to the immaturity of the evidence at the time of its assessment (2018 and 2019), ICERs were highly uncertain[249] and in TA510[246] a plausible ICER could even not be identified. Daratumumab could, therefore, not be recommended for routine use. However, in order to address the clinical uncertainties and to ensure early access to this promising new treatment, daratumumab was recommended as an option for use within the Cancer Drugs Fund.[246, 249]

4.7.5 Summary

Observational data

- Observational data show an increase in survival for patients diagnosed between 2004 and 2017. The 3-years observed survival probability increased from 56.4% (95%CI 52.6-60.0) in 2004 to 67.4% (95%CI 63.9-70.5) in 2017. Median survival was 3.7 years (95%CI 3.3-4.2) in 2004 and 5.0 years (95%CI 4.4-NA) in 2015 (and not reached at the end of the follow-up period for patients diagnosed in 2016-2017).
- Total yearly oncology drug expenses for multiple myeloma increased overtime from almost non-existing before 2005 to €90 million in 2018.
- During the first two years after incidence, drug expenditures sharply raised from about €2.5 million for patients diagnosed in 2004 to approximately €41 million for those diagnosed in 2018.
    - This rise was mainly due to the uptake of bortezomib and lenalidomide.
    - The number of multiple myeloma patients for whom oncology drug expenditures were identified, sharply increased over the years from less than 400 in 2004 to almost 2000 in 2018.
    - The mean cost per multiple myeloma patient with drug expenses for the first two year after incidence raised from less than €10 000 before 2006 to about €60 000 in 2018.

Medical literature

- Trials published in the medical literature indicate that the combination lenalidomide-dexamethasone (RD) improved overall survival in patients who are not eligible for ASCT, compared with older treatment schedules. The triplet bortezomib-lenalidomide-dexamtasone (VRD) may further improve overall survival compared with RD but results remain inconclusive.
- For patient with recurrent or refractory multiple myeloma, pomalidomide with low dose dexamethasone improves overall survival and QoL compared to high dose dexamethasone. The addition of daratumumab to lenalidomide and dexamethasone also improved overall survival at 12 months in the group of recurrent multiple myeloma, however the difference was not statistically significant. The results for the triplet daratumumab-bortezomib-dexamethasone were unclear due to early cross-over after the interim analysis.

Economic literature

- With one exception, the economic evaluations of the identified TA reports all used the confidential discounts negotiated for the interventions and/or the comparators (and follow-up treatments) in their computations. There was no discount for bortezomib that was assessed based on its published list price.
- QoL was usually not measured with a generic utility instrument within the underlying head-to-head trial comparing the interventions of interest. Instead utilities were mostly obtained from indirect sources and were thus modelled per health state (instead of per treatment arm at different time points).
- In most TAs the appraisal committee acknowledged the uncertainty around the ICERs, which reflected the uncertainty in the elicitation of the treatment effect (i.e. the impact on overall survival). The main reasons for this were the absence of head-to-head trials, treatment cross-over in existing trials, the immaturity of the data and the plausibility of the extrapolations of overall survival data.
- There was only one intervention (bortezomib) for which the committee concluded that it was cost-effective at its official list price.
- With inclusion of the confidential discounts, other interventions (lenalidomide and pomalidomide) assessed in the identified TAs were considered cost-effective either at the conventional £20 000 - £30 000 per QALY threshold, or at the £50 000 per QALY threshold when they met the end-of-life criteria (i.e. meeting both the life

expectancy (<2 years) and the extension-to-life (>3 months) criteria). Daratumumab was not considered cost-effective but was recommended as an option for use in the Cancer Drug Fund while more evidence is being collected to address the clinical uncertainties.

- Decision-making ICERs were usually transparently reported. In some cases exact ICERs could not be reported for reasons of confidentiality. On the other hand, information about the incremental costs and effects was barely reported in the reviewed documents.

4.8 Non-Hodgkin Lymphoma

4.8.1 Introduction

Non-Hodgkin lymphomas encompass a heterogeneous group of cancers that arise from lymphocytes that are at various stages of development. The vast majority of non-Hodgkin lymphomas arise from B lymphocytes and range from more indolent forms such as follicular lymphoma to more aggressive diffuse large B-cell lymphomas (DLBCL).[253, 254]

In 2018, 2052 patients were diagnosed with a non-Hodgkin lymphoma in Belgium (https://kankerregister.org).

In this chapter, included types of non-Hodgkin lymphoma are limited to 1) B-cell chronic lymphocytic leukaemia (CLL) and small lymphocytic lymphoma (SLL), 2) diffuse large B-cell lymphoma (DLBCL), and 3) mantle cell lymphomas.

Historically, SLL and CLL were believed to be two distinct diseases, but they are now considered to be different clinical manifestations of the same disease. It occurs mainly in elderly people. Treatment is only initiated if patients are symptomatic or have progressive disease. Chlorambucil and the purine analogues cladribine and fludarabine have been treatment options historically. More recently, new drugs have been introduced for the treatment of CLL/SLL. Rituximab is reimbursed in this indication since 2009, ibrutinib and obinutuzumab since 2015 (see appendix for current reimbursement criteria).[253, 254]

DLBCL is the most common subtype of non-Hodgkin lymphoma, having many subtypes on its own. In the 1980s, radiotherapy and combination chemotherapy became the standard treatment. Later rituximab was added to the combination therapy to further improve outcomes. Patients with localised DLBCL have a very good prognosis. However, patients with DLBCL lymphoma subtypes that originate from activated B cells have a poorer prognosis. Rituximab is reimbursed for DLBCL in Belgium since 2002.[253, 254]

The median age at diagnosis of mantle-cell lymphoma is 58 years. Mantle cell lymphoma has one of the poorest prognoses of the various subtypes of lymphoma, with a median survival of about 3 years. Combination chemotherapy with or without rituximab was considered standard treatment, but now new treatment options including combinations with lenalidomide or ibrutinib are being considered. Lenalidomide and ibrutinib are already reimbursed in Belgium for the treatment of relapsed mantle cell lymphoma, since 2018 and 2015 respectively (see appendix for current reimbursement criteria).[253, 254]

Table 37 – Selected drugs non-Hodgkin lymphoma

Drug	Year#	Trade Name	Company$	Mechanism of action
Rituximab*	2000	MabThera	Roche	Monoclonal antibody that binds to the CD20 antigen on B lymphocytes
Ibrutinib	2006	Imbruvica	Janssen-Cilag	small-molecule inhibitor of Bruton's tyrosine kinase (BTK)
Obinutuzumab	2015	Gazyvaro	Roche	recombinant monoclonal humanised and glycol-engineered Type II anti-CD20 antibody of the IgG1 isotype

**biosimilar available $ of the originator; # year of start reimbursement first indication in Belgium*

4.8.2 Observational data

4.8.2.1 Patient characteristics, survival and expenditures

CLL & SLL

Patient characteristics did not substantially change over the years (Table 38A). A larger proportion of patients with WHO PS '0' was seen, probably related to an increase of patients for whom the performance status was reported. Overall survival and relative survival slightly improved over the years (Table 38B&C). Three-year observed survival was 76.7% (95%CI 73.3-79.7) for patients diagnosed in 2004, 81.9% (95%CI 79.0-84.5) for patients diagnosed in 2009 and 84.9% (95%CI 81.2-88.0) for patients diagnosed in 2017. Median survival was already 9.7 (95%CI 8.6-10.8) years for patients diagnosed in 2004, hence follow-up was too short to evaluate the evolution of median survival for patients diagnosed in more recent years (Table 38D).

Total yearly oncology drug expenditures were about €363 000 and rose to about €2.1 million in 2009, mainly due to an increase of the number of patients who received oncology drugs (Table 39A). After 2009, drug expenditures more than doubled to about €4.5 million in 2011, due to increased expenditures for rituximab. Furthermore, after 2014, a sharp increase of oncology drug expenditures is observed due to the use of ibrutinib and obinutuzumab up to about €13.3 million in 2018 (numbers not 100% complete).

Drug expenditures during the first two years after diagnosis were about €925 000 for patients diagnosed in 2004, then started to increase in 2008 till 2011 (almost €2.5 million), and then further increased in 2015 up to €5 million (Table 3B). Expenditures were lower in 2017 (about €3.8 million), mainly because of the lower number of patients (Table 39B), however, we remind that data for the last period is not 100% complete. Mean cost per patient who received oncological drugs was about €3 300 for patients diagnosed in 2004, about €9 200 for patients diagnosed in 2011 and about €19 200 in 2016 (Table 39C).

DLBCL

Patient characteristics did not substantially change during the studied period, although the proportion of patients older than 80 years old slightly increased (Table 40A). Overall survival and relative survival slightly increased between 2004-2008 and 2009-2013; no further improvement was seen for the period 2014-2017 (Table 40B). Three-year survival was 58.3% (95%CI 54.2-62.2) for patients diagnosed in 2004 and 62.6% (95%CI 58.9-66.1) in 2017 (Table 40C). Median survival was 5.4 (95%CI 3.8-7.2) years for patients diagnosed in 2004 and 5.9 (95%CI 4.9-not reached) years for patients diagnosed in 2013. Median survival was not reached for patients diagnosed after 2013 (Table 40D).

Yearly expenditures for all patients with DLBCL increased from about €4.1 million in 2004 to €9 million in 2017, mainly due to an increase of the number of DLBCL patients who received oncological drugs during that year (Table 41A). Expenditures during the first two years after diagnosis slightly increased over the years, from about €5.8 million for patients diagnosed in 2004 to €7.4 million for patients diagnosed in 2017 (Table 41B). Mean cost per patient during the first two years after diagnosis for those who received oncological drugs remained more or less stable over the years: about €12 300 for patients diagnosed in 2004 and about €11 300 for patients diagnosed in 2017 (Table 41C).

Mantle cell lymphoma

Overview of the patient characteristics shows that age at diagnosis increased over the years, with 13.2% of patients older than 80 years for the period 2004-2008 and 26.5% of patients in the same age group in the period 2014-2017 (Table 42A).

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 (Table 42B). The 3-year observed survival probability was variable over the years (Table 42C). This was 63% (95%CI 53.1-71.3) in 2004 and 70.3% (95%CI 59.8-78.6) in 2017. Median survival was 4.1 years (95%CI 3.2-5.5) for patients diagnosed in 2004 and 4.2 years (95%CI 3.3-5.4) for patients diagnosed in 2015. Median survival was not reached for patients diagnosed after 2015 (Table 42D).

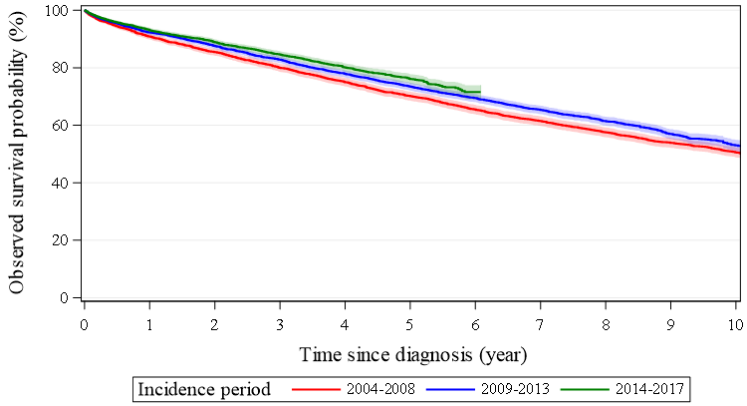
Yearly expenditures on oncological drugs for mantle cell patients was about 520 000 in 2004, increasing year by year with the biggest increase in the most recent years, up to about €7 million in 2017 (Table 43A). This increase can be explained by both an increase in the number of patients with drug expenditures and an increase in the cost per patient. The drug expenditures during the first 2 years after diagnosis was about €800 000 for patients diagnosed in 2004, started to increase rapidly for patients diagnosed after 2013 up to a maximum of about €4 million for patients diagnosed in 2016 (Table 43B). For patients who received oncological drugs, mean cost per patient during the first two years after diagnosis was about €8 800 in 2004 and increased up to about €30 300 in 2016 (Table 43C, data for 2017 are not 100% complete).

Table 38 – B-cell chronic lymphocytic leukaemia (CLL) and small lymphocytic lymphoma (SLL) (2004-2017) (observed survival): A) Patient characteristics; B) Kaplan-Meier graph per incidence period; C) Time trend with incidence year*; D) Median survival time* **

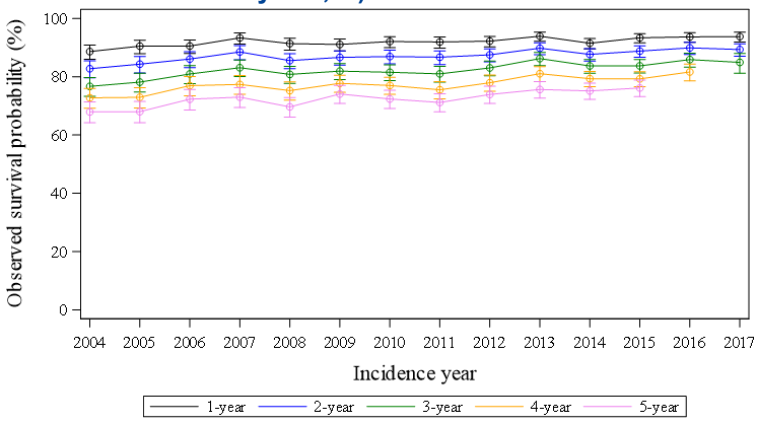
A

Characteristic	Incidence period		
	2004-2008	2009-2013	2014-2017
Overall	3,301	4,093	3,526
Gender			
Male	1,937 (58.7)	2,368 (57.9)	2,092 (59.3)
Female	1,364 (41.3)	1,725 (42.1)	1,434 (40.7)
Age at diagnosis (year)			
<50 years	226 (6.8)	229 (5.6)	170 (4.8)
50-59 years	534 (16.2)	656 (16.0)	553 (15.7)
60-69 years	881 (26.7)	1,144 (28.0)	976 (27.7)
70-79 years	1,111 (33.7)	1,218 (29.8)	1,063 (30.1)
80+ years	549 (16.6)	846 (20.7)	764 (21.7)
WHO - Performance Status			
0 – Asymptomatic	1,131 (34.3)	1,866 (45.6)	1,770 (50.2)
1 – Symptomatic but completely ambulatory	743 (22.5)	1,298 (31.7)	1,097 (31.1)
2 – Symptomatic, <50% in bed during the day	99 (3.0)	88 (2.2)	94 (2.7)
3 – Symptomatic, >50% in bed, but not bedbound	28 (0.8)	24 (0.6)	34 (1.0)
4 – Bedbound	20 (0.6)	10 (0.2)	17 (0.5)
Not reported	1,280 (38.8)	807 (19.7)	514 (14.6)

B

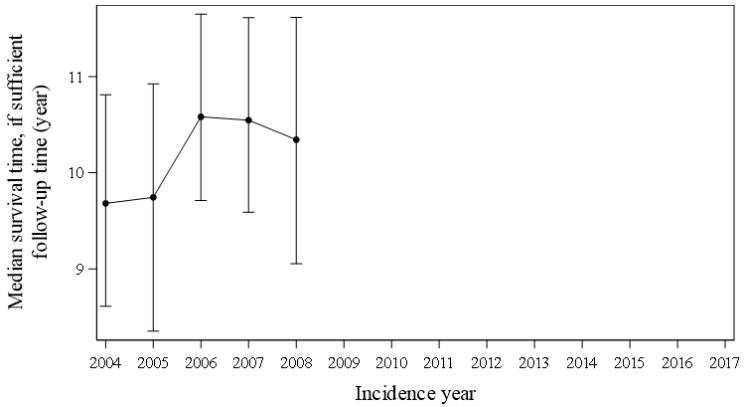


C



Year: 3-y OS [95%CI]
2004: 76.7 [73.3, 79.7]
2005: 78.2 [74.7, 81.2]
2006: 81.0 [77.7, 83.8]
2007: 83.1 [80.0, 85.8]
2008: 80.8 [77.7, 83.5]
2009: 81.9 [79.0, 84.5]
2010: 81.5 [78.7, 84.1]
2011: 81.0 [78.1, 83.5]
2012: 83.0 [80.3, 85.4]
2013: 86.2 [83.8, 88.4]
2014: 83.7 [81.2, 85.9]
2015: 83.7 [81.3, 85.9]
2016: 85.9 [83.3, 88.1]
2017: 84.9 [81.2, 88.0]

D

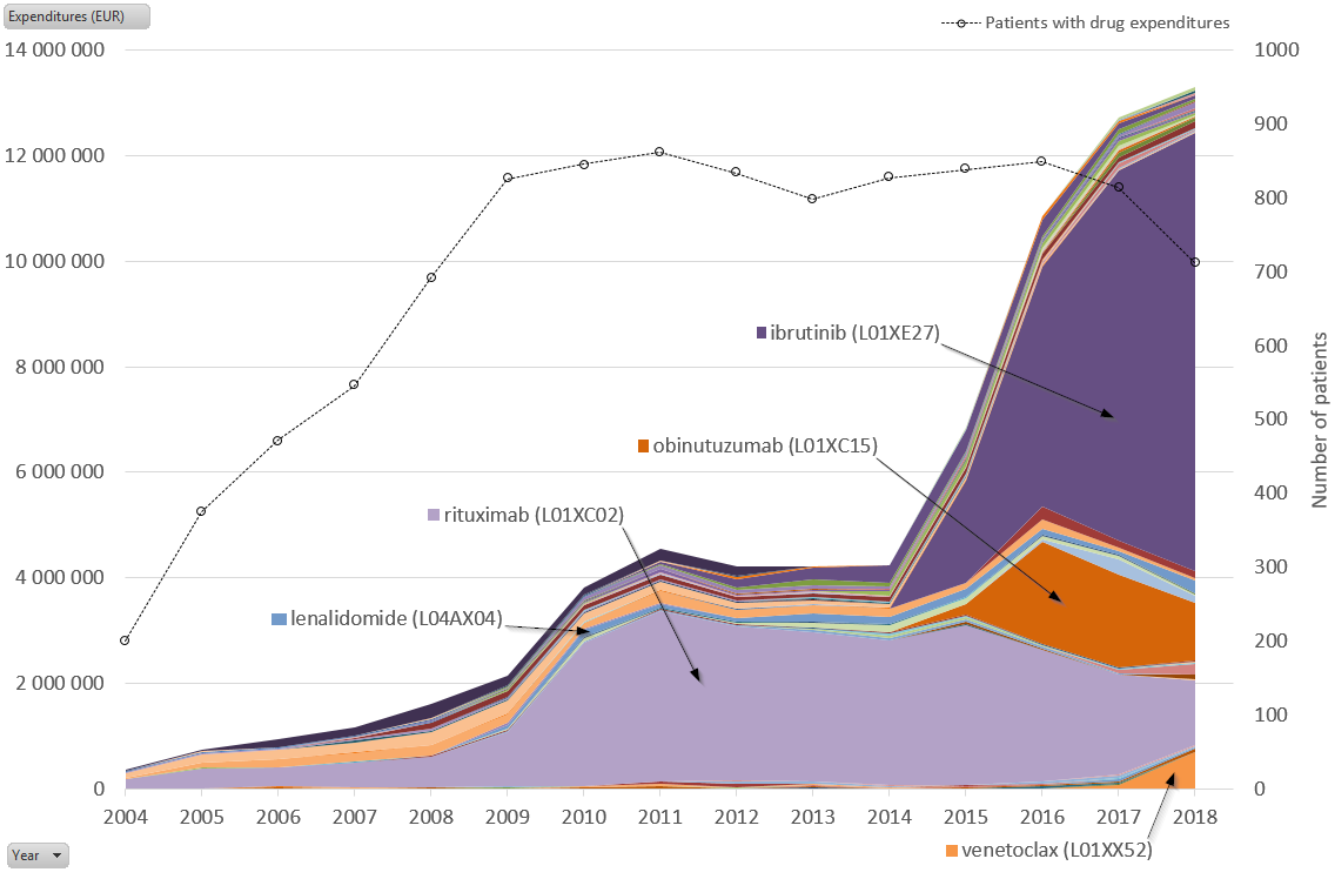


Year: Med. ST [95%CI]
2004: 9.7 [8.6, 10.8]
2005: 9.7 [8.4, 10.9]
2006: 10.6 [9.7, 11.6]
2007: 10.5 [9.6, 11.6]
2008: 10.3 [9.1, 11.6]
2009: >11
2010: >10
2011: >9
2012: >8
2013: >7
2014: >6
2015: >5
2016: >4
2017: >3

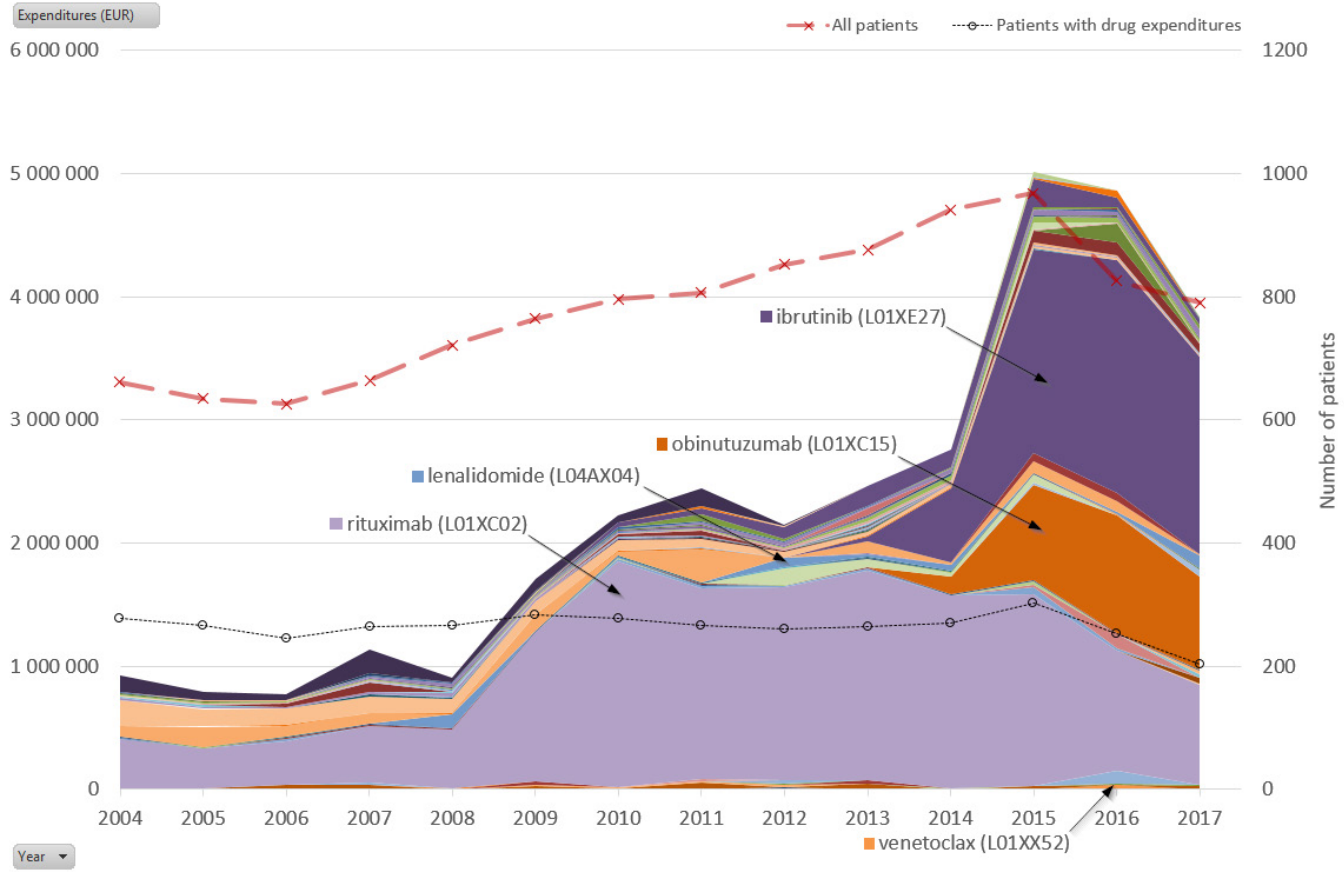
*Med. ST: median survival time; 3-y OS: 3-year observed survival; * the error bars represent the 95%CI. ** When the upper error is not plotted, the upper limit could not be determined with the available follow-up data. Source: BCR.*

Table 39 – B-cell chronic lymphocytic leukaemia (CLL) and small lymphocytic lymphoma (SLL): drug expenditures

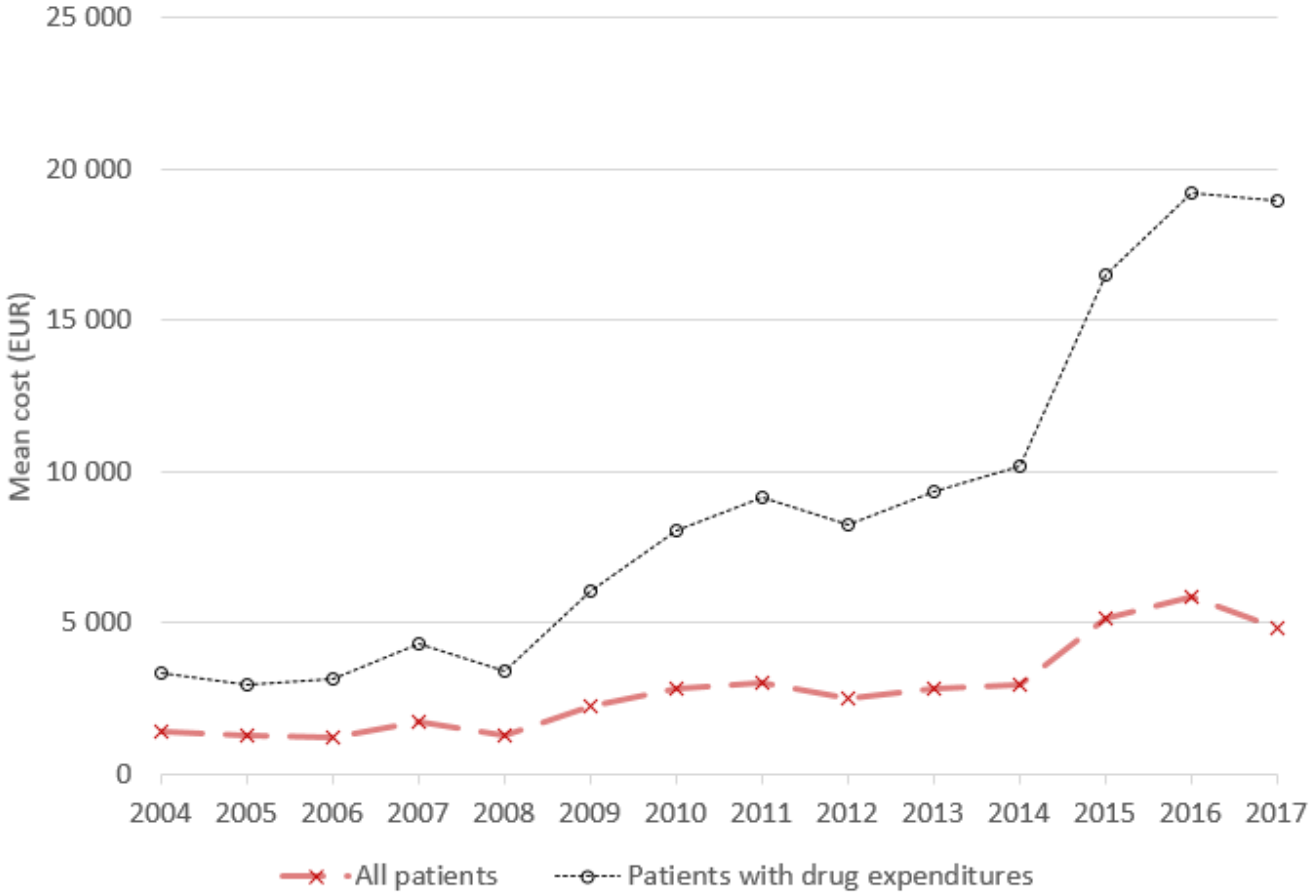
A) Oncological drug expenses per calendar year



B) Expenses for the first two years after incidence, per incidence year



C) Mean cost per patient for the first two years after incidence, per incidence year



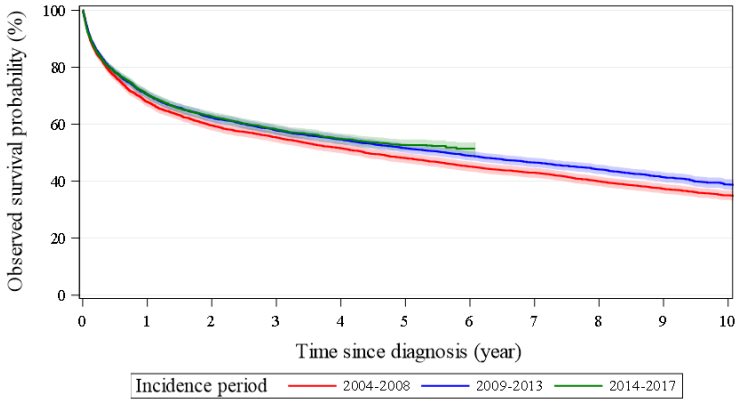
Source: BCR-IMA.

Table 40 – Diffuse large B-cell lymphoma (DLBCL) (2004-2017) (observed survival): A) Patient characteristics; B) Kaplan-Meier graph per incidence period; C) Time trend with incidence year*; D) Median survival time* **

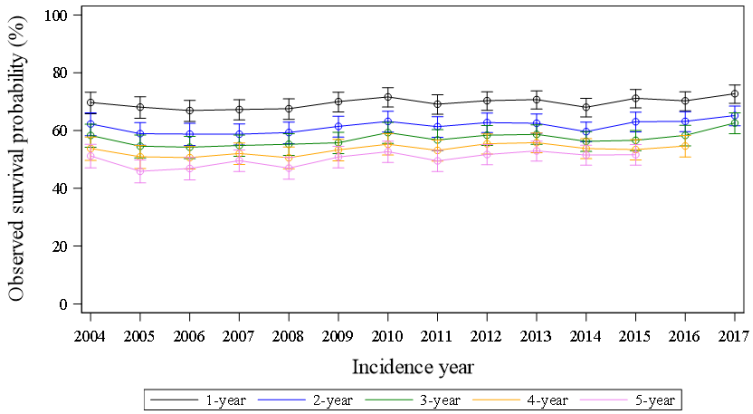
A

Characteristic	Incidence period		
	2004-2008	2009-2013	2014-2017
Overall	3,172	3,695	3,084
Gender			
Male	1,656 (52.2)	1,970 (53.3)	1,672 (54.2)
Female	1,516 (47.8)	1,725 (46.7)	1,412 (45.8)
Age at diagnosis (year)			
<50 years	456 (14.4)	451 (12.2)	323 (10.5)
50-59 years	427 (13.5)	465 (12.6)	388 (12.6)
60-69 years	638 (20.1)	758 (20.5)	668 (21.7)
70-79 years	976 (30.8)	1,118 (30.3)	872 (28.3)
80+ years	675 (21.3)	903 (24.4)	833 (27.0)
WHO - Performance Status			
0 – Asymptomatic	289 (9.1)	464 (12.6)	399 (12.9)
1 – Symptomatic but completely ambulatory	1,041 (32.8)	1,870 (50.6)	1,635 (53.0)
2 – Symptomatic, <50% in bed during the day	320 (10.1)	333 (9.0)	331 (10.7)
3 – Symptomatic, >50% in bed, but not bedbound	118 (3.7)	141 (3.8)	165 (5.4)
4 – Bedbound	47 (1.5)	69 (1.9)	64 (2.1)
Not reported	1,357 (42.8)	818 (22.1)	490 (15.9)

B

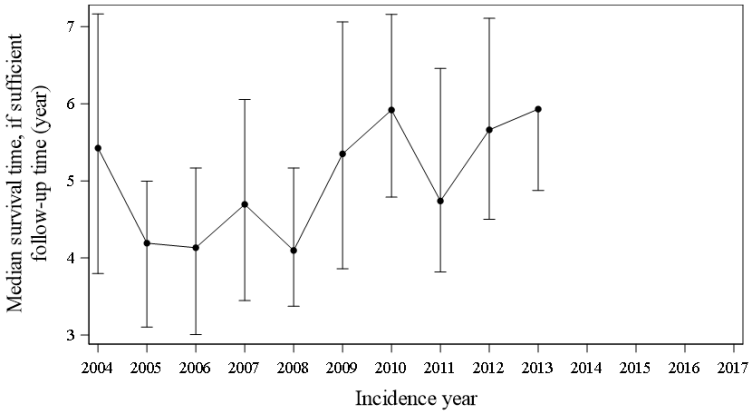


C



Year: 3-y OS [95%CI]
2004: 58.3 [54.2, 62.2]
2005: 54.6 [50.5, 58.5]
2006: 54.2 [50.3, 58.0]
2007: 54.8 [51.0, 58.5]
2008: 55.3 [51.4, 58.9]
2009: 55.8 [52.0, 59.4]
2010: 59.3 [55.6, 62.8]
2011: 56.8 [53.0, 60.3]
2012: 58.4 [54.9, 61.8]
2013: 58.7 [55.2, 62.0]
2014: 56.3 [52.8, 59.6]
2015: 56.6 [53.1, 60.0]
2016: 58.3 [54.7, 61.8]
2017: 62.6 [58.9, 66.1]

D

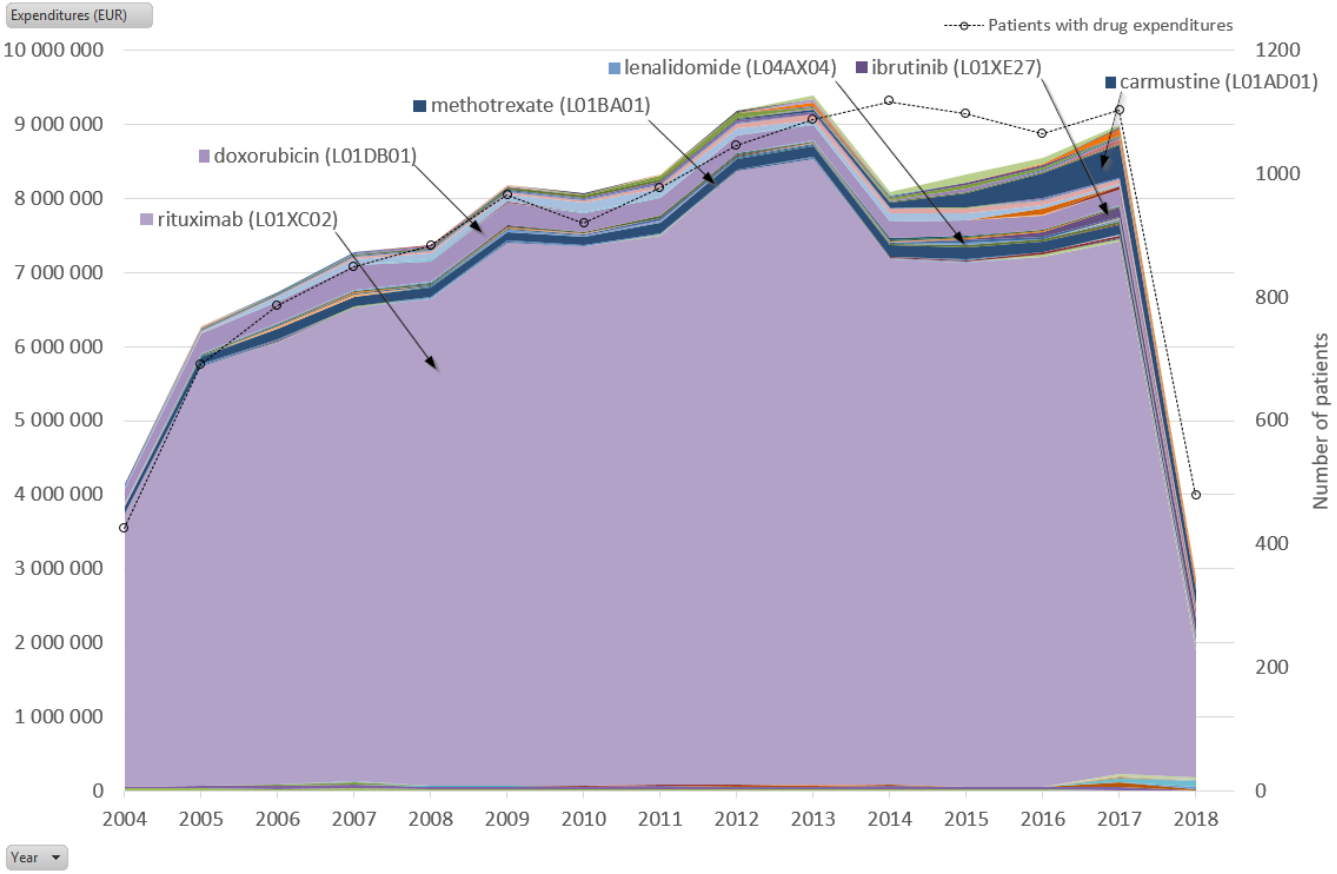


Year: Med. ST [95%CI]
2004: 5.4 [3.8, 7.2]
2005: 4.2 [3.1, 5.0]
2006: 4.1 [3.0, 5.2]
2007: 4.7 [3.4, 6.1]
2008: 4.1 [3.4, 5.2]
2009: 5.3 [3.9, 7.1]
2010: 5.9 [4.8, 7.2]
2011: 4.7 [3.8, 6.5]
2012: 5.7 [4.5, 7.1]
2013: 5.9 [4.9, .]
2014: >6
2015: >5
2016: >4
2017: >3

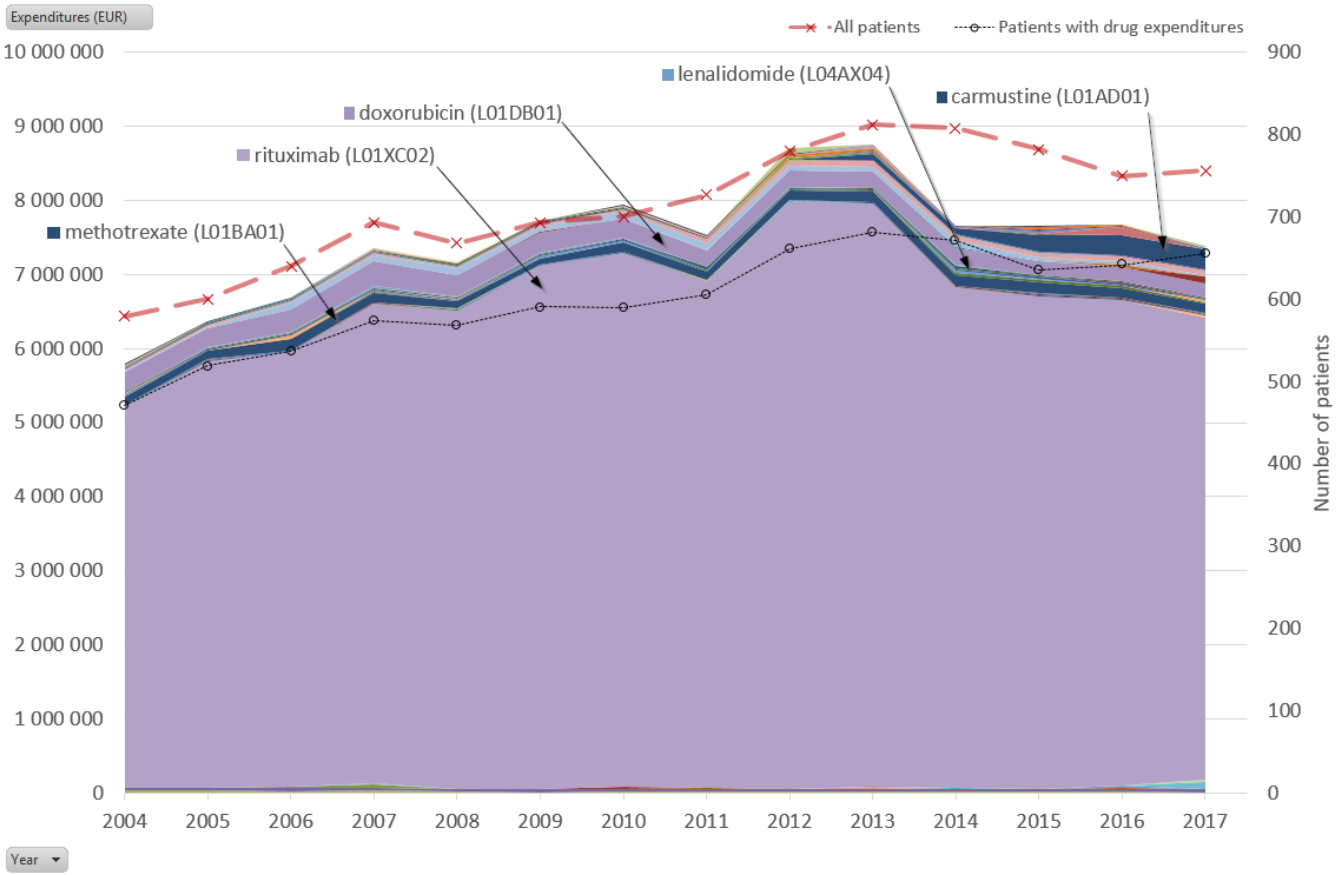
*Med. ST: median survival time; 3-y OS: 3-year observed survival; * the error bars represent the 95%CI. ** When the upper error is not plotted, the upper limit could not be determined with the available follow-up data. Source: BCR.*

Table 41 – Diffuse large B-cell lymphoma (DLBCL): drug expenditures

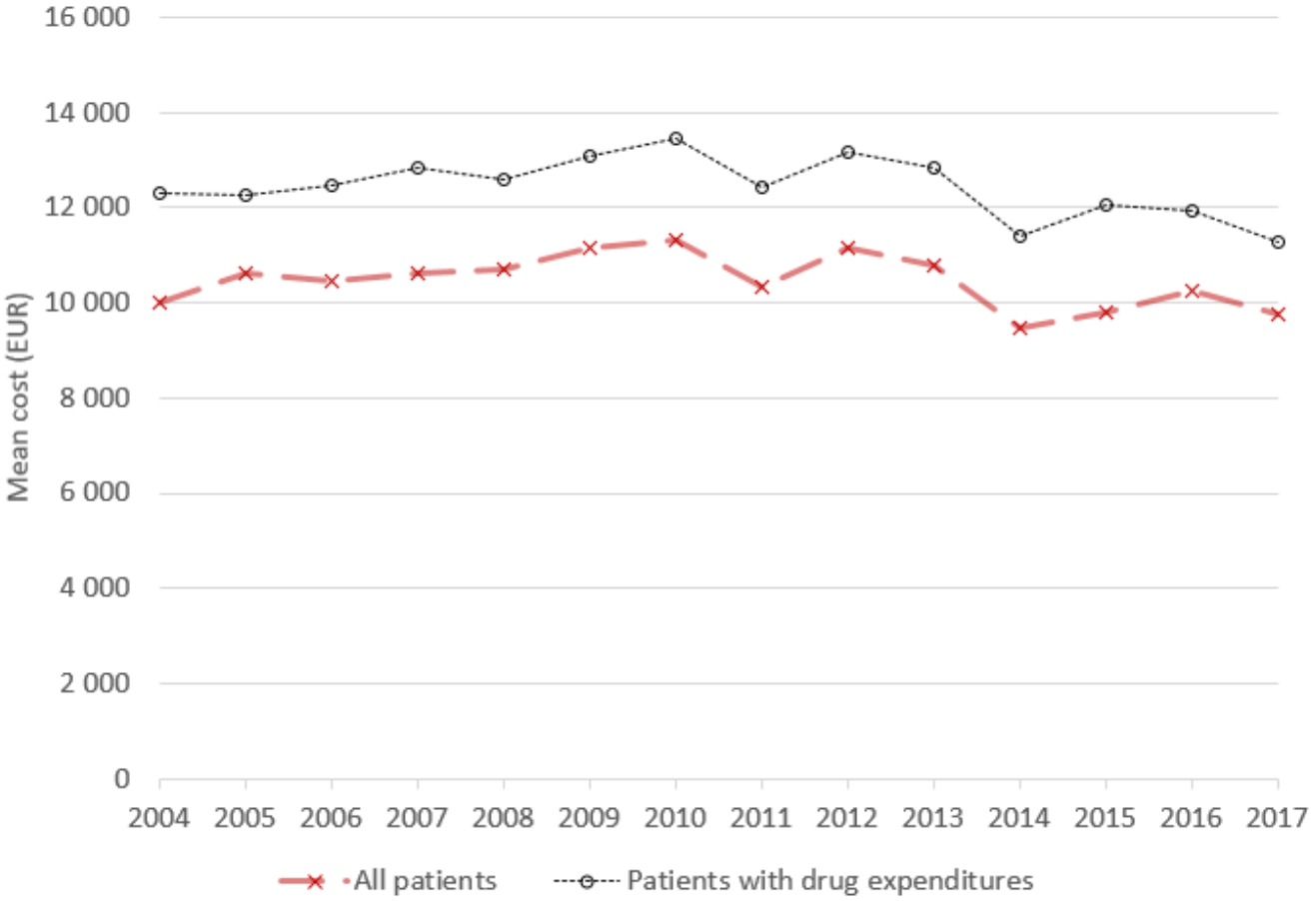
A) Oncological drug expenses per calendar year



B) Expenses for the first two years after incidence, per incidence year



C) Mean cost per patient for the first two years after incidence, per incidence year



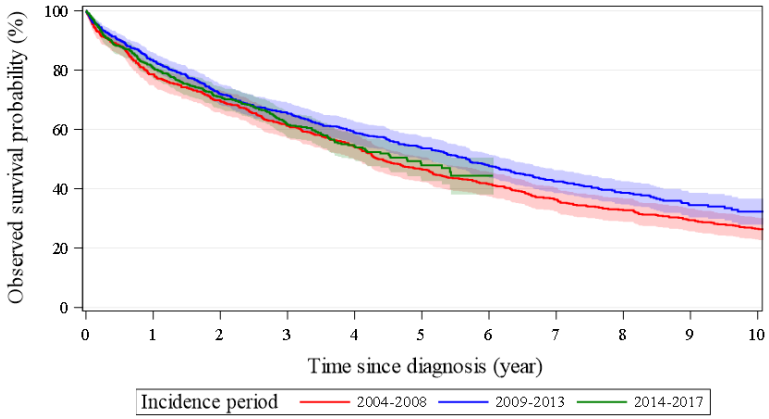
Source: BCR-IMA.

Table 42 – Mantle cell lymphoma (2004-2017) (observed survival): A) Patient characteristics; B) Kaplan-Meier graph per incidence period; C) Time trend with incidence year*; D) Median survival time* **

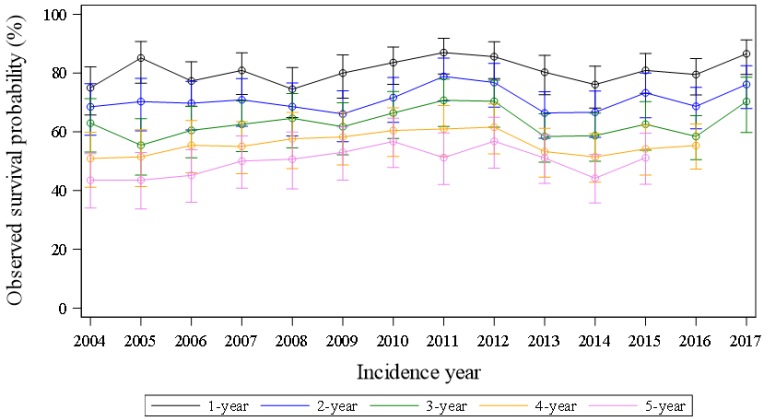
A

Characteristic	Incidence period		
	2004-2008	2009-2013	2014-2017
Overall	552	634	569
Gender			
Male	391 (70.8)	436 (68.8)	403 (70.8)
Female	161 (29.2)	198 (31.2)	166 (29.2)
Age at diagnosis (year)			
<50 years	35 (6.3)	38 (6.0)	27 (4.7)
50-59 years	79 (14.3)	90 (14.2)	76 (13.4)
60-69 years	171 (31.0)	167 (26.3)	135 (23.7)
70-79 years	194 (35.1)	217 (34.2)	180 (31.6)
80+ years	73 (13.2)	122 (19.2)	151 (26.5)
WHO - Performance Status			
0 – Asymptomatic	98 (17.8)	138 (21.8)	138 (24.3)
1 – Symptomatic but completely ambulatory	186 (33.7)	313 (49.4)	306 (53.8)
2 – Symptomatic, <50% in bed during the day	41 (7.4)	40 (6.3)	29 (5.1)
3 – Symptomatic, >50% in bed, but not bedbound	7 (1.3)	15 (2.4)	16 (2.8)
4 – Bedbound	3 (0.5)	4 (0.6)	7 (1.2)
Not reported	217 (39.3)	124 (19.6)	73 (12.8)

B

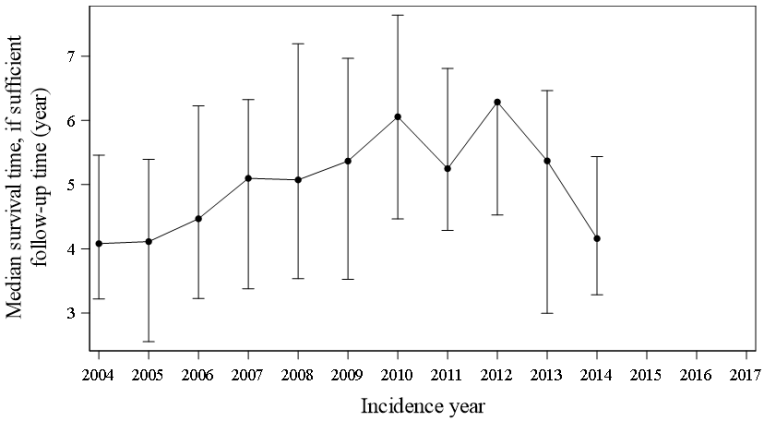


C



Year: 3-y OS [95%CI]
2004: 63.0 [53.1, 71.3]
2005: 55.4 [45.2, 64.5]
2006: 60.5 [51.1, 68.6]
2007: 62.6 [53.3, 70.5]
2008: 64.6 [54.5, 73.0]
2009: 61.7 [52.2, 69.9]
2010: 66.4 [57.7, 73.7]
2011: 70.7 [61.8, 77.9]
2012: 70.4 [61.6, 77.6]
2013: 58.4 [49.7, 66.1]
2014: 58.7 [50.0, 66.4]
2015: 62.6 [53.7, 70.2]
2016: 58.4 [50.6, 65.5]
2017: 70.3 [59.8, 78.6]

D

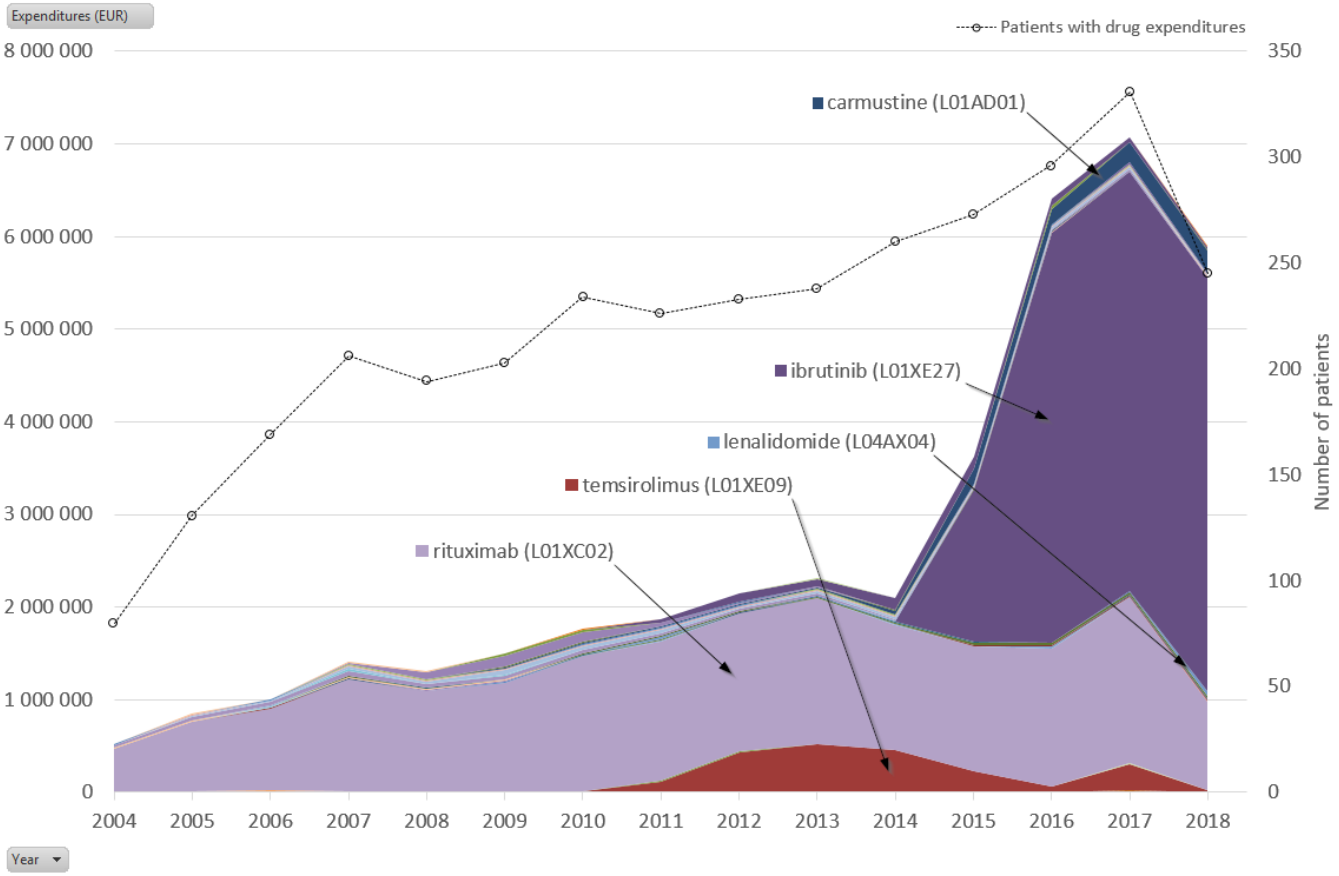


Year: Med. ST [95%CI]
2004: 4.1 [3.2, 5.5]
2005: 4.1 [2.6, 5.4]
2006: 4.5 [3.2, 6.2]
2007: 5.1 [3.4, 6.3]
2008: 5.1 [3.5, 7.2]
2009: 5.4 [3.5, 7.0]
2010: 6.1 [4.5, 7.6]
2011: 5.2 [4.3, 6.8]
2012: 6.3 [4.5, .]
2013: 5.4 [3.0, 6.5]
2014: 4.2 [3.3, 5.4]
2015: >5
2016: >4
2017: >3

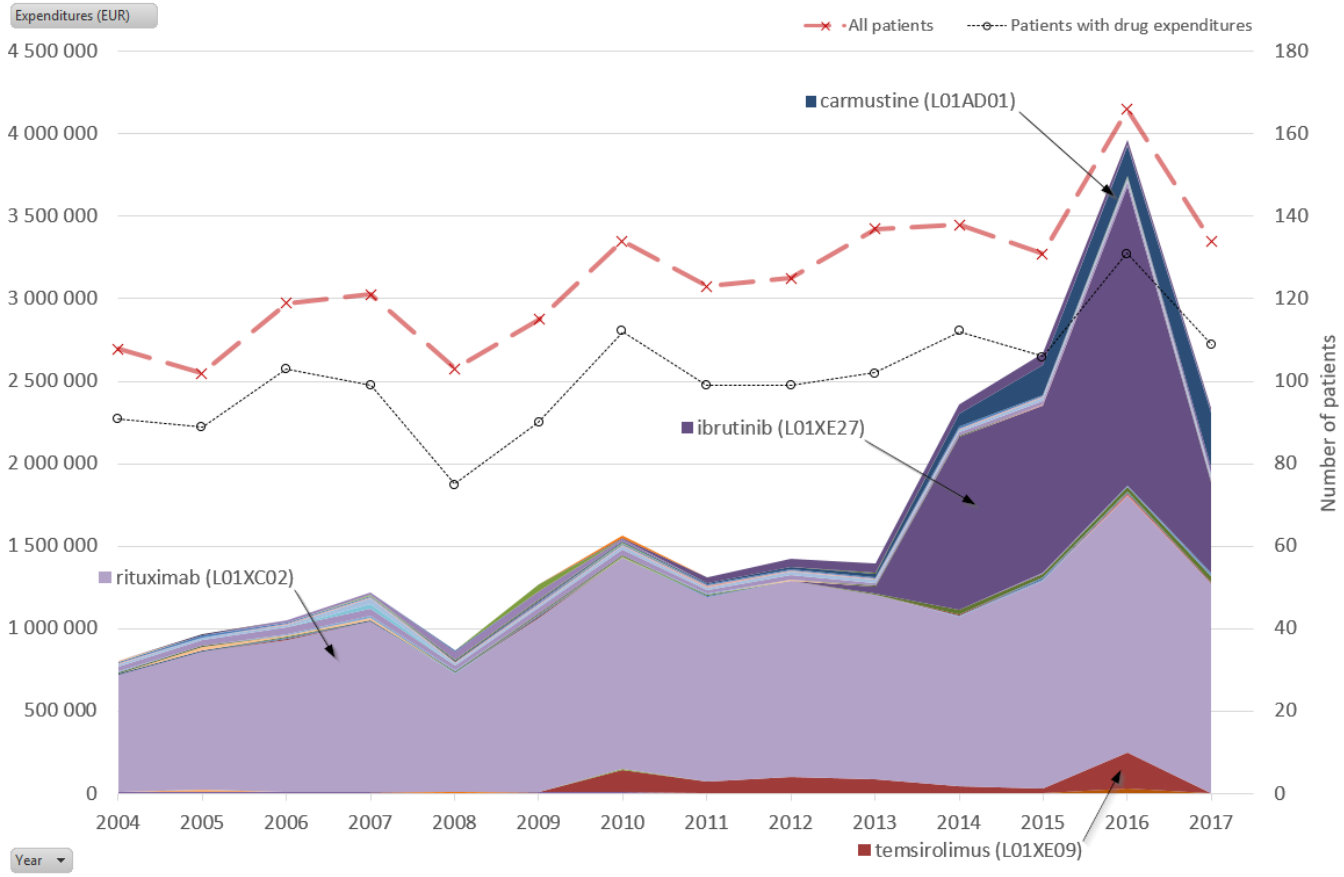
*Med. ST: median survival time; 3-y OS: 3-year observed survival; * the error bars represent the 95%CI. ** When the upper error is not plotted, the upper limit could not be determined with the available follow-up data. Source: BCR.*

Table 43 – Mantle cell lymphoma: drug expenditures

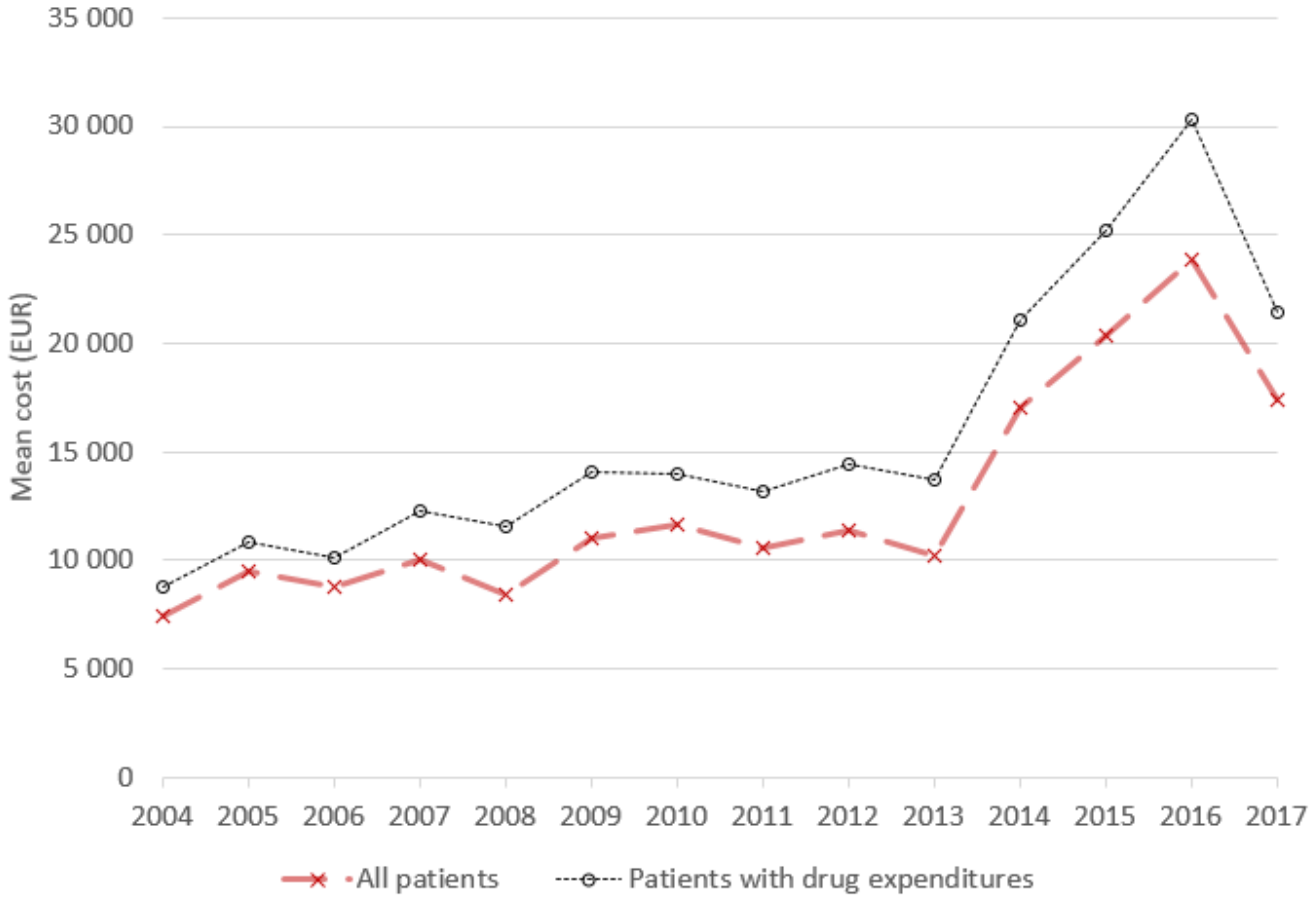
A) Oncological drug expenses per calendar year



B) Expenses for the first two years after incidence, per incidence year



C) Mean cost per patient for the first two years after incidence, per incidence year



Source: BCR-IMA.

4.8.2.2 *Drug uptake for a selection of drugs during the first 5 years after diagnosis*

CLL/SLL

Rituximab had an uptake of 10% in patients who were diagnosed with CLL/SLL in 2004. Uptake increased over the years with a maximum uptake of 28% in patients diagnosed in 2010. Uptake in patients diagnosed in 2016 and 2017 was lower, with an uptake of 14% and 12% respectively, but the 5-year follow-up period is not complete for the last years.

The use of ibrutinib started in patients diagnosed in 2010 and remained low with a maximum uptake of 7% in patients diagnosed 2014. It must be noted that only the first five years after diagnosis are reported in the uptake tables.

Uptake of obinutuzumab started with a very limited uptake of 0.3% for incidence year 2010 and slowly increased to a maximum uptake of 5.7% for incidence year 2016.

Table 44 – CLL/SLL: uptake of selected drugs

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. $ IMA data were only available up to the second trimester of 2019 and might have a delay of two years. Five-year follow-up data are thus not 100% complete from incidence year 2012 onwards (see part 3.1.3). Source: BCR-IMA.*

Table 45 – DLBCL: uptake of selected drugs

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%

**Rituxmab is reimbursed for DLBCL since 2002. $ IMA data were only available up to the second trimester of 2019 and might have a delay of two years. Five-year follow-up data are thus not 100% complete from incidence year 2012 onwards (see part 3.1.3). Source: BCR-IMA.*

Table 46 – Mantle cell lymphoma: uptake of selected drugs

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%

** Rituxmab is reimbursed for mantle cell lymphoma since 2002.*
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. $ IMA data were only available up to the second trimester of 2019 and might have a delay of two years. Five-year follow-up data are thus not 100% complete from incidence year 2012 onwards (see part 3.1.3). Source: BCR-IMA.

4.8.3 Medical literature: efficacy

4.8.3.1 CLL/SLL

Clinical trials show an improvement in overall survival in patients with indolent lymphoma when rituximab is added to chemotherapy, both in newly diagnosed patients and in patients who received prior therapy.[255] For maintenance therapy with rituximab, a clear survival benefit is not proven.[256]

In patients with relapsed or refractory CLL following one or more previous lines of systemic therapy, treatment with ibrutinib results in better overall survival compared to other therapy.[257] Ibrutinib may also improve survival in first-line treatment, but results are not conclusive.[258]

Obinutuzumab may improve overall survival for patients with treatment-naïve CLL but results are inconclusive.[259]

Rituximab

Reference + search date	Intervention and comparator + indication	OS	Quality of life	Other outcomes
Schulz 2007[255] Search date: December 2005	All persons older 18 years with histologically proven indolent lymphoma and mantle cell lymphoma (excluded: T-cell lymphoma, primary central nervous system lymphoma) Intervention: chemotherapy + rituximab Comparator: identical chemotherapy	Overall group: HR 0.65 (95%CI 0.54-0.78) Patients who received no prior treatment: HR 0.66 (95%CI 0.52-0.84) Patients who received prior treatment: HR 0.63 (95%CI 0.46-0.86)		The relative risk for developing fever or leukocytopenia was statistically significantly higher in patients treated with R-chemo than in patients treated with chemotherapy alone RR = 3.79 (95%CI 1.47-9.78) RR=1.31 (95%CI 1.11-1.55)

Rituximab maintenance

Reference + search date	Intervention and comparator + indication	OS	Quality of life	Other outcomes
Lee 2020[256] Search date: 6 March 2019	Patients with CLL who had achieved at least a partial response after previous treatment and received subsequent maintenance therapy. Intervention: Maintenance therapy with Rituximab Comparator: observation	HR:0.86 (95%CI 0.58–1.28)		SAE for maintenance therapy with rituximab, lenalidomide, or ofatumumab: RR: 1.54 (95%CI 1.19–1.99)

Ibrutinib

Reference + search date	Intervention and comparator + indication	OS	Quality of life	Other outcomes
Molica 2020*[258] Search date: 31 July 2019	Previously untreated patients with CLL Intervention: ibrutinib alone or in association with other agents Comparator: another treatment regimen	HR 0.289 (95%CI 0.071-1.175)		
Chen 2019[257] Search date: 6 January 2019	Patients with a diagnosis of relapsed or refractory CLL following one or more previous lines of systemic therapy Intervention: ibrutinib or ibrutininib – bendamustine - rituximab Comparator: ofatumumab or rituximab or bendamustine – rituximab	HR 0.361 (95%CI 0.208-0.627)		

** searched only 1 database but included as no other recent SR was found*

Obinutuzumab

Reference + search date	Intervention and comparator + indication	OS	Quality of life	Other outcomes
Amitai 2020*[259] search date: 4 July 2020 Goede 2015[260, 261]	Treatment-naïve patients with CLL in need of therapy and with significant comorbidity burden Intervention: obinutuzumab + chlorambucil (G-Clb) Comparator: rituximab + chlorambucil (R-Clb) or chlorambucil alone (Clb)	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)		

** included for search and critical appraisal. As the SR did not report on OS, results were taken from the only RCT in CLL patients included in the SR.*

4.8.3.2 DLBCL

Overall, rituximab added to chemotherapy improves overall survival for DLBCL patients, compared to chemotherapy alone.[262] Six out of ten studies included in the meta-analysis were in patients with previously untreated DLBCL.

Rituximab salvage therapy in people with relapsed DLBCL improves overall survival compared to observation, at the cost of an increase of infection-related events.[263] Maintenance therapy with rituximab appears not to improve overall survival.[264, 265]

Rituximab

Reference + search date	Intervention and comparator + indication	OS	Quality of life	Other outcomes
Wang 2020[262] Search date: December 2019	Patients diagnosed with DLBCL (newly diagnosed or recurrent) Intervention: rituximab or other targeted therapy + chemotherapy Comparator: placebo or other targeted therapy (network meta-analysis) + chemotherapy	Rituximab + chemotherapy vs chemotherapy HR 0.79 (95%CI 0.70-0.89) (6 out of 10 studies in previously untreated DLBCL)		
Ren 2015[263] Search date: unknown	Patients with histologically confirmed DLBCL who relapse Intervention: Rituximab salvage therapy Comparator: observation	HR 0.72 (95%CI 0.55-0.94)		Infection-related adverse events RR 1.37 (95%CI 1.14-1.65)

Rituximab maintenance therapy

Reference + search date	Intervention and comparator + indication	OS	Quality of life	Other outcomes
Rozental 2019[264] Search date: January 2018	Patients with newly diagnosed diffuse large B-cell lymphoma who achieved CR or PR after first-line treatment with chemotherapy, with or without rituximab Intervention: maintenance therapy Comparator: observation or placebo	9 trials of which 4 with rituximab and 1 with lenalidomide maintenance: OR 0.91 (95%CI 0.78-1.07) "Results were not changed in a subgroup analysis of trials evaluating rituximab as a maintenance therapy."		risk of grade 3 to 4 adverse events (5 trials, 3 with rituximab): RR 1.69 (95%CI 1.29-2.22)
Zhou 2017[265] search date: May 2016	Patients with untreated, relapsed, and refractory diffuse large B-cell lymphoma who had reached complete remission, unconfirmed complete remission or partial remission (PR) after induced chemotherapy Intervention: rituximab maintenance Comparator: observation only	HR 0.66 (95% CI: 0.27-1.29)		leukopenia: RR 0.94 (95% CI 0.92-0.97) Infection: RR 0.93 (95%CI 0.90-0.96) (both in favour of observation)

4.8.3.3 Mantle cell lymphoma

A systematic review of studies in indolent lymphoma and mantle cell patients shows a survival benefit for adding rituximab to chemotherapy, both in the first-line setting and in the recurrent setting.[255] For maintenance therapy with rituximab, no clear survival benefit has been proven.[266]

Compared to temsirolimus, ibrutinib may improve overall survival in relapsed or refractory mantle cell lymphoma but results are inconclusive.[267]

Rituximab

Reference + search date	Intervention and comparator + indication	OS	Quality of life	Other outcomes
Schulz 2007[255] Search date: December 2005	All persons older 18 years with histologically proven indolent lymphoma and mantle cell lymphoma (excluded: T-cell lymphoma, primary central nervous system lymphoma) Intervention: chemotherapy + rituximab Comparator: identical chemotherapy	Overall group: HR 0.65 (95%CI 0.54-0.78) Patients who received no prior treatment: HR 0.66 (95%CI 0.52-0.84) Patients who received prior treatment: HR 0.63 (95%CI 0.46-0.86) Mantle cell lymphoma: HR 0.60 (95%CI 0.37-0.098)		The relative risk for developing fever or leukocytopenia was statistically significantly higher in patients treated with R-chemo than in patients treated with chemotherapy alone RR 3.79 (95%CI 1.47-9.78) RR 1.31 (95%CI 1.11-1.55)

Rituximab maintenance

Reference + search date	Intervention and comparator + indication	OS	Quality of life	Other outcomes
Vidal 2018[266]	Patients with mantle cell lymphoma, after induction treatment. Intervention: any maintenance treatment Comparator: no maintenance (observation or placebo) or other type of maintenance	Rituximab maintenance vs observation or interferon-alfa: HR 0.79 (95%CI 0.58-1.06)		

Ibrutinib

Reference + search date	Intervention and comparator + indication	OS	Quality of life	Other outcomes
Dreyling 2016[267] Rule 2018*[268]	Patients with relapsed or refractory mantle cell lymphoma Intervention: ibrutinib Comparator: temsirolimus	HR 0.74 (95%CI 0.54-1.02) (cross-over was allowed after disease progression)		Frequency of grade ≥3 treatment-emergent AEs 75% in ibrutinib groups vs 87% in temsirolimus group

** As no systematic review could be identified in the literature, results of the one RCT included in the NICE Single Technology appraisal[269] are reported here.*

4.8.3.4 Discussion

CLL/SLL

An increase in the use of rituximab in the second time period (2009-2013) and the introduction of ibrutinib and obinutuzumab during the last observation period (2014-2017) appear to be associated with a slight improvement of overall survival, in spite of the modest or low uptake rates. For rituximab, RCTs show indeed an improved survival if added to chemotherapy (but not for maintenance therapy). For ibrutinib, a large beneficial effect was seen in clinical trials, but results remained inconclusive (wide confidence interval).

DLBCL

Although a positive effect of rituximab on overall survival has not been shown in RCTs, a small overall survival improvement is observed between the first and second observation period. Possibly, a further increase in uptake of rituximab is one of the underlying factors. Uptake of rituximab was already 68% in 2004 however.

Mantle cell lymphoma

In spite of an increasing uptake of rituximab and ibrutinib over time, no clear improvement of observed survival is seen in our study. For ibrutinib, an effect on survival was not clearly proven in RCTs.

Findings in other countries

Non-Hodgkin lymphoma

In Canada, Ye et al. investigated time trends for mortality for non-Hodgkin patients and four subtypes between 1984 and 2014. An increase in relative survival is seen over the years for patients with non-Hodgkin lymphoma. Age-standardised 5-year relative survival was 57.0% for patients diagnosed in 1984-1993, 57.9% in 1994-2003 and 67.5% 2004-2013 (p-value for time trend test <0.0001).[270]

CLL/SLL

In the study of Ye et al. in Canada, age-standardised 5-year relative survival for CLL/SLL patients improved from 74.3% in 1984-1993 to 82.6% in 1994-2003 and 89.3% in 2004-2013 (p-value for time trend test <0.0001).[270]

Also in the Netherlands, an improvement of 5-year and 10-year relative survival in all age groups is observed. For example, for patients aged 70-79 years, 5-year relative survival was 64% (95%CI 61-68) in 1989-1995, 71% (95%CI 68-74) in 1995-2002, 81% (95%CI 78-84) in 2003-2008 and 85% (95%CI 83-88) in 2009-2016 (p<0.001).[271]

Chihara et al. followed 5-year relative survival over time for CLL/SLL patients in Japan. Five-year relative survival was 56.8% (95%CI 49.5-63.5) for the time period 1993-1997, 52.2% (95%CI 44.5-59.3) for 1998-2002 and 55.1% (95%CI 45.8-63.4) for 2003-2006.[272]

Pulte et al. compared age-adjusted 5-year relative survival over time in Germany and the USA. In Germany, age-adjusted 5-year relative survival was 77.8% in 2003-2005, 80.5% in 2006-2008 and 80.2% in 2009-2011 (p-value for trend 0.004). For the USA, respective relative survival was 80.7%, 83.8% and 82.4% (p-value for trend 0.1).[273]

Another study by Pulte et al. looked at American CLL patients in different age groups. An increase of 5-year overall survival was seen for all age groups over 3 time periods: 1997-2000, 2001-2004, 2005-2008. A further increase was seen in 2009-2012 for the age group 50-59 years only.[274]

In Canada, a gradual improvement of 5-year age-standardized relative survival was seen between 1992 and 2008. Five-year age-standardized relative survival ratio was 68.6% (95%CI 66.2-70.9) in 1992-1994 and 80.9% (95%CI 79.1-82.5) in 2006-2008.[275]

Lenartova et al. included all Norwegian patients diagnosed with CLL or SLL between 1953 and 2012 in their study. Median observed survival for the whole series was 5.7 years (range 0.7-43 years) and 25% of patients survived ten years or longer. Median survival increased over time, with a median survival of 3.0 years in 1953-1962, 5.3 years in 1993-2002 and 8.5 years in 2003-2012. Five-year and 10-year relative survival were

respectively 33.25% and 12.76% in 1953-1962, 67.19% and 45.82% in 1993-2002 and 81.12% and 61.94% in 2003-2012.[276]

DLBCL

Epperla et al. compared relative survival of American DLBCL patients diagnosed between 2002-2007 (years of early adoption of rituximab) with patients diagnosed in 2008-2013 (introduction of novel agents, broader use of autologous hematopoietic cell transplantation and improvement of supportive care). Five-year relative survival probability improved slightly from 61% to 64% in the second period.[277] Also in the USA, researchers investigated the 24-month overall survival for patients with DLBCL who were older than 80 years and 90 years for three time periods: 1983-1996, 1997-2005 and 2006-2013. Overall survival increased for both groups over all time periods. Rituximab was approved for treatment of DLBCL in the USA in 2006.[278]

Dinmohamed et al. performed a similar study in the Netherlands and compared OS and relative survival in DLBCL patients older than 80 years in three time periods: the pre-rituximab (1989-2002), the period in which rituximab was gradually introduced (2003-2007) and the last period in which rituximab was considered part of standard first-line treatment (2008-2015). Overall and relative survival improved over time. Relative survival improved significantly only in patients between 80 and 84 years old, with the most pronounced improvement in the period 2008-2015.[279]

In Sweden, the loss in expectation of life in newly diagnosed DLBCL patients decreased in the time period from 2000 and 2013. On average, DLBCL patients lost 8.0 years (95%CI 7.7-8.3 years) in 2000 and 4.3 years (95%CI 4.5-4.6 years) in 2013.[280]

In the study of Ye et al. in Canada, age-standardised 5-year relative survival for DLBCL patients improved from 44.7% in 1984-1993 to 45.9% in 1994-2003 and 55.0% in 2004-2013 (p-value for time trend test <0.0001).[270]

Chihara et al. saw a clear improvement in 5-year relative survival over time for DLBCL patients in Japan. Five-year relative survival was 43.7% (95%CI 40.3-47.0) for the time period 1993-1997, 48.2% (95%CI 45.4-50.8) for 1998-2002 and 57.2% (95%CI 54.8-59.5) for 2003-2006.[272]

Another Dutch study in DLBCL noted an increase of the 5-year relative survival for patients under 65 years of age, from 57% (95%CI 54-59) in the period 1989-1993 to 75% (95%CI 73-77) in the period 2005-2010. For patients over 75 years of age, a similar increase was seen from 28% (95%CI 24-32) in 1989-1993 to 41% (95%CI 38-44) in 2005-2010.[281]

Mantle cell lymphoma

In Spain (Girona), an increase in 5-year relative survival was seen for mantle cell lymphoma during the period 1996-2015. Five-year relative survival was 42.5% (95%CI 26.2-68.9) in 1996-2002, 36.6% (95%CI 21.5-62.2) in 2003-2008 and 67.7% (95%CI 49.2-93.1) in 2009-2015.[282]

In a Dutch study, an increase in 5-year survival was seen for patients with mantle cell lymphoma, in all age groups. For example, for patients younger than 65, 5-year relative survival rose from 52% (95%CI 44-60) in 2001-2004.[281]

Based on data from the population-based haematological malignancy research network, Smith et al. noted an improvement of overall and relative survival at three years of patients with mantle cell lymphoma. For patients diagnosed between 2004 and 2011, overall and relative 3-year survival were 37.9% (95%CI 30.8-44.8) and 43.3% (95%CI 35.2-51.11), respectively. Both increased to 50.1% (95%CI 39.1-60.1) and 57.8% (95%CI 44.8-68.7) for patients diagnosed in 2012-2015.[283]

Another study in the UK, based on data from the Nottinghamshire Lymphoma registry, noted a 5-year overall survival of 41% between 1996 and 2005 and of 52.1% between 2006 and 2015 (p=0.34). Improvement of overall survival appeared to be limited to patients younger than 70 years old.[284]

Limitations

- Follow-up and data on uptake of drugs may be too short to see a possible effect, especially for CLL/SLL, where treatment is only initiated when symptoms or progressive disease occur.
- Changes in the use of autologous stem cell transplant over the years may also influence survival outcomes.[284] Data on the use of autologous stem cell transplant were not available for this study.

4.8.4 Economic literature: cost-effectiveness

For more information about the economic evaluations in the identified HTA reports, we refer to the Appendix.

4.8.4.1 Chronic lymphocytic leukaemia

The search identified six NICE Technology Appraisals (TAs) assessing the effectiveness and cost-effectiveness of treatments against chronic lymphocytic leukaemia (CLL). Two of them were terminated (TA437[285] evaluating ibrutinib with bendamustine and rituximab against relapsed or refractory CLL and TA452[286] evaluating ibrutinib for untreated CLL without a 17p deletion or TP53 mutation), because no evidence submission was received from the company producing this technology. A total of 4 NICE TAs were thus reviewed.[287-290]

Confidential prices

In two of the four TAs,[287, 288] both the interventions and the comparators were provided under a patient access scheme (PAS) in which discounts to the list prices of the drugs were negotiated with the companies and were commercial in confidence. This was the case for ibrutinib and it comparator idealisib plus rituximab in TA429 (2017)[287] and for venetoclax plus rituximab and its comparator ibrutinib in TA561 (2019).[288]

In the two oldest TAs, dating back to 2009[290] and 2010,[289] there was no discount on the prices of the drugs investigated (for both the interventions and the comparators) and the drugs were assessed at their list prices. Both TAs compared the combination rituximab plus fludarabine and cyclophosphamide (RFC) with fludarabine and cyclophosphamide (FC).

Quality of life

Quality of life (QoL) estimates directly measured with a generic utility instrument administered alongside the underlying head-to-head trial were available in only one TA.[287] In the three other TAs, QoL estimates were obtained from indirect sources.[288-290]

First, in TA561[288] a trial directly comparing the scope intervention and the comparator was lacking (i.e. venetoclax plus rituximab versus ibrutinib). EQ-5D QoL estimates came then from two previous NICE TAs performed in the same population (CLL) for venetoclax monotherapy[291] and for the combination idelalisib plus rituximab.[292]

Second, in TA193[289] and in TA174[290] the underlying trials did well directly compare the interventions in scope (i.e. rituximab plus fludarabine and cyclophosphamide compared with fludarabine and cyclophosphamide) but no generic measure of health-related quality of life (e.g. the EQ-5D) was collected in the trials. Instead, disease-specific quality of life questionnaires were administered, i.e. the Functional Assessment of Cancer Therapy – General (FACT-G) questionnaire in the REACH trial,[289] and the European Organisation for Research and Treatment of Cancer-Quality of Life Questionnaire Core 30 (EORTC-QLQC30) in the CLL-8 trial.[290] In both TAs, utility values were then derived from a 2002 HTA report that assessed the cost-effectiveness of fludarabine against CLL.[293] However, these estimates of utility were also obtained using disease-specific quality of life instruments (EORTC QLQ-C30 and the FACT-G) and, as such, they did not constitute a preference-based measure of health utility. This led the Committee to conclude that "*the evidence base for these estimates did not reflect the NICE reference case; in particular, preference-based methods were not used*."[289] The Committee further added 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*."[290]

This lack of direct evidence to measure the impact on quality of life gives rise to uncertainty in the results of the economic evaluations.

Third, in TA429 comparing ibrutinib with the combination idelalisib plus rituximab,[287] utility estimates were directly measured with the EQ-5D

generic instrument administered alongside the RESONATE trial. However, "*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, (…), the committee was concerned that benefits may not have been appropriately captured, noting that the EQ-5D does not directly measure fatigue.*"[287] The Committee further reported that "*(…) the base case may have underestimated the quality-of-life benefit with ibrutinib.*"[287] This illustrates a possible limitation of the generic utility instruments that may not be sensitive enough or may not have sufficient coverage of symptoms to adequately measure the impact of some diseases on health-related quality of life.

All TAs modelled QoL per health state, attributing a mean utility value to the progression-free and post-progression health states (and death), irrespective of the treatments administered. QoL input data (0.8 for progression-free state and 0.6 for post-progression state) were reported in 2 out of the 4 TAs.[289, 290]

Uncertainty and influential parameters

The greatest uncertainty in the economic evaluations of the 4 identified TAs was the relative impact of the treatments on overall survival (OS), which further generated uncertainty in the estimated QALYs and incremental cost-effectiveness ratios (ICERs). Several reasons led to this uncertainty.

First, there was the problem of a lack of head-to-head trial for at least one comparison in 3 out of the 4 TAs. This was the case in TA561[288] comparing venetoclax plus rituximab with ibrutinib for the second-line treatment of CLL, in TA429[287] comparing ibrutinib with idelalisib plus rituximab for the first-line treatment of CLL, and in TA193[289] comparing rituximab plus fludarabine and cyclophosphamide (RFC) with fludarabine and cyclophosphamide (FC) for the second-line treatment of CLL in 2 specific sub-populations: people who have previously received treatment with rituximab (the 'rituximab pre-treated population') and people who have previously received treatment with fludarabine and who are refractory to fludarabine combination therapy (the 'fludarabine-refractory disease'). In the absence of direct evidence from RCT, clinical effectiveness was informed based on other sources with varying degrees of quality. In TA561,[288] several types of indirect comparisons (among others matched-adjusted indirect comparison (MAIC) and fixed-effect network meta-analysis) were simulated by the manufacturer and the ERG, but none was deemed satisfactory. The Committee reported indeed that "*indirect comparisons of venetoclax plus rituximab with ibrutinib have limitations, (…)*" and 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.*"[288]. In TA429,[287] because evidence for the first-line treatment of CLL was not available, evidence from the second-line treatment of CLL was used: "*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.*"[287] In TA193,[289] only limited evidence from poor-quality studies was available for the 2 sub-populations specified above: "*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.*"[289]

Second, when a head-to-head trial was available (i.e. for at least one comparison in 3 out of the 4 TAs) there was a problem of data immaturity that affected all those analyses.[287, 289, 290] In two TAs (TA429[287] and TA174[290]) this was due to premature termination of the underlying trials, each time in favour of the study interventions: for ibrutinib versus idelalisib plus rituximab for the second-line treatment of CLL (RESONATE trial)[287] and for RFC versus FC for the first-line treatment of CLL (CLL-8 trial).[290] In both TAs,[287, 290] the immaturity of the data reflected a successful treatment effect and was viewed positively, but this led to uncertainty as "*the committee was mindful that it [the immaturity of the data] did mean that a greater proportion of the modelled time horizon depended on extrapolations.*"[287] A further problem related to the immaturity of the data is indeed the difficulty to model and extrapolate progression-free survival (PFS) and overall survival (OS) in the absence of long-term trial data to appropriately inform the survival curves in the economic model, as illustrated in TA174:[290] "*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) (…). 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."[290] In the third TA (TA193[289]) the data from the underlying REACH trial (that compared RFC with FC in the sub-population of patients who have not previously received rituximab or fludarabine combination therapy and those whose disease is not refractory to fludarabine, the 'REACH trial population') were also immature but this immaturity was rather inherently related to CLL disease itself: "*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.*"[289]

Third, there was the problem of treatment crossover that occurred at disease progression in the two RCTs that were prematurely terminated.[287, 290] In TA429,[287] The results of the RESONATE trial were adjusted to avoid an underestimation of the treatment effect. In TA174,[290] the CLL-8 trial failed to demonstrate a statistically significant difference in overall survival between treatment groups (RFC versus FC) but "*the Committee accepted that crossover and subsequent lines of treatment in the trial made the overall survival benefit difficult to prove.*"[290] Duration of progression-free survival was then used as surrogate for overall survival and several parametric models for the extrapolation were presented. The Committee acknowledged 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.*"[290]

Four, the REACH (in TA193[289]) and the CLL-8 (in TA174[290]) trials were potentially biased, as reported in TA193: "*The Committee noted there was potential for bias in outcome assessment because of the open-label design of the trial.*"[289]

Finally, in TA429[287] the comparator from the underlying RESONATE trial did not match with the scope comparator of the TA. Indeed, the trial provided results for idelalisib plus ofatumumab rather than idelalisib plus rituximab as a comparator to ibrutinib. The use of this proxy comparator, although validated by the Committee, led to uncertainties in the transferability of the trial results to the scope comparison assessed in the TA: "*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.*"[287].

To sum-up, there was no single economic evaluation in which the extend of the benefit in OS between treatments could be clearly demonstrated. All studies reported high uncertainty surrounding the estimate of OS benefit and further stated that the assumptions used to derive the OS benefits (the indirect comparison methods, the long-term extrapolation methods, the use of surrogate endpoints, the cross-over adjustment methods, the use of a surrogate comparator…) had a large impact on the estimates of cost-effectiveness.

The second main source of uncertainty in the TAs identified was related to the elicitation of the quality of life for CLL patients. Indeed, when QoL was not measured with a generic, sensitive enough, utility instrument in the underlying trials (which was the case in all 4 TAs, see the previous section on Quality of Life), utility values and hence the overall results were uncertain; as illustrated in the evaluation of rituximab in combination with fludarabine and cyclophosphamide (TA174): "*The Committee considered the lack of appropriate utility data contributed to substantial uncertainty in the economic modelling.*"[290]

Results

The ICERs supporting the committee's conclusions were (see more details in Appendix):

First-line treatment

- Ibrutinib
  - Patients with untreated CLL who have a 17p deletion or TP53 mutation and in whom chemo-immunotherapy is unsuitable:[287]

    Ibrutinib versus idelalisib plus rituximab (including confidential PAS for ibrutinib and idealisib):

    "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. (…) 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."[287]

- Rituximab plus fludarabine and cyclophosphamide
  - People with previously untreated chronic lymphocytic leukaemia:[290]

    Rituximab plus fludarabine and cyclophosphamide (RFC) compared with fludarabine and cyclophosphamide (list prices for all drugs):

    - Company ICER: £13 189 per QALY gained (IC: £11 617, IE: 0.88 QALY)
    - ERG ICER (assuming no difference in OS between treatment groups): £30 304 per QALY gained (IC: £7 228, IE: 0.24 QALY)
    - ERG ICER (assuming OS benefit from RFC is between the company's base-case and the assumption of no OS benefit): 72% probability of being cost-effective at £20 000 per QALY, 88% probability of being cost-effective at £30 000 per QALY

Second-line treatment

Ibrutinib

- Patients with relapsed or refractory CLL who have had at least 1 prior therapy:[287]

  Ibrutinib versus idelalisib plus rituximab (including confidential PAS for ibrutinib and idealisib):

  - Not adjusting for crossover: around £50 000 per QALY gained
  - Adjusting for crossover: below £50 000 per QALY gained

Venetoclax plus rituximab

- Patients with relapsed or refractory CLL who have had at least 1 previous therapy:[288]

  Venetoclax plus rituximab compared with ibrutinib:

  - Including PAS for venetoclax plus rituximab (company results): venetoclax plus rituximab dominates ibrutinib
  - Including PAS for venetoclax plus rituximab and ibrutinib (ERG results): "*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.*"[288]

Rituximab plus fludarabine and cyclophosphamide

- Patients with relapsed or refractory CLL:[289]

  Rituximab plus fludarabine and cyclophosphamide (RFC) compared with fludarabine and cyclophosphamide (list prices for all drugs):

  - People who have not previously received rituximab or fludarabine combination therapy and those whose disease is

not refractory to fludarabine monotherapy ('REACH trial population'):

Company ICER: £15 593 per QALY gained (IC: £9 128, IE: 0.585 QALY)

ERG 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

- People who have previously received treatment with rituximab ('rituximab pre-treated population'):

  Company ICER: £22 519 per QALY gained (IC: £9 134, IE: 0.406 QALY)

  ERG ICER: none reported

  Committee: "*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.*"[289]

- People who have previously received treatment with fludarabine and who are sensitive to a fludarabine treatment ('fludarabine-sensitive disease'):

  No ICER was derived. Results from population A were generalised to population C: "*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.*"[289]

- People who have previously received treatment with fludarabine and who are refractory to a fludarabine treatment ('fludarabine-refractory disease'):

  No ICER was derived. The Committee concluded that RFC is not cost-effective: "*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.*"[289].

In the two TAs[287, 288] where negotiated discounts for the interventions (and the comparators) were confidential, exact ICERs (and incremental costs and incremental effects) were not transparently presented. Instead, an indication of the relative position of the decision-making ICER with respect to the official NICE threshold was reported, i.e. £20 000 - £30 000 per QALY gained or £50 000 in case of an end-of-life treatment.[x] This was the case for the assessments of ibrutinib[287] and of the combination venetoclax plus rituximab[288] both used for the second-line treatment of CLL.

In the two older TAs (2009[290] and 2010[289]) based on list prices to compare rituximab plus fludarabine and cyclophosphamide with fludarabine and cyclophosphamide used first-line[290] or second-line[289] against CLL, exact ICERs were transparently reported (as well as incremental costs and incremental effects).

Despite the high uncertainties prevailing in the TAs and relating mainly to efficacy estimates, utility values and long-term outcomes, the four TAs had positive conclusions regarding the cost-effectiveness of the scope treatments against CLL (this, however, with the exception of two specific sub-populations considered in TA193,[289] see later). In the two most recent TAs,[287, 288] treatments were recommended for routine use only when they

[x] To qualify as an "end-of-life' treatment, the following two criteria must be fulfilled: 1) the treatment is indicated for patients with a short life expectancy, normally less than 24 months; 2) there is sufficient evidence to indicate that the treatment has the prospect of offering an extension to life, normally of a mean value of at least an additional three months, compared with current NHS treatment.

were provided with the discounts negotiated with the manufacturer. In the two oldest TAs,[289, 290] treatments were recommended for routine use at their list price.

Two TAs reported ICERs below the usual NICE threshold of £20 000 - £30 000 per QALY gained when no discount to the drug prices was applied (i.e. at list prices). This was the case in TA174[290] and in TA193[289] both evaluating rituximab plus fludarabine and cyclophosphamide versus fludarabine and cyclophosphamide as first-line[290] or second-line[289] treatment. In TA193,[289] the cost-effectiveness of RFC used second-line could however only be demonstrated for the following sub-populations: 1) patients with relapsed or refractory CLL who have not previously received rituximab or fludarabine combination therapy and those whose disease is not refractory to fludarabine monotherapy (the 'REACH trial population'), and 2) patients with relapsed or refractory CLL who have previously received treatment with fludarabine and who are sensitive to fludarabine combination therapy (the 'fludarabine-sensitive disease' population). For this last population, although no decision-making ICER was available, "*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.*"[289]

A third TA (TA561[288]) comparing venetoclax plus rituximab with ibrutinib for the second-line treatment of CLL, also referred to ICERs below the NICE threshold of £20 000 - £30 000 per QALY gained when discount prices were used: "*It [The Committee] 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.*"[288]

For the comparison ibrutinib versus idelalisib plus rituximab for the second-line treatment of CLL and for which discounts were applied to both the intervention and the comparator, the Committee reported decision-making ICERs around (not adjusting for cross-over) or below (adjusting for cross-over) £50 000 per QALY gained. The Committee concluded that ibrutinib was a cost-effective use of NHS resources as it was an innovative treatment in CLL and as it fulfilled the end-of-life criteria. Further, for the use of ibrutinib in people with untreated CLL who have a 17p deletion or TP53 mutation, "*the committee agreed that, in the absence of clinical evidence in this population, the data from the previously treated population could be taken into account (…).*"[287] Hence, "*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".*[287]

Finally, negative reimbursement decisions were reached in TA193[289] for two sub-populations: 1) adults with relapsed or refractory CLL who have previously received treatment with rituximab (the 'rituximab pre-treated population') and 2) adults with relapsed or refractory CLL who have previously received treatment with fludarabine and who are refractory to a fludarabine treatment (the 'fludarabine-refractory disease'). For both populations, no decision-making ICERs was available because of the absence of (or the weak) clinical evidence, which led the Committee to conclude that the intervention (RFC) could not be recommended for routine use in those sub-populations. In the 'rituximab pre-treated population' 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.*"[289]

4.8.4.2 Mantel-cell lymphoma

The search identified one NICE Technology Appraisal (TA502) assessing the effectiveness and cost-effectiveness of ibrutinib (versus rituximab plus chemotherapy) in patients with relapsed or refractory mantel cell lymphoma (R/R MCL).[294]

Confidential prices

In this TA,[294] ibrutinib was provided under a patient access scheme (PAS) in which a discount to the list price of the drug was negotiated with the company and whose financial terms were commercial in confidence.[294]

Quality of life

There was no underlying head-to-head trial comparing ibrutinib with rituximab plus chemotherapy, the scoping interventions in TA502.[294] As QoL estimates directly measured with a generic utility instrument were not available, QoL was derived from two previous studies (the RAY trial and the SPARK study) that elicited EQ-5D-5L utilities from R/R MCL patients.

QoL was modelled per health state, attributing a mean utility value to the progression-free and post-progression health states (and death), irrespective of the treatment administered. QoL input data used in the economic evaluation were not reported.

Uncertainty and influential parameters

The greatest uncertainty in this evaluation was the size of the benefit (in terms of overall survival) for ibrutinib compared with rituximab plus chemotherapy.

Given the absence of a head-to-head trial for ibrutinib versus rituximab plus chemotherapy in patients with R/R MCL, an indirect comparison (a network meta-analysis informed by the RAY trial and the OPTIMAL study) was performed. The robustness of this indirect comparison was however questioned: "*The committee acknowledged the limitations of the indirect comparison (…), such as differences in the patient populations in OPTIMAL and RAY.*"[294]

Besides, many patients crossed over to the ibrutinib arm in the RAY trial, which diluted the ibrutinib effect and further added to the uncertainty of the results of the indirect comparison: "*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.*"[294]

Despite this, the Committee concluded that although "*there is considerable uncertainty associated with the indirect comparisons and that the size of the benefit of ibrutinib compared with R-chemo is unclear, (…) it accepted that the available evidence and experience from clinical practice strongly suggest that ibrutinib is more effective.*"[294]

Results

- **Ibrutinib**
  - Ibrutinib versus rituximab plus chemotherapy (including PAS for ibrutinib):[294]
    - Overall relapsed or refractory MCL population: above £59 000 per QALY gained
    - Patients with relapsed or refractory MCL who have had only 1 previous treatment: below £49 848 per QALY gained

Although a confidential discount for ibrutinib was negotiated, exact ICERs were transparently reported (but not the incremental costs).

A negative reimbursement decision was reached for the overall relapsed or refractory MCL population. Despite fulfilling the end-of-life criteria and despite taking discounted prices into account, ibrutinib was indeed associated with an ICER above £59 000 per QALY gained. In the subgroup of R/R MCL patients who have had one prior therapy, however, "*the committee concluded that the most plausible ICER (…) is likely to be lower than £49 848 per QALY gained.*"[294] Ibrutinib was then recommended as an option for treating R/R MCL in adults, only if they have had only one previous line of therapy and the company provides ibrutinib with the discount agreed in the commercial access agreement with NHS England.

4.8.5 Summary

4.8.5.1 CLL/SLL

Observational data

- Observational data show a slight improvement of overall and relative survival. Three-year observed survival was 76.7% (95%CI 73.3-79.7) for patients diagnosed in 2004, 81.9% (95%CI 79.0-84.5) for patients diagnosed in 2009 and 84.9% (95%CI 81.2-88.0) for patients diagnosed in 2017. Median survival was already 9.7 (95%CI 8.6-10.8) years for patients diagnosed in 2004, hence follow-up was too short to evaluate the evolution of median survival for patients diagnosed in more recent years.
- Total yearly oncology drug expenditures were about €360 000 and rose to about €2.1 million in 2009, mainly due to an increase of the number of patients who received oncology drugs. After 2009, drug expenditures rose more sharply, due to increased use of rituximab and later, after 2014, ibrutinib and obinutuzuab to about €13.3 million in 2018.
- Drug expenditures during the first two years after diagnosis were about €925 000 for patients diagnosed in 2004, then started to increase in 2008 till 2011 (almost €2.5 million), and then further increased in 2014-2015 up to €5 million.
    - The number of patients with oncology drug expenditures remained rather stable (277 in 2004 and 303 in 2015).
    - The mean cost per patient with drug expenses for the first two years after incidence increased from about €3 300 in 2004 to about €19 000 in patient diagnosed in the years 2017.

Medical literature

- Clinical trials show an improvement in overall survival in patients with indolent lymphoma when rituximab is added to chemotherapy, both in newly diagnosed patients and in patients who received prior therapy. For maintenance therapy with rituximab, a clear survival benefit is not proven.
- In patients with relapsed or refractory CLL following one or more previous lines of systemic therapy, treatment with ibrutinib results in better overall survival compared to other therapy. Ibrutinib may also improve survival in first-line treatment, but results are not conclusive.
- Obinutuzumab may improve overall survival for patients with treatment-naïve CLL but results are inconclusive.

Economic literature

- In 2 of the 4 NICE TAs identified assessing treatments against chronic lymphocytic leukaemia, discounts to the list prices of the interventions considered were negotiated.[287, 288] The discounts were confidential implying that exact decision-making ICERs were not reported. Instead an indication of the relative position of the decision-making ICER with respect to the official NICE threshold was reported. There was no price discount for the interventions assessed in the two oldest TAs (2009[290] and 2010[289]), and the resulting ICERs (and incremental costs and effects) based on list prices were transparently reported.
- QoL data were mostly obtained from indirect sources because of the absence of a head-to-head trial[288] or because of a lack of generic utility measures in the underlying trials.[289, 290] Further in two of those TAs,[289, 290] the utility estimates used in the model did not reflect the NICE reference case as they were obtained from indirect sources with a non-preference based instrument. One TA directly measured the utility estimates with the EQ-5D instrument within the underlying trial,[287] but the results indicated that this instrument may not be sensitive enough to fully captured the experience of CLL

patients (e.g. whether fatigue is sufficiently covered in the EQ-5D). The impact on QoL was always modelled by assuming a mean utility value for each health state modelled (e.g. progression-free survival, progressed disease, death) irrespective of the treatments administered. QoL input data for the health states modelled were transparently reported in 2 out of the 4 TAs.

- In all economic evaluations, the greatest uncertainty related to the estimation of the treatment effect in terms of overall survival. This was mainly due to the absence of head-to-head comparisons or, when such a trial was available, to the immaturity of the trial data and/or to treatment crossover, which complicated the extrapolation of the survival data. Another reason was the long natural history of CLL that made OS difficult to prove in trials and implied the recourse to surrogate measures (i.e. progression-free survival) and extrapolations to demonstrate efficacy in OS. The second main source of uncertainty was the lack of good quality of life estimates that affected all identified TAs.
- Two TAs (the oldest ones) concluded that the treatments were cost-effective at their official list prices. In the two other TAs, treatments were cost-effective only when the confidential discounts were applied to the drug prices.
- In two TAs, the combination rituximab plus fludarabine and cyclophosphamide, valued at list prices and used for the first- or the second-line treatment of CLL, was cost-effective at the usual £20 000 - £30 000 per QALY threshold. For patients with relapsed or refractory CLL (second-line), this positive recommendation was however limited to two specific subpopulations (i.e. the patients represented in the 'REACH trial' and the 'fludarabine-sensitive disease' patients). The combination venetoclax plus rituximab (used second-line) was also considered cost-effective at the same threshold when discounted prices were used. Higher ICERs (around or below £50 000 per QALY gained) were still accepted, i.e. for ibrutinib used first line (for at-risk patients: 17p deletion or TP53 mutation) and second-line because it fulfilled the end-of-life criteria and was an innovative treatment. Finally, due to the absence of (or the weak) clinical evidence a negative reimbursement decision was reached, against the routine use of the combination rituximab plus fludarabine and cyclophosphamide in the 'rituximab pre-treated' and the 'fludarabine-refractory disease' CLL patients.

4.8.5.2 DLBCL

Observational data

- Overall survival and relative survival slightly increased between 2004-2008 and 2009-2013; no further improvement was seen for the period 2014-2017. Three-year survival was 58.3% (95%CI 54.2-62.2) for patients diagnosed in 2004 and 62.6% (95%CI 58.9-66.1) in 2017. Median survival was 5.4 (95%CI 3.8-7.2) years for patients diagnosed in 2004 and 5.9 (95%CI 4.9-not reached) years for patients diagnosed in 2013. Median survival was not reached for patients diagnosed after 2013.
- Yearly expenditures for all patients with DLBCL increased from about €4.1 million in 2004 to €9 million in 2017, mainly due to an increase of the number of DLBCL patients who received oncological drugs during that year.
- Expenditures during the first two years after diagnosis slightly increased over the years, from about €5.8 million for patients diagnosed in 2004 to €7.4 million for patients diagnosed in 2017.
    - The number of patients with oncology drug expenditures went up from 471 in 2004 to 655 in 2017.
    - The mean cost per patient with drug expenses for the first two years after incidence remained stable, with a mean cost of about €12 300 in 2004 and about €11 300 in patient diagnosed in the years 2017.

Medical literature

- Overall, rituximab added to chemotherapy improves overall survival for DLBCL patients, compared to chemotherapy alone. Six out of ten studies included in the meta-analysis were in patients with previously untreated DLBCL. Rituximab salvage therapy in people with relapsed DLBCL improves overall survival compared to observation, at the cost of an increase of infection-related events.

Economic literature

- No HTA reports with an economic evaluation were selected within this indication.

4.8.5.3 Mantle cell lymphoma

Observational data

- Observational data indicate that overall survival and relative have not clearly improved over the years. Observed 3-year survival probability was volatile over the years. This was 63% (95%CI 53.1-71.3) in 2004 and 70.3% (95%CI 59.8-78.6) in 2017. Median survival was 4.1 years (95%CI 3.2-5.5) for patients diagnosed in 2004 and 4.2 years (95%CI 3.3-5.4) for patients diagnosed in 2015. Median survival was not reached for patients diagnosed after 2015.
- Yearly expenditures on oncological drugs for mantle cell patients was about 520 000 in 2004, increasing year by year with the biggest increase in the most recent years, up to about €7 million in 2017.
- The drug expenditures during the first 2 years after diagnosis was about €800 000 for patients diagnosed in 2004, started to increase rapidly for patients diagnosed after 2011 up to a maximum of about €4 million for patients diagnosed in 2016.
    - The number of patients with oncology drug expenditures went up from 91 in 2004 to 131 in 2016.
    - For patients who received oncological drugs, mean cost per patient during the first two years after diagnosis was about €8 800 in 2004 and increased up to about €30 300 in 2016.

Medical literature

- A systematic review of studies in indolent lymphoma and mantle cell patients shows a survival benefit for adding rituximab to chemotherapy, both in the first-line setting and in the recurrent setting. For maintenance therapy with rituximab, no clear survival benefit has been proven.
- Compared to temsirolimus, ibrutinib may improve overall survival in relapsed or refractory mantle cell lymphoma but results are inconclusive.

Economic literature

- In the unique NICE TA identified assessing treatments against relapsed or refractory mantel cell lymphoma (R/R MCL), a discount to the list price of ibrutinib was negotiated.[294] Although the discount was confidential, exact decision-making ICERs were reported (but not the incremental costs).
- EQ-5D QoL data was obtained from indirect sources because of the absence of a head-to-head trial comparing ibrutinib with rituximab plus chemotherapy in R/R MCL patients. The impact on QoL was modelled by assuming a mean utility value for each health state modelled (e.g. progression-free survival, progressed disease, death) irrespective of the treatments administered. QoL input data for the health states modelled was not reported.
- The greatest uncertainty related to the estimation of the treatment effect in terms of overall survival. This was due to the absence of head-to-head comparison of ibrutinib versus rituximab plus chemotherapy in R/R CML patients and to a problem of patient crossover in a trial used to inform the indirect comparison between the scoping interventions.

- Ibrutinib was cost-effective only when the confidential discounts were applied.
- With an ICER above £50 000 per QALY gained despite applying discounted prices and despite fulfilling the end-of-life criteria, a negative reimbursement decision was reached for ibrutinib for the whole population of patients with relapsed or refractory mantel cell lymphoma. By contrast, with an ICER likely below £50 000 per QALY, ibrutinib was considered cost-effective in R/R MCL patients who have had only 1 previous line of therapy.

4.9 Non-small cell lung cancer

4.9.1 Introduction

In 2018, 8815 lung cancers were newly diagnosed in Belgium. Non-small cell lung cancer (NSCLC) is the most frequent form of lung cancer. It presents most often in an advanced stage and more than half of the patients die within the first year after diagnosis.[33]

Treatment of locally advanced and metastatic NSCLC with chemotherapy, often a cisplatin containing doublet, can extend survival compared to best supportive care.[295]

Since 2006, treatment targeted at the epidermal growth factor receptor (EGFR) is available in Belgium. Gefitinib and erlotinib were the first generation small molecule tyrosine kinase inhibitors, followed by second and third generation treatments such as afatinib and osimertinib. It is estimated that 10% to 15% of the non-squamous NSCLC tumours are EGFR positive.[295] Erlotinib was the first to be reimbursed for all advanced NSCLC patients with at least 10% cells positive for EGFR on immunohistochemistry in patients who received prior chemotherapy. From 2011 onwards, erlotinib is also reimbursed in patients whose tumour carries an activating EGFR mutation.[296]

Another class of targeted treatment that has emerged for some NSCL cancers are the ALK-inhibitors such as crizotinib. Five percent of the NSCLC tumours harbour the anaplastic lymphoma kinase gene.[297] Crizotinib also shows activity in tumours carrying chromosomal rearrangements of the gene encoding ROS1 proto-oncogene receptor tyrosine kinase.[298]

Most recently, immunotherapy was introduced as new treatment for NSCLC, with nivolumab and pembrolizumab being reimbursed since 2017. Later, also atezolizumab and durvalumab started to be reimbursed for NSCLC patients in Belgium.

Table 47 presents the list of selected drugs for the NSCLC indication.

Table 47 – Drugs selected for NSCLC

Drug	Year#	Trade Name$	Company$	Mechanism of action
Erlotinib	2006	Tarceva	Roche	epidermal growth factor receptor/human epidermal growth factor receptor type 1 (EGFR also known as HER1) tyrosine kinase inhibitor
Gefitinib	2010	Iressa	Astra Zenica	selective small molecule inhibitor of the epidermal growth factor receptor tyrosine kinase
Afatinib	2014	Giotrif	Boehringer Ingelheim	selective, irreversible ErbB Family Blocker (EGFR (ErbB1), HER2 (ErbB2), ErbB3 and ErbB4)
Crizotinib	2006	Xalkori	Pfizer	selective small-molecule inhibitor of the ALK receptor tyrosine kinase (RTK)
Nivolumab	2016	Opdivo	Bristol-Myers Squibb	monoclonal antibody (HuMAb), which binds to the programmed death-1 (PD-1) receptor
Pembrolizumab	2016	Keytruda	MSD	Monoclonal antibody which binds to the programmed cell death-1 (PD-1) receptor

$ of the originator; # year of start reimbursement first indication in Belgium

4.9.2 Observational data

4.9.2.1 Patient characteristics, survival and expenditures

The general composition of the whole NSCLC population has changed over the incidence periods. Stage IV NSCLC accounts for 31.5%, 38.9% and 44.4% of the reported cases over the three incidence periods 2004-2008, 2009-2013, and 2014-2017, respectively (see appendix). The percentage of female patients increased in all NSCLC stages (Table 48A and appendix).

For patients with stage IV NSCLC, observed survival seems relative stable during the incidence period 2004-2013 (Table 48B&C). Compared to earlier incidence years, observed survival of patients diagnosed in 2014-2017 seems to have improved. Observed survival at 3-years was 5.6% (95%CI 4.6-6.7) in 2004 and 15.5% (95%CI 14.1-17.1) in 2017. However, median survival has remained constant at 0.5-0.6 years (Table 48D). Evaluation of changes in overall survival by mutation status for EGFR or ALK was not possible based on the data available at BCR.

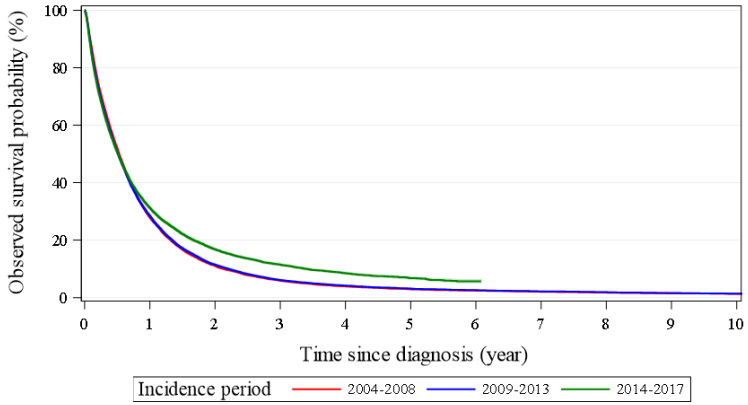
There is a large increase in drug expenditures since the reimbursement of immunotherapy (nivolumab and pembrolizumab) (Table 49A). Whereas yearly total drug expenditures were less than €40 million before 2010, this amount more than tripled in 2017 to more than €120 million. Also for stage IV NSCLC, this steep increase in expenditures is observed (Table 49B). This increase is not mainly due to a volume effect (i.e. the yearly number of patients with pharmaceutical expenses), but rather a price effect with the reimbursement of nivolumab and pembrolizumab. The mean cost per stage IV NSCLC patient with drug expenses for the first two years after incidence increased from less than €5 000 before 2006, to about €10 000 in 2010, and more than €35 000 in 2017 (Table 49C).

Table 48 – Non-small-cell lung carcinoma (2004-2017), combined stage IV (observed survival): A) Patient characteristics; B) Kaplan-Meier graph per incidence period; C) Time trend with incidence year*; D) Median survival time* **

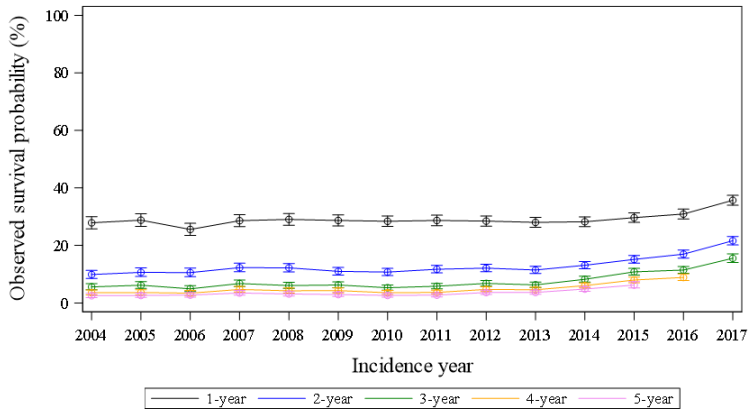
A

Characteristic	Incidence period		
	2004-2008	2009-2013	2014-2017
Overall	8,819	12,039	11,342
Gender			
Male	6,577 (74.6)	8,404 (69.8)	7,581 (66.8)
Female	2,242 (25.4)	3,635 (30.2)	3,761 (33.2)
Age at diagnosis (year)			
<50 years	632 (7.2)	687 (5.7)	510 (4.5)
50-59 years	1,803 (20.4)	2,456 (20.4)	1,998 (17.6)
60-69 years	2,655 (30.1)	3,748 (31.1)	3,881 (34.2)
70-79 years	2,801 (31.8)	3,581 (29.7)	3,320 (29.3)
80+ years	928 (10.5)	1,567 (13.0)	1,633 (14.4)
WHO - Performance Status			
0 – Asymptomatic	778 (8.8)	1,196 (9.9)	969 (8.5)
1 – Symptomatic but completely ambulatory	4,680 (53.1)	7,129 (59.2)	6,913 (61.0)
2 – Symptomatic, <50% in bed during the day	1,539 (17.5)	1,793 (14.9)	1,873 (16.5)
3 – Symptomatic, >50% in bed, but not bedbound	598 (6.8)	687 (5.7)	679 (6.0)
4 – Bedbound	167 (1.9)	188 (1.6)	154 (1.4)
Not reported	1,057 (12.0)	1,046 (8.7)	754 (6.6)

B

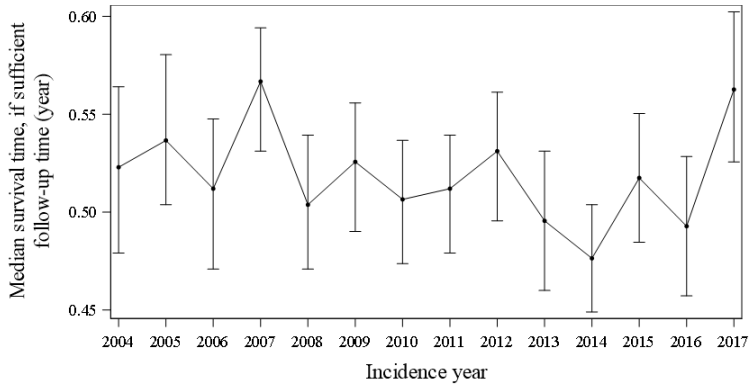


C



Year: 3-y OS [95%CI]
2004: 5.6 [4.6, 6.7]
2005: 6.2 [5.1, 7.4]
2006: 4.9 [3.9, 6.0]
2007: 6.8 [5.7, 8.0]
2008: 6.1 [5.0, 7.2]
2009: 6.3 [5.3, 7.3]
2010: 5.3 [4.4, 6.2]
2011: 5.8 [4.9, 6.8]
2012: 6.8 [5.8, 7.8]
2013: 6.3 [5.4, 7.3]
2014: 8.2 [7.2, 9.3]
2015: 10.8 [9.7, 12.0]
2016: 11.4 [10.3, 12.7]
2017: 15.5 [14.1, 17.1]

D

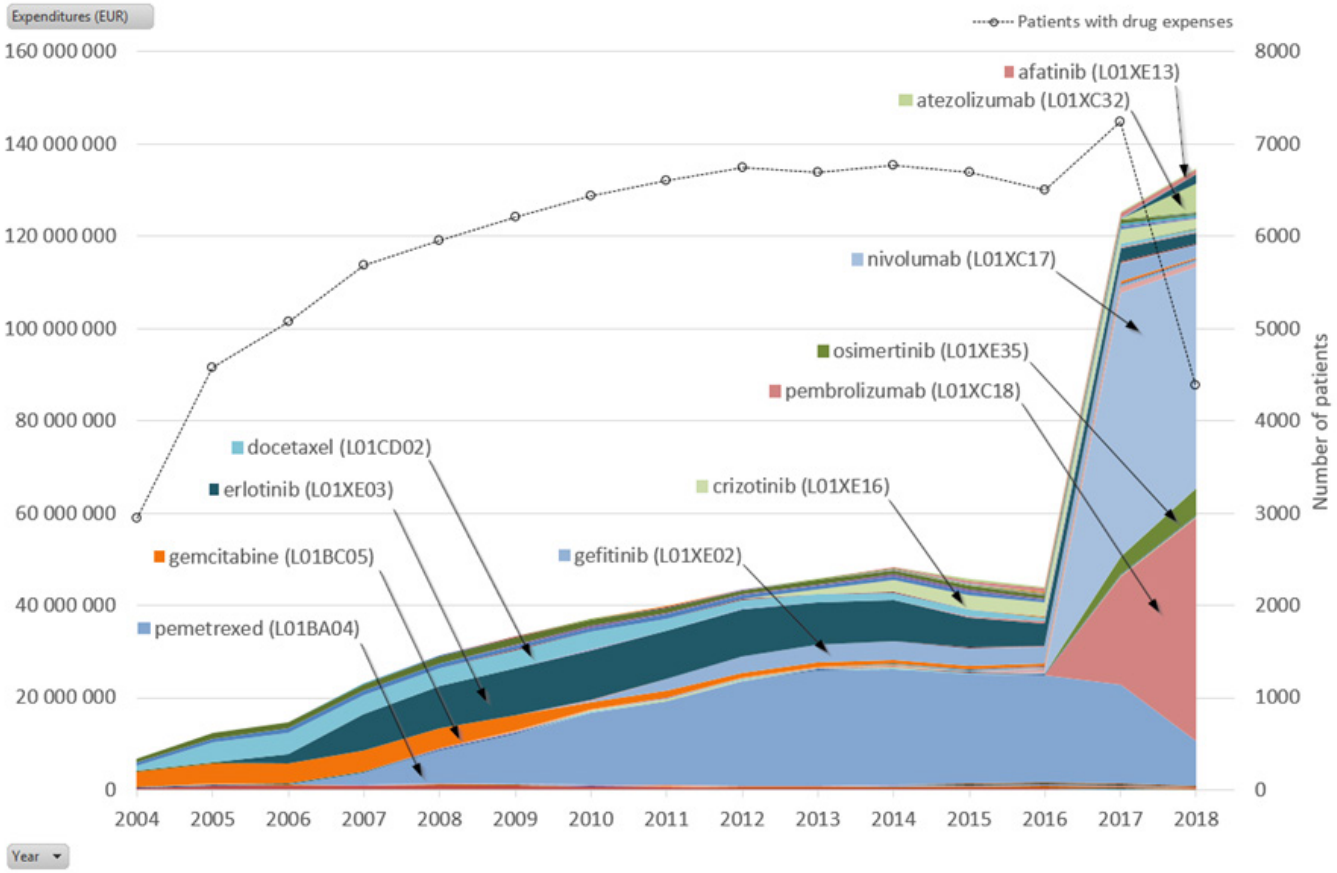


Year: Med. ST [95%CI]
2004: 0.5 [0.5, 0.6]
2005: 0.5 [0.5, 0.6]
2006: 0.5 [0.5, 0.5]
2007: 0.6 [0.5, 0.6]
2008: 0.5 [0.5, 0.5]
2009: 0.5 [0.5, 0.6]
2010: 0.5 [0.5, 0.5]
2011: 0.5 [0.5, 0.5]
2012: 0.5 [0.5, 0.6]
2013: 0.5 [0.5, 0.5]
2014: 0.5 [0.4, 0.5]
2015: 0.5 [0.5, 0.6]
2016: 0.5 [0.5, 0.5]
2017: 0.6 [0.5, 0.6]

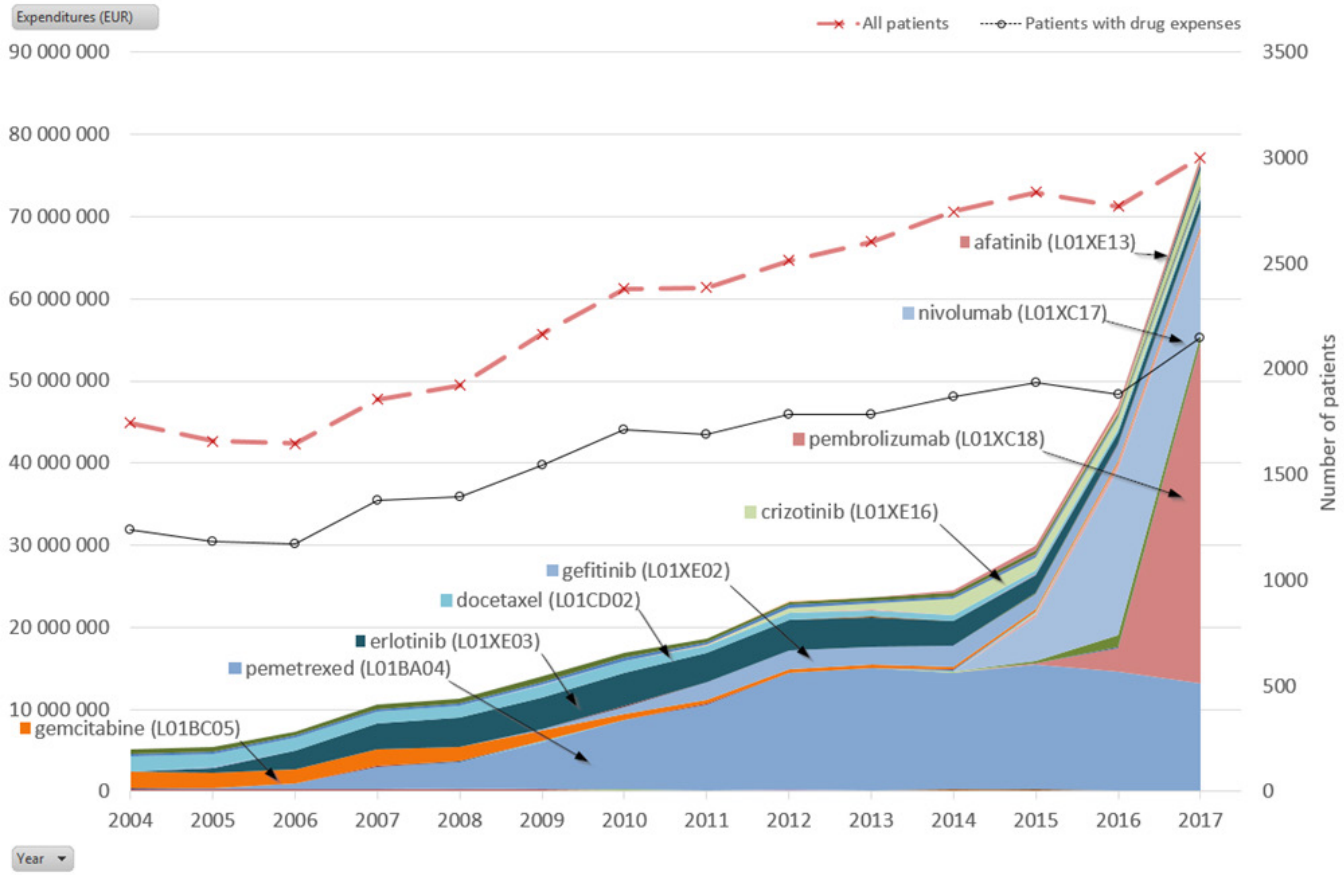
*Med. ST: median survival time; 3-y OS: 3-year observed survival; * the error bars represent the 95%CI. ** When the upper error is not plotted, the upper limit could not be determined with the available follow-up data. Source: BCR.*

Table 49 – Non-small-cell lung carcinoma: drug expenditures

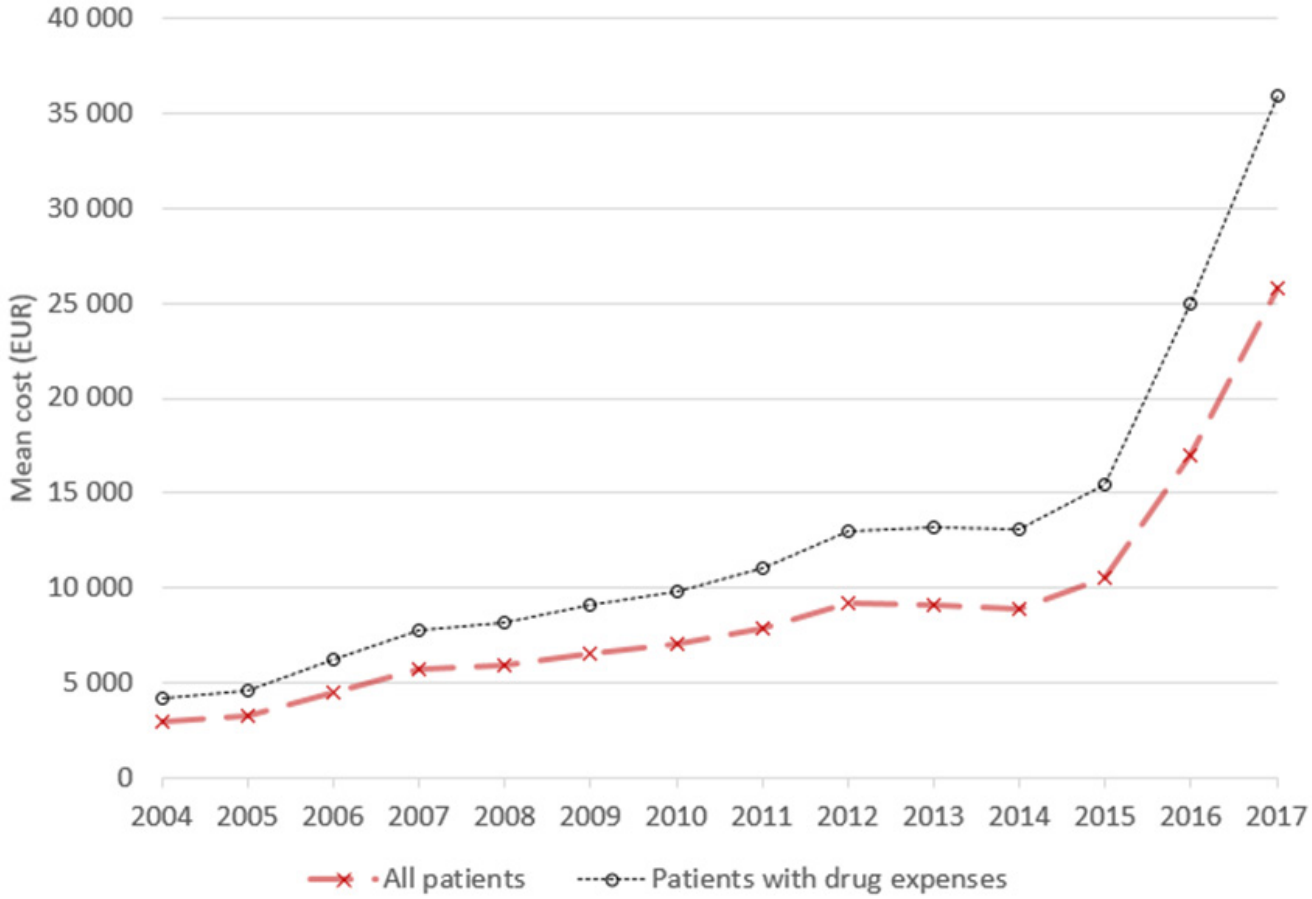
A) Oncological drug expenses per calendar year (all stages)



B) Expenses for the first two years after incidence, per incidence year (stage IV)



C) Mean cost per patient for the first two years after incidence, per incidence year (stage IV)



Source: BCR-IMA.

4.9.2.2 *Drug uptake for a selection of drugs during the first 5 years after diagnosis*

Uptake of anti-EGFR medication (erlotinib, gefitinib) has been modest (maximum 23-24%) with a highest uptake in incidence years 2007-2012, going down again to 2.9% in 2017 (Table 50). This decrease cannot be explained by an increase in uptake of second or third line anti-EGFR treatments. Second and third line anti-EGFR treatment (afatinib, osimertinib) got a very low uptake remaining below 1.3% for all incidence years. In 2013, KCE published a guideline recommending anti-EGFR treatment should only be prescribed if an activating mutation is present, also in second line. This can explain why uptake for erlotinib decreases from the incidence year 2013 onwards.

Uptake of Crizotinib, an ALK-inhibotor remained very low, with a maximum uptake of 1.3% in 2014.

Immunotherapy got a limited uptake from the incidence year 2012 onwards with an uptake of 15% and 21% in 2017 for nivolumab and pembrolizumab respectively.

Table 50 – 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. $ IMA data were only available up to the second trimester of 2019 and might have a delay of two years. Five-year follow-up data are thus not 100% complete from incidence year 2012 onwards (see part 3.1.3). Source: BCR-IMA.*

4.9.3 *Medical literature: efficacy*

Systematic reviews in the medical literature show no clear benefit in overall survival in first-line treatment of EGFR-mutation positive tumours for both erlotinib and gefitinib in monotherapy compared to chemotherapy, but QoL and symptom control seem to be in favour of the anti-EGFR inhibitors. On the contrary, erlotinib added to chemotherapy can improve overall survival compared to chemotherapy in chemo-naïve patients, but it is only reimbursed in monotherapy in Belgium. As second- or third-line treatment, erlotinib may also improve OS, but only if the tumour carries an activating EGFR mutation.[296] Studies could not show a clear OS benefit for afatinib compared to chemotherapy, although second-generation anti-EGFR

agents have found to be better than first-generation anti-EGFR treatments in terms of overall survival.

Crizotinib may have some survival benefit in patients with an ALK-positive and/or ROS1-positive NSCLC, but evidence remains inconclusive.

Systematic reviews show a survival benefit for immunotherapy such as nivolumab and pembrolizumab compared to platinum-based chemotherapy. For nivolumab, a survival benefit is seen in the recurrent setting, for pembrolizumab in both the first-line and the recurrent setting. There may be no effect in the first-line setting in tumours with a PD-L1.[299]

4.9.3.1 Anti-EGFR therapy in NSCLC

Reference + search date	Intervention and comparator + indication	OS	Quality of life	Other outcomes
Greenhalgh 2016[295] Search date: June 2015	Chemotherapy-naive patients with locally advanced or metastatic (stage IIIB or IV) EGFR M+ NSCLC who were not suitable for treatment with curative intent, such as surgery or radical radiotherapy. Intervention: erlotinib Comparator: chemotherapy	Erlotinib vs chemotherapy HR 0.95 [0.75, 1.22] Erlotinib vs vinorelbine HR 2.16 [0.58, 8.10] Erlotinib + chemotherapy vs Chemotherapy + placebo HR 0.48 [0.27, 0.85]	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." OPTIMAL study: "in favour of erlotinib" Ensure study: time to deterioration in QoL was 8.2 months for erlotinib compared to 2.8 months for chemotherapy HR 0.64 (95%CI 0.44-0.93) P = 0.0168	**Symptom palliation** TORCH study: no major differences were observed OPTIMAL study: time to improvement of symptoms was significantly shorter for erlotinib compared to chemotherapy: e.g. FACT-L 1.51 versus 3.19 months (P = 0.0067) ENSURE trial: preliminary data using the FACT-L showed that time to symptomatic progression was 13.8 months for erlotinib compared to 5.5 months for chemotherapy HR 0.56 (95%CI 0.36-0.87) P = 0.0076
Greenhalgh 2016[295] Search date: June 2015	Chemotherapy-naive patients with locally advanced or metastatic (stage IIIB or IV) EGFR M+ NSCLC who were not suitable for treatment with curative intent, such as surgery or radical radiotherapy.	Gefitinib vs gemcitabine + cisplatin HR 1.04 [0.50, 2.20] Gefitinib vs paclitaxel + carboplatin HR 0.95 [0.77, 1.18]	IPASS study: "Gefitinib was significantly favoured over carboplatin plus	**Symptom palliation** NEJSG study: "participants who received gefitinib had a significantly

	Intervention: Gefitinib Comparator: chemotherapy	Gefitinib vs docetaxel + cisplatin HR 1.25 [0.88, 1.78]	paclitaxel in the proportion of participants showing improvement." NEJSG study: "the physical and life scales were all better for gefitinib than for cytotoxic chemotherapy."	longer time to deterioration up to 20 weeks than participants who received paclitaxel plus carboplatin using both 9.1% and 27.3% levels of deterioration."
Greenhalgh 2016[295] Search date: June 2015	Chemotherapy-naive patients with locally advanced or metastatic (stage IIIB or IV) EGFR M+ NSCLC who were not suitable for treatment with curative intent, such as surgery or radical radiotherapy. Intervention: Afatinib Comparator: chemotherapy	Afitinib vs pemetrexed + cisplatin HR 0.91 [0.66, 1.25] Afatinib vs gemcitabine + cisplatin HR 0.95 [0.68, 1.33]	LUX-Lung 3 study: in favour of afatinib over cisplatin plus pemetrexed chemotherapy LUX-lung 6 study: A greater percentage of participants showed improvement in global health scores/QoL scores (P < 0.0001), physical function (P < 0.0001), and social function (P < 0.0001) with afatinib when compared to cisplatin plus gemcitabine.	**Symptom palliation** LUX-Lung 3 study: time-to-deterioration curves for cough and dyspnoea showed a significant effect in favour of afatinib. The HR for pain was 0.83 (95% CI 0.62 to 1.10). LUX-lung 6 study: time to deterioration for cough (HR 0.45; P= 0.0003), dyspnoea (HR 0.54; P < 0.0001), and pain (HR 0.70; P =0.003) showed a significant effect in favour of afatinib HR 0.56 (95%CI 0.41-0.77) P = 0.0002.
Zhang 2019[300] Search date: 1 March 2019	advanced EGFR-mutated NSCLC patients Interventions: First-generation TKIs (F-TKI): gefitinib, erlotinib, icotinib Second-generation TKIs (S-TKI): afatinib, dacomitinib third-generation TKIs: osimertinib chemotherapy (CT)	F-TKI vs chemotherapy: HR 1.01 (95%CI 0.88-1.15) S-TKIs vs F-TKIs: HR 0.81 (95%CI 0.67-0.97) F-TKIs + CT vs F-TKIs: HR 0.70 (95%CI 0.54-0.92) F-TKIs + CT vs CT HR 0.71 (95%CI 0.35-1.46)		
Sim 2018[301]	Patients with advanced NSCLC; second-line therapy	All patients HR 1.02 (95%CI 0.91-1.15)		

Search date: February 2017	Intervention: gefitinib comparator: chemotherapy	EGFR mutation + patients HR 0.83 (95%CI 0.41-1.66)	
*Wang 2017 Search date: 2017	second-line treatment for NSCLC Intervention: gefitinib comparator: docetacel		"The pooled OR for quality-of-life improvement was 2.49 (95%CI 1.77-3.49)."
*Ellis 2015[302] Search date: March 2014	patients with advanced NSCLC who received prior treatment Interventions: gefitinib, erlotinib, afatinib alone or in combination with chemotherapy comparator: placebo, best supportive care or chemotherapy	**unselected population 2nd line** EGFR inhibitor vs chemotherapy HR 1.02 (95%CI 0.95-1.09) EGFR inhibitor + chemotherapy vs chemotherapy HR 0.63 (95%CI 0.44-0.90) EGFR inhibitor vs placebo only erlotinib showed better OS (see RCT Shepherd 2005 below)	
Shepherd 2005[303] RCT	Patients with stage IIIB or IV non–small-cell lung cancer who received one or two prior chemotherapy regimens Intervention: erlotinib Comparator: 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	
Connock 2019[299] Search date: February 2019	patients with advanced or metastatic (IIIB and/or IV) NSCLC with non-squamous (adenocarcinoma, large cell) or squamous histology who had experienced failure to prior first line chemotherapy (i.e., those receiving second line treatment and beyond); had either predominantly negative or 100% negative expression of anaplastic lymphoma kinase (ALK); had either predominantly negative or 100% negative expression of epidermal growth factor receptor (EGFR). Intervention: erlotinib Comparator: docetaxel	From observed data: Restricted mean survival gain compared to docetaxel over 19 months: erlotinib: 0.48 months (95%CI 0.23-1.18) From extrapolated data: overall survival gain erlotinib over docetaxel: no gain	

**no critical appraisal but included as no other recent systematic review identified*

4.9.3.2 *ALK inhibitors for non-small cell lung cancer*

Reference + search date	Intervention and comparator + indication	OS	Quality of life	Other outcomes
Elliot 2020[297] Search date: 23 July 2020	Treatment-naïve or experienced participants with phase III or IV *ALK*-positive and/or *ROS1*-positive NSCLC Intervention: Crizotinib Comparator: chemotherapy	HR 0.83 (0.69, 1.00)		"ALK inhibitors increased the risk of SAE relative to chemotherapy" OR 1.67 (95%CI 1.34-2.08) Crizotinib: OR 2.08 (95%CI 1.56-2.79)

4.9.3.3 *Immunotherapy*

Reference + search date	Intervention and comparator + indication	OS	Quality of life	Other outcomes
Wang 2020[304]* Search date: July 2019	Pathologically confirmed advanced patients with NSCLC (first-line or recurrent) Interventions: immunotherapy or immunotherapy + chemotherapy Included immunotherapy: Nivolumab, pembrolizumab, avelumab, atezolizumab, ipilimumab Comparator: platinum-based chemotherapy	Immunotherapy +/- chemotherapy vs chemotherapy HR 0.76 (95%CI 0.70-0.82) 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)		**Grade 3-5 treatment-related adverse events** Immunotherapy monotherapy vs chemotherapy: RR 0.31 (95%CI 0.25-0.38) Immunotherapy + chemotherapy vs chemotherapy: RR 1.18 (95%CI 1.07-1.30)
Carbone 2017[305] RCT	Patients with untreated stage IV or recurrent NSCLC, who received no prior systemic treatment for metastatic or recurrent disease. Intervention: nivolumab Comparator: platinum-based chemotherapy	HR 1.02 (95%CI 0.80-1.30)		
Borghaei 2021[306] RCT	Patients with previously treated, advanced squamous or nonsquamous NSCLC Intervention: nivolumab Comparator: docetaxel	HR 0.68 (95%CI 0.59-0.78) Median OS 11.1 months (95%CI 9.2-13.1) with nivolumab vs 8.1% (95%CI 7.2-9.2) 5-year OS rate 13.4% (95%CI 10.4-16.9) with nivolumab vs 2.6% (95%CI 1.4-4.5) with docetaxel.		

Herbst 2020[307] RCT	Previously treated, PD-L1-expressing advanced NSCLC Intervention: pembrolizumab Comparator: docetaxel	Tumour proportion score PD-L1 ≥ 50% HR 0.53 (95%CI 0.42-0.66) Median survival 16.9 months (95%CI 12.3-21.4) vs 8.2 months (95%CI 6.1-9.8) Tumour proportion score PD-L1 ≥ 1% HR 0.69 (95%CI 0.60-0.80) Median survival 11.8 months (95%CI 7.6-9.5) vs 8.4 months (95%CI 7.6-9.5)
Reck 2019 RCT	Patients with previously untreated advanced NSCLC with PD-l1 tumour proportion score ≥ 50% Intervention: pembrolizumab Comparator: platinum-based chemotherapy	HR 0.63 (95%CI 0.47-0.86) Median OS 30 months (95%CI 18.3- not reached) with pembrolizumab vs 14.2 months (95%CI 9.8-19.0) with chemotherapy
Mok 2019 RCT	Patients with previously untreated advanced NSCLC with PD-l1 tumour proportion score ≥ 1% Intervention: pembrolizumab Comparator: platinum-based chemotherapy	HR 0.81 (95%CI 0.71-0.93) Median survival was 16.7 months (95%CI 13.9-19.7) with pembrolizumab vs 12.1 months (95%CI 11.3-13.3) PD-L1 score 1-49% HR 0.92 (95%CI 0.77-1.11) Median survival 13.4 months (95%CI 10.7-18.2) with pembrolizumab vs 12.1 months (95%CI 11.0-14.0- with chemotherapy
Connock 2019[299] Search date: February 2019	patients with advanced or metastatic (IIIB and/or IV) NSCLC with non-squamous (adenocarcinoma, large cell) or squamous histology who had experienced failure to prior first line chemotherapy (i.e., those receiving second line treatment and beyond); had either predominantly negative or 100% negative expression of anaplastic lymphoma kinase (ALK); had either predominantly negative or 100% negative expression of epidermal growth factor receptor (EGFR). Intervention: nivolumab, pembrolizumab Comparator: docetaxel	From observed data: Restricted mean survival gain compared to docetaxel over 19 months: Pembrolizumab: 1.58 months (95%CI 0.48-2.68) From extrapolated data: overall survival gain pembrolizumab over docetaxel: 5.04 months (95%CI 1.57-8.52)

**For more detailed results, results from selected primary studies are reported in the following lines in this table.*

4.9.3.4 Discussion

No clear improvement in overall survival was seen after the introduction of erlotinib in 2006. This may be partly due to a rather limited uptake of maximum 22% in 2010. In addition, meta-analysis of trial results does not show a clear survival advantages of erlotinib monotherapy compared to chemotherapy in first or second line, only compared to placebo. Furthermore, although erlotinib only is advantageous in tumours carrying an activating EGFR mutation, it is reimbursed as second line therapy independent of mutation status. Uptake of gefitinib, afatinib and crizotinib remained below 5%, too low to possibly having an effect on the survival curves.

The uptake of nivolumab and pembrolizumab in the most recent observed incidence years was associated with an improvement of survival. Also in RCTs, a positive effect on survival is seen.

Findings in other countries

In the Netherlands, also a small overall survival improvement was seen for the period 2014-2018 compared with 2004-2008, but the median survival did not change significantly (from 4.1 months in 2004-2008 to 4.4 months in 2014-2018).[184]

In a recent study in the United States, including all stages of NSCLC, an improvement was seen in the 2-year relative survival among men with lung cancer, from 26% in 2001 to 35% in 2014. For women, the 2-year relative survival was 35% in 2001 and 44% in 2014. Among men, the incidence of NSCLC decreased by 1.9% annually from 2001 to 2008 and by 3.1 annually from 2008 through 2016. The incidence-based mortality in men decreased by 3.2% annually from 2006 through 2013, then decreased by 6.3% annually from 2013 through 2016. The authors relate the quicker decrease of the incidence-based mortality compared to the decrease of the incidence to the introduction of new therapies, namely anti-EGFR treatment.[308] However, this conclusion has been criticized as the incidence of the prevalence of the activating EGFR mutation and the effect on OS seen in clinical trials would be too low to explain such an effect on lung-cancer specific mortality in the population.

Limitations

Separate survival curves for patients with an EGFR-activating mutation carrying tumour could not be obtained with the data available at the Belgian Cancer Registry. A possible survival improvement in this group of patients could hence not be detected. In the medical literature a survival benefit is also not shown but cross-over after progression may partly explain the lack of survival benefit seen in clinical studies. The same holds true for the group of patients with an ALK mutation carrying tumour.

For Nivolumab and Pembrolizumab, publications on quality of life and longer time follow-up were not included in the systematic reviews.[309, 310] As these drugs have been introduced into NSCLC treatment only recently, the full effect on overall survival will probably become apparent during the coming years.

4.9.4 Economic literature: cost-effectiveness

For more information about the economic evaluations in the identified HTA reports, we refer to Appendix.

Confidential prices

In all identified UK evaluations, there are confidential price discounts for the intervention and/or the included comparators. For two comparators, the price discount is transparent. For gefitinib, there is a single fixed cost of £12 200 per patient when the third monthly pack of gefitinib is supplied.[311] In another evaluation, “the normal acquisition cost of a pack of 30 tablets [erlotinib] (150 mg) is £1 631.53 (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, £1 394.96 for a pack of 30 tablets [150 mg]).”[312] Since there is a confidential price discount for at least one of the pharmaceuticals in the evaluation, exact ICERs cannot be calculated by external parties not having access to these discounts.

Another problem is linked to discounts that may also apply to other indications. This was the case in evaluations of both immunotherapies nivolumab and pembrolizumab. In the case of nivolumab, "the committee was aware that the company had proposed scenario analyses incorporating cost savings for nivolumab in other indications based on the updated proposed patient access scheme for NSCLC. It was also aware that there would be a wider benefit to the NHS because the simple discount agreed in the patient access scheme would apply across all indications. However, it noted that taking this into account was outside its approved methods. The committee was also concerned that there were no details on how the discounts were calculated and applied. It concluded that it was not appropriate to incorporate these benefits into the economic model, taking into account the most plausible ICER and the uncertainty identified."[313, 314] In the case of pembrolizumab, the committee was also aware "that there would be a wider benefit to the NHS because the simple discount agreed in the patient access scheme would apply across all indications."[315]

Quality of life

Measuring QoL with a generic utility instrument, as recommended in the EUnetHTA 'Health-Related Quality of Life and Utility Measures' guidelines, is not yet fully established in oncology RCTs. In all studies with erlotinib and gefitinib, QoL was not measured with a generic utility instrument in the underlying trial.[311, 312, 316, 317] This was also the case in the most recent study with crizotinib.[318] QoL was measured with the EQ-5D instrument in the previous studies with crizotinib, but there was a lack of data in the post-progression period.[319, 320] Several studies refer to utilities measured via the EQ-5D, but the results are not transparently published in the identified HTA reports.[313, 316, 318, 320-322] An assessment of pembrolizumab involves informative censoring, because EQ-5D assessments for people whose disease progressed were done only shortly after disease progression.[321] Another problem is the failure to complete questionnaires and thus high levels of missing data.[313, 314, 322]

No study models utilities as measured in the two treatment arms of the comparative RCT. Utilities are modeled in most studies via PFS or PD (progressed disease). In an assessment of pembrolizumab,[323] utilities are based on time to death. Modeling QoL through PFS and PD includes modeling an improvement in QoL. This contrasts with the lack of clear evidence for an improvement in QoL measured with a generic utility instrument. We come back to this assumption in our general discussion.

Uncertainty & influential parameters

One of the greatest uncertainties is the estimation of the treatment effect. Many assessments refer to the absence of a head-to-head comparison. This is the case in assessments of afatinib,[324]crizotinib,[318] erlotinib and gefitinib,[311, 312, 316, 317], and pembrolizumab.[322] The greatest uncertainty in the identified analyses refers to the impact on OS and/or modeling/extrapolation of OS.[311, 313, 314, 316-324]

In addition to the lack of a head-to-head trial, this is also related to using immature data in a number of analyses. For example, the following is stated in the two 2019 assessments of pembrolizumab: "Because the clinical evidence is immature, the cost-effectiveness estimates for pembrolizumab combination therapy are very uncertain."[321] … "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."[321] 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."[322]The extrapolation scenarios often have a major impact on the ICERs, which is even more the case in models based on immature data.

Other important variables with a major impact on the ICERs are the modeled utility parameters.[313, 316, 318, 323] Where there is a population to be tested to be eligible for treatment, information about the prevalence and cost of the test is also important. For example, in the assessment of gefitinib "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."[317] "The results from any cost-effectiveness model of gefitinib treatment for EGFR M+ patients should not be taken to be a blanket assessment of gefitinib in isolation from the method of selecting

eligible patients, but only an assessment of a specific test+gefitinib combination which may not be valid when other testing procedures are used."[325]

Obviously, the price of the intervention (and therefore also the discount) is of great importance. For example, the following is stated in an assessment of nivolumab: "An analysis of the company's base case model results shows that, when treatment with nivolumab is compared with docetaxel, 89.4% of the incremental cost is attributable to differences in direct treatment costs (drug acquisition and administration). This means that the cost of nivolumab plays a pivotal role in determining the incremental cost per patient, and that all other costs have no real effect on the size of the ICER per QALY gained."[326]

Results

The above mentioned price negotiations and uncertainties have their impact on the transparency and reliability/uncertainty of the results from the underlying economic evaluations. There is no single assessment where the authors conclude an intervention being cost-effective if the official list prices are used. In all dossiers, confidential prices are negotiated.

The ICERs are as follows (see more details in appendix):

- **Afatinib**
  - Epidermal growth factor receptor mutation-positive locally advanced or metastatic NSCLC:[324]

    "the ERG [Evidence Review Group] is of the opinion that there is no reliable cost-effectiveness evidence available to support the use of afatinib compared with erlotinib or compared with gefitinib."
- **Crizotinib**
  - ROS1-positive advanced NSCLC (including discounts – exact ICERs were presented as commercial in confidence):[318]

    crizotinib compared with pemetrexed plus platinum-based chemotherapy in untreated disease: "around or above £50 000 per quality-adjusted life year (QALY) gained."

    crizotinib compared with docetaxel in previously treated disease: "well above £50 000 per QALY gained"
  - Previously treated anaplastic lymphoma kinase (ALK)-positive advanced NSCLC (including revised PAS):[319]

    Crizotinib versus docetaxel: <£50 000 per QALY gained.
  - Untreated anaplastic lymphoma kinase-positive advanced NSCLC (including PAS):[320]

    Company's revised base case: £49 200/QALY gained; ERG's revised exploratory analysis: £58 000/QALY gained
- **Erlotinib and gefitinib**
  - Locally advanced or metastatic NSCLC that has progressed after prior chemotherapy (commercial in confidence information removed):[316]

    Gefitinib: no economic evaluation performed
    - Erlotinib vs. docetaxel second-line treatment in the EGFR mutation-negative population: dominated (higher costs and less QALYs for erlotinib)
    - Erlotinib vs. BSC second-line treatment in the EGFR mutation-negative population: £54 687 per QALY gained
    - Erlotinib vs. BSC second-line treatment in the EGFR mutation-unknown population: £61 162 per QALY gained
- **Erlotinib**
  - First-line treatment of locally advanced or metastatic EGFR-TK mutation-positive NSCLC (including discount):[311]

    Erlotinib versus gefitinib: £21 874 per QALY gained (£74 300 per QALY gained without the confidential discount)

- Locally advanced or metastatic NSCLC who have stable disease after platinum-based first-line chemotherapy (with PAS):[312]
  - Stable, squamous disease: £44 812 per QALY gained versus best supportive care
  - Stable, non-squamous disease: £68 120 per QALY gained versus best supportive care

- **Gefitinib**
  - Locally advanced or metastatic NSCLC in EGFR-TK mutation-positive patients (with Patient Access Scheme (PAS)):[317]

    Gefitinib/carboplatin versus six other comparators: ICERs of £59 000 per QALY gained (versus gemcitabine/cisplatin) to being dominated (versus pemetrexed/cisplatin)

- **Nivolumab**
  - Previously treated locally advanced or metastatic non-squamous NSCLC (including new commercial access agreement):[314]

    Nivolumab compared with docetaxel: £49 160 per QALY gained

    Nivolumab compared with nintedanib plus docetaxel: >£100 000 per QALY gained
  - Patients with previously treated locally advanced or metastatic squamous non-small-cell lung cancer (with and without commercial access agreement):[313]

    Nivolumab compared with docetaxel: £85 950 (company's base case) or £132 989 (ERG's revised base case) per QALY gained with list prices. £50 014 per QALY gained including commercial access agreement.

- **Pembrolizumab**
  - Untreated metastatic squamous NSCLC (including confidential price for pembrolizumab):[321]

    Pembrolizumab combination therapy versus platinum+gemcitabine: £51 240 per QALY gained
  - Untreated, metastatic, non-squamous NSCLC, tumours with no epidermal growth factor receptor (EGFR)- or anaplastic lymphoma kinase (ALK)-positive mutations (including tentative commercial access agreement for pembrolizumab, not including existing agreements for comparators):[322]

    Pembrolizumab combination versus standard of care: £37 622 per QALY gained
  - Untreated PD-L1-positive metastatic NSCLC (not including the discount for pemetrexed):[323]

    ICERs ranging from £30 244 to £44 483 per QALY gained. Decision-making ICERs cannot be presented because they include the commercial access agreement reduction for pemetrexed.
  - PD-L1-positive NSCLC who received chemotherapy (including discount):[315]

    Pembrolizumab versus docetaxel: ICERs ranging from £61 954 to £44 490 per QALY gained.

The absence of a head-to-head comparison or the use of immature data (see above) means that the cost-effectiveness cannot always be determined with great certainty. For example, in the assessment of afatinib, the ERG was of the opinion that "there is no reliable cost-effectiveness evidence available to support the use of afatinib compared with erlotinib or compared with gefitinib."[324] Contrasts between ERG's and the Committee's conclusions are observed. For example, in the case of afatinib, 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."[324] In contrast, "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."[324]

Exact ICERs and the ICERs used by decision makers are not always presented since they are considered as commercial in confidence. This is the case for evaluations of crizotinib[318, 319] and pembrolizumab.[322, 323] In the

case of the latter, the presented ICERs include a discount for the intervention, but existing agreements for comparators are not included.

In several other cases, ICERs, including confidential price discounts, are presented, but information about the incremental costs or effects remains confidential (e.g. crizotinib,[320] erlotinib,[311] nivolumab[314]). In a number of cases, the ICER is presented with and without a discount. This is the case in the assessment of erlotinib where the ICER without the confidential discount is £74 300 per QALY gained, while this is about £21 900 per QALY gained including the confidential patient access scheme.[311] Also in an assessment of nivolumab, both ICERs with (£50 000/QALY) and withouth discount (£86 000/QALY (company's base case) 133 000/QALY (ERG's revised base case)) are presented.[313] Only the evaluation of gefitinib[317] explicitly states which price agreements have been made and present the IC, IE & ICERs in a transparent manner.

ICERs of £50 000 per QALY and above are no exception. The lowest ICERs are observed where products are compared to other products that are relatively expensive (e.g., erlotinib versus gefitinib[311]) or where the presented ICERs could not take into account the discount for one of the comparators (e.g., pembrolizumab versus a treatment including a combination with pemetrexed[323]). It is not clear under which price agreements a particular ICER is reached. Any statement about whether or not an intervention is cost-effective in a particular indication must therefore be interpreted with the necessary nuance.

When the end-of-life criteria apply (i.e. meeting both the life expectancy (<2 years) and the extension-to-life (>3 months) criteria), higher ICERs (£50 000/QALY gained) are possibly accepted in the NICE assessments. This is the case in assessments of crizotinib[318-320] en pembrolizumab.[323] For example, "the committee felt confident that pembrolizumab is likely to offer, on average, considerably more than 3 months' extension to life compared with standard care. The committee concluded that pembrolizumab met the life expectancy and life extension criteria to be considered a life-extending, end-of-life treatment."[323] If the ICER was too high to recommend the intervention for routine use, and more evidence was needed to address clinical uncertainties, then the intervention was often recommended as an option for use within the Cancer Drugs Fund (crizotinib,[318] nivolumab,[313, 314] and pembrolizumab[321, 322]). For example, in an assessment of pembrolizumab,[322] "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" … "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."[322]

4.9.5 Summary

Observational data

- Observational data indicate that overall survival in Belgian stage IV NSCLC patients has not improved between 2004 and 2013. An improvement in the observed survival probability is observed in the incidence period 2014-2017. The 3-yearly survival increased from 6.3% in 2013 to 15.5% in 2017. However, the median survival for this population remains stable over the period 2004-2017 at around half a year.
- NSCLC, all stages: yearly oncology drug expenditures tripled when comparing expenses before and after 2016 from about €44 million in 2016 to more than €134 million in 2018.
- NSCLC, stage IV: oncology drug expenditures during the first two years after incidence increased steadily over the years with a steep increase during the last observed period from €30 million in 2015 to €77 million in 2017.
    - The number of patients with stage IV NSCLC for which oncology drug expenditures were identified increased over the years: 1242 (2004), 1716 (2010), 1939 (2015) and 2151 (2017).
    - The mean cost per stage IV NSCLC patient with drug expenses for the first two years after incidence increased from less than

€5 000 before 2006, to about €10 000 in 2010, and more than €35 000 in 2017.

- Uptake of anti-EGFR medication (erlotinib, gefitinib) has been modest (maximum 23-24%) with a highest uptake in incidence years 2007-2012, going down again to 2.9% in 2017. Uptake of second and third generation anti-EGFR drugs (afatinib, osimertinib) remained very low (<2%) in Belgium.
- Prevalence of ALK mutations in NSCLC tumours is only 5%. Uptake of crizotinib remained below 1.5%.
- Immunotherapy got a limited uptake from the incidence year 2012 onwards with an uptake of 15% and 21% in 2017 for nivolumab and pembrolizumab respectively

Medical literature

- Anti-EGFR treatment (erlotinib, gefitinib, afatinib)
  - Data available in the medical literature do not show a clear survival benefit with the use of erlotinib, gefitinib or afitinib in monotherapy compared to chemotherapy. In terms in quality of life, these products are beneficial compared to chemotherapy, however.
- ALK inhibitors (crizotinib)
  - Studies show no clear OS benefit for crizotinib compared to chemotherapy. Crizotinib increases the risk for serious adverse events.
- Immunotherapy (nivolumab, pembrolizumab)
  - Nivolumab and pembrolizumab result in a benefit in overall survival compared to standard treatment with chemotherapy. The effect is seen for both nivolumab and pembrolizumab in the recurrent setting and pembroluzimab also in the first-line setting.

Economic literature

- In the economic evaluations of the identified HTA reports in NSCLC, a confidential price discount is present for the interventions and/or the included comparators.
- Measuring QoL with a generic utility instrument is not present in a large part of the underlying trials on which the economic evaluations rely. Studies referring to utilities measured with the EQ-5D do not always transparently publish results (i.e. provide results separately for all treatment arms at all points in time).
- One of the greatest uncertainties in the economic evaluations is the estimation of the treatment effect. In first instance, this is most of the times linked to a lack of head-to-head comparisons. Furthermore, reference is made to use of immature data and uncertainty around the impact/extrapolation of overall survival data. The uncertainty around modelled utility parameters also have a (major) impact on the ICERs.
- As a result of the above mentioned uncertainties, calculated ICERs are also very uncertain.
- There is no single assessment in which the authors of the HTA report conclude the intervention under consideration is cost-effective using official list prices.
- As a result of the confidential prices, exact ICERs used for decision making are not transparently reported.
- In the identified NICE assessments, interventions with higher ICERs (£50 000/QALY gained) are possibly accepted when the end-of-life criteria apply (i.e. meeting both the life expectancy (<2 years) and the extension-to-life (>3 months) criteria). Furthermore, if the estimated ICER was too high to recommend the intervention for routine use, and more evidence was needed to address clinical uncertainties, then the intervention was often recommended as an option for use within the Cancer Drugs Fund.

4.10 Ovarian cancer

4.10.1 Introduction

In Belgium, ovarian cancer is the eight most frequent cancer in women and the fifth in terms of female cancer mortality. In 2018, 748 women were diagnosed with ovarian cancer in Belgium. Approximately 70% of ovarian cancers are diagnosed in an advanced stage since the disease remains asymptomatic for a long time. Epithelial ovarian cancer (EOC) is the most represented histological type whereas germ cell and sex cord-stromal tumours are rarer.[327] Among EOC, high-grade serous ovarian carcinoma is the most frequent type and accounts for 75% of all EOC.[328] In this report, only epithelial ovarian cancers are included.

Primary cytoreductive surgery followed with platinum-based chemotherapy was the mainstay of care in patients with advanced stages over decades.[328] An alternative approach that was proven to be non-inferior in terms of survival consists of neoadjuvant chemotherapy and interval cytoreductive surgery.[329, 330] Since the nineties, the standard first-line chemotherapy include carboplatin-paclitaxel.[331, 332]

Vascular endothelial growth factor (VEGF) and angiogenesis are found to be key actors of tumour growth and spreading.[333] Bevacizumab is a monoclonal anti-VEGF antibody that has been developed to halt tumour growth in tumours such as ovarian cancer. Clinical trials have shown a prolonged progression-free survival when bevacizumab is added to chemotherapy in phase III trials with stage III-IV ovarian cancer patients.[334, 335]

Approximately 70% of women relapse within the 3 years after initial treatment.[336] In recurrent ovarian cancer, surgery is considered in selected patients.[328] However, when surgery is not indicated, chemotherapy along with bevacizumab have been proposed by several clinical trials for both platinum-sensitive and platinum-resistant tumours.[337-339]

Recently, Poly (ADP-ribose) polymerase (PARP) inhibitors (olaparib, niraparib, rucaparib) have also been considered in recurrent high-grade serous ovarian carcinoma with platinum-sensitivity and mutations in BRCA 1/2 genes.[340-342]

Bevacizumab is reimbursed in Belgium in addition of chemotherapy for first-line treatment of ovarian cancer and platinum sensitive recurrent ovarian cancer since 2014 and for platinum-resistant recurrent ovarian cancer since 2015.

Table 51 presents the list of selected drugs for ovarian cancer.

Table 51 – Selected drugs ovarian cancer

Drug	Year#	Trade Name$	Company$
Bevacizumab	2008	Avastin	Roche

$ of the originator; # year of start reimbursement first indication in Belgium

4.10.2 Observational data

4.10.2.1 Patient characteristics, survival and expenditures

The overall number of reported stage IV ovarian cancers has increased over the three incidence periods[y] and patient characteristics remained stable (Table 9A). No clear improvement in observed survival is perceptible over the three incidence periods (Table 52B). The 3-years observed survival probability maintained globally the same level overtime with values of 29.0% (95%CI 21.7-36.7) in 2004 and 28.8% (95% CI 19.1-39.2) in 2017 (Table 52C). Likewise, the median survival time did not display any meaningful variation throughout the incidence periods with values between 1.3 and 2.3 years for all observed incidence years (Table 52D). For stage IIIC ovarian cancer, we see a similar pattern: no improvement of overall survival over time (see appendix). An additional analysis comparing the period before a high uptake of bevacizumab (2004-

[y] the 3rd incidence period (2014-2017) covers 3 years, while the first two incidence periods cover 4 years.

2001) with the period with a high uptake of bevacizumab (2013-2017) shows only a slight improvement in overall survival (Figure 7). It must be noted that the proportion of stage IV patients who underwent debulking surgery also increased over time, from 32.8% in 2004-2011 to 46.3% in 2013-2017 (see appendix).

Separate results depending on the debulking status are presented in Table 53 (no debulking) and Table 54 (debulking). The proportion of stage IV patients who underwent debulking surgery has increased over the years from 21% in 2004-2008 to 50% in 2009-2013 and 45% in 2014-2017. For patients who did not undergo debulking, a worse survival was seen in the second and third incidence period (Table 53B). This may, at least partially, be explained by the increase of patients who are debulked and hence only the most frail persons probably remain in this category.

For patients who underwent debulking surgery, an improvement in overall survival is seen when comparing the second incidence period (2009-2013) compared with the first incidence period (2004-2008). However, no further improvement is noticed in the third incidence period (2014-2017) (Table 54B).

Yearly oncology drug expenditures for ovarian cancer patients (all stages) was about €4.1 million in 2004 and increased in the following years mainly due to the number of patients receiving oncological drugs with an expenditure of about €9.3 million in 2008 (Table 3A). In the following years, total oncology drug expenditures decreased to less than €5 million in 2012. Afterwards, a steep increase was seen linked to the expenditures for bevacizumab from 2014 onwards to more than €17 million in 2016 and 2017 (data for 2018 are incomplete).

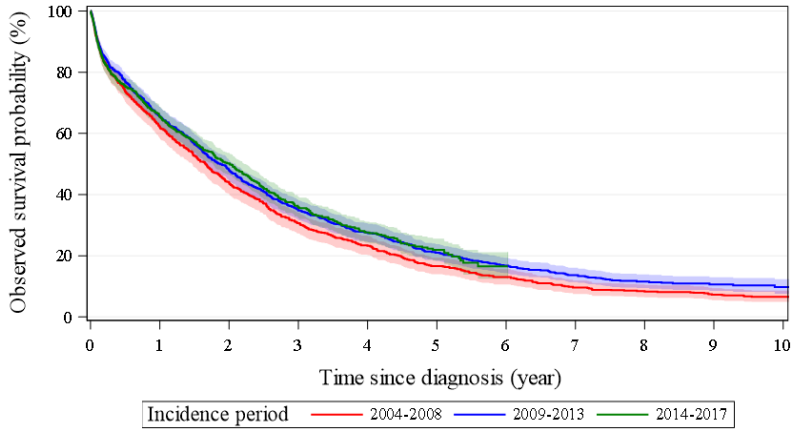
For stage IV ovarian cancer, we see a similar pattern (Table 55B). Overall expenditures during the first two years after diagnosis were between €0.8 and €1.8 million for incidence years 2004-2013. From incidence year 2014 onwards expenditures surpassed €4 million, without a clear rise in the number of patients treated with oncological drugs. The same evolution is observed for the mean cost per patient. For patients diagnosed in 2004, the mean cost per patient treated with oncological drugs was about €12 500, which doubled to about €25 000 per patient for patients diagnosed in 2014 or later (Table 55C).

Table 52 – Epithelial Ovarian Cancer (2004-2017), combined stage IV (observed survival): A) Patient characteristics; B) Kaplan-Meier graph per incidence period; C) Time trend with incidence year*; D) Median survival time* **

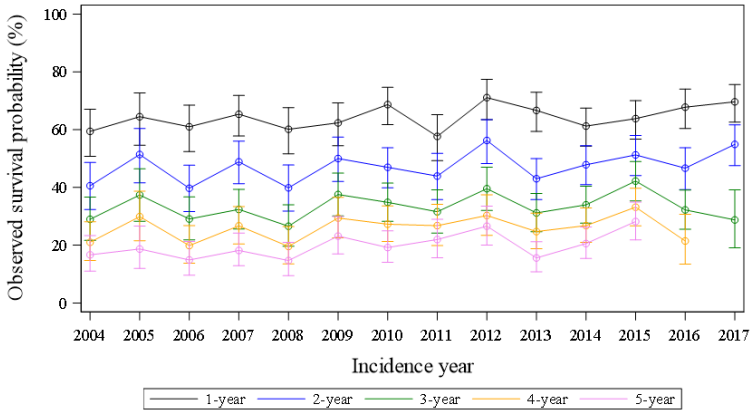
A

Characteristic	Incidence period		
	2004-2008	2009-2013	2014-2017
Overall	705	856	779
Gender			
Female	705 (100.0)	856 (100.0)	779 (100.0)
Debulking	149 (21.1)	431 (50.4)	354 (45.4)
Age at diagnosis (year)			
<50 years	56 (7.9)	69 (8.1)	49 (6.3)
50-59 years	114 (16.2)	135 (15.8)	106 (13.6)
60-69 years	183 (26.0)	222 (25.9)	205 (26.3)
70-79 years	212 (30.1)	260 (30.4)	239 (30.7)
80+ years	140 (19.9)	170 (19.9)	180 (23.1)
WHO - Performance Status			
0 – Asymptomatic	73 (10.4)	115 (13.4)	102 (13.1)
1 – Symptomatic but completely ambulatory	320 (45.4)	481 (56.2)	470 (60.3)
2 – Symptomatic, <50% in bed during the day	123 (17.4)	121 (14.1)	100 (12.8)
3 – Symptomatic, >50% in bed, but not bedbound	62 (8.8)	42 (4.9)	39 (5.0)
4 – Bedbound	14 (2.0)	12 (1.4)	8 (1.0)
Not reported	113 (16.0)	85 (9.9)	60 (7.7)

B

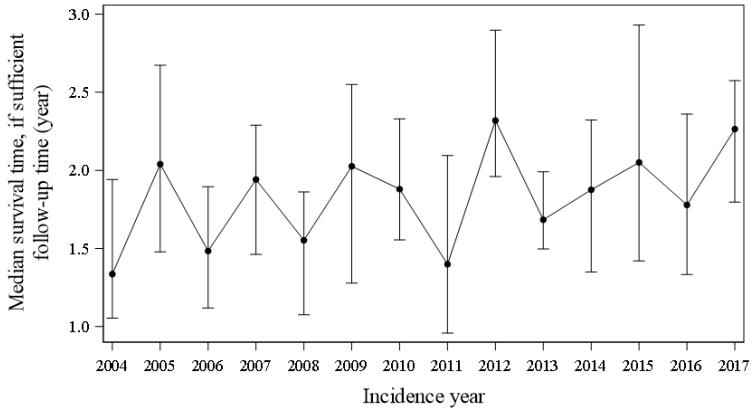


C



Year: 3-y OS [95%CI]
2004: 29.0 [21.7, 36.7]
2005: 37.4 [28.3, 46.4]
2006: 29.1 [21.8, 36.7]
2007: 32.4 [25.6, 39.3]
2008: 26.6 [19.6, 34.0]
2009: 37.5 [30.1, 45.0]
2010: 34.8 [28.3, 41.5]
2011: 31.6 [24.2, 39.2]
2012: 39.6 [32.0, 47.0]
2013: 31.2 [24.7, 37.9]
2014: 34.0 [27.6, 40.4]
2015: 42.2 [35.3, 49.0]
2016: 32.2 [25.5, 39.1]
2017: 28.8 [19.1, 39.2]

D



Year: Med. ST [95%CI]
2004: 1.3 [1.1, 1.9]
2005: 2.0 [1.5, 2.7]
2006: 1.5 [1.1, 1.9]
2007: 1.9 [1.5, 2.3]
2008: 1.6 [1.1, 1.9]
2009: 2.0 [1.3, 2.5]
2010: 1.9 [1.6, 2.3]
2011: 1.4 [1.0, 2.1]
2012: 2.3 [2.0, 2.9]
2013: 1.7 [1.5, 2.0]
2014: 1.9 [1.3, 2.3]
2015: 2.1 [1.4, 2.9]
2016: 1.8 [1.3, 2.4]
2017: 2.3 [1.8, 2.6]

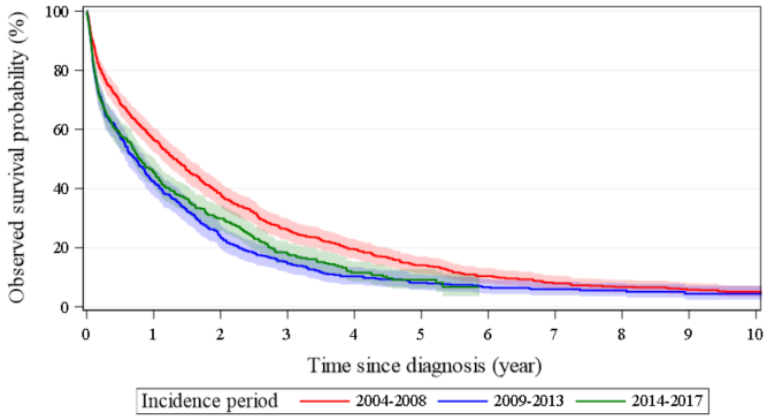
*Med. ST: median survival time; 3-y OS: 3-year observed survival; * the error bars represent the 95%CI. ** When the upper error is not plotted, the upper limit could not be determined with the available follow-up data. Source: BCR.*

Table 53 – Epithelial Ovarian Cancer (2004-2017), combined stage IV – no debulking (observed survival): A) Patient characteristics; B) Kaplan-Meier graph per incidence period; C) Time trend with incidence year*; D) Median survival time* **

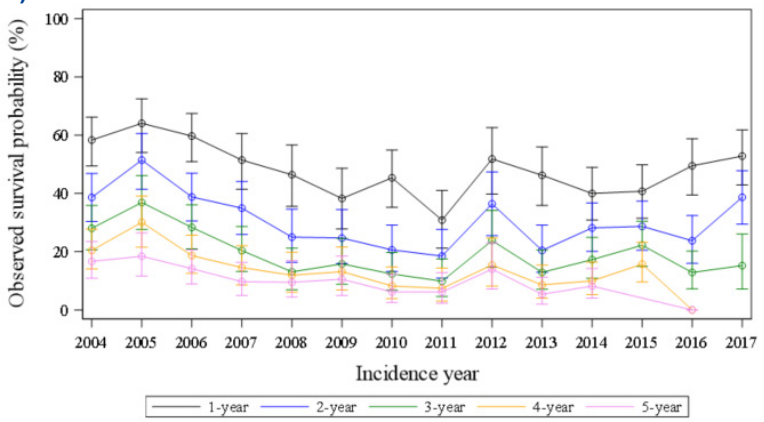
A

Characteristic	Incidence period		
	2004-2008	2009-2013	2014-2017
Overall	556	425	425
Gender			
Female	556 (100.0)	425 (100.0)	425 (100.0)
Age at diagnosis (year)			
<50 years	40 (7.2)	26 (6.1)	16 (3.8)
50-59 years	77 (13.8)	34 (8.0)	34 (8.0)
60-69 years	130 (23.4)	79 (18.6)	84 (19.8)
70-79 years	176 (31.7)	137 (32.2)	133 (31.3)
80+ years	133 (23.9)	149 (35.1)	158 (37.2)
WHO - Performance Status			
0 – Asymptomatic	55 (9.9)	41 (9.6)	33 (7.8)
1 – Symptomatic but completely ambulatory	233 (41.9)	194 (45.6)	232 (54.6)
2 – Symptomatic, <50% in bed during the day	104 (18.7)	87 (20.5)	74 (17.4)
3 – Symptomatic, >50% in bed, but not bedbound	59 (10.6)	37 (8.7)	37 (8.7)
4 – Bedbound	14 (2.5)	12 (2.8)	8 (1.9)
Not reported	91 (16.4)	54 (12.7)	41 (9.6)

B

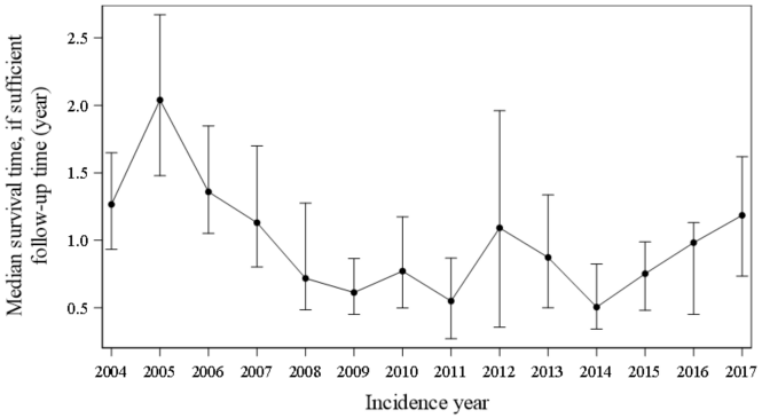


C



Year: 3-y OS [95%CI]
2004: 28.0 [20.7, 35.8]
2005: 36.9 [27.7, 46.1]
2006: 28.4 [21.0, 36.1]
2007: 20.4 [13.2, 28.6]
2008: 13.1 [7.0, 21.2]
2009: 15.8 [8.8, 24.6]
2010: 12.4 [6.8, 19.8]
2011: 9.9 [4.6, 17.5]
2012: 23.8 [14.7, 34.1]
2013: 12.9 [7.1, 20.6]
2014: 17.3 [10.9, 24.9]
2015: 22.2 [14.9, 30.4]
2016: 12.9 [7.2, 20.2]
2017: 15.2 [7.2, 26.1]

D



Year: Med. ST [95%CI]
2004: 1.3 [0.9, 1.6]
2005: 2.0 [1.5, 2.7]
2006: 1.4 [1.1, 1.8]
2007: 1.1 [0.8, 1.7]
2008: 0.7 [0.5, 1.3]
2009: 0.6 [0.5, 0.9]
2010: 0.8 [0.5, 1.2]
2011: 0.6 [0.3, 0.9]
2012: 1.1 [0.4, 2.0]
2013: 0.9 [0.5, 1.3]
2014: 0.5 [0.3, 0.8]
2015: 0.8 [0.5, 1.0]
2016: 1.0 [0.5, 1.1]
2017: 1.2 [0.7, 1.6]

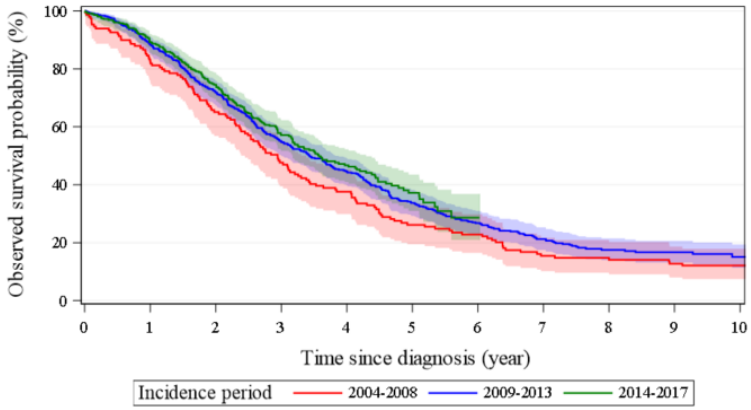
*Med. ST: median survival time; 3-y OS: 3-year observed survival; * the error bars represent the 95%CI. ** When the upper error is not plotted, the upper limit could not be determined with the available follow-up data. Source: BCR.*

Table 54 – Epithelial Ovarian Cancer (2004-2017), combined stage IV – debulking (observed survival): A) Patient characteristics; B) Kaplan-Meier graph per incidence period; C) Time trend with incidence year*; D) Median survival time* **

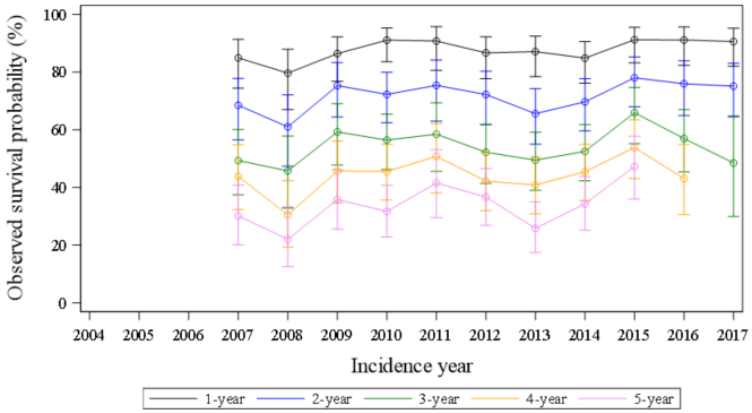
A

Characteristic	Incidence period 2004-2008	2009-2013	2014-2017
Overall	149	431	354
Gender			
Female	149 (100.0)	431 (100.0)	354 (100.0)
Age at diagnosis (year)			
<50 years	16 (10.7)	43 (10.0)	33 (9.3)
50-59 years	37 (24.8)	101 (23.4)	72 (20.3)
60-69 years	53 (35.6)	143 (33.2)	121 (34.2)
70-79 years	36 (24.2)	123 (28.5)	106 (29.9)
80+ years	7 (4.7)	21 (4.9)	22 (6.2)
WHO - Performance Status			
0 – Asymptomatic	18 (12.1)	74 (17.2)	69 (19.5)
1 – Symptomatic but completely ambulatory	87 (58.4)	287 (66.6)	238 (67.2)
2 – Symptomatic, <50% in bed during the day	19 (12.8)	34 (7.9)	26 (7.3)
3 – Symptomatic, >50% in bed, but not bedbound	3 (2.0)	5 (1.2)	2 (0.6)
4 – Bedbound	0	0	0
Not reported	22 (14.8)	31 (7.2)	19 (5.4)

B

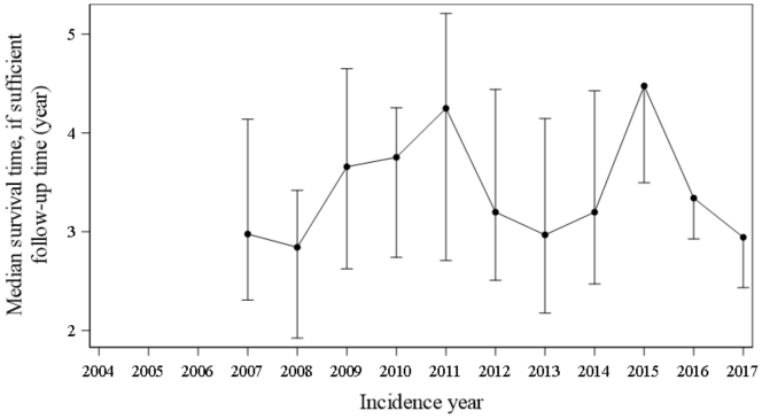


C



Year: 3-y OS [95%CI]
2004: N<35
2005: N<35
2006: N<35
2007: 49.3 [37.4, 60.1]
2008: 45.8 [32.8, 57.8]
2009: 59.3 [47.8, 69.0]
2010: 56.4 [46.2, 65.4]
2011: 58.5 [45.6, 69.3]
2012: 52.2 [41.5, 61.9]
2013: 49.5 [39.0, 59.1]
2014: 52.5 [42.3, 61.8]
2015: 65.9 [55.2, 74.7]
2016: 57.0 [45.3, 67.0]
2017: 48.5 [29.9, 64.8]

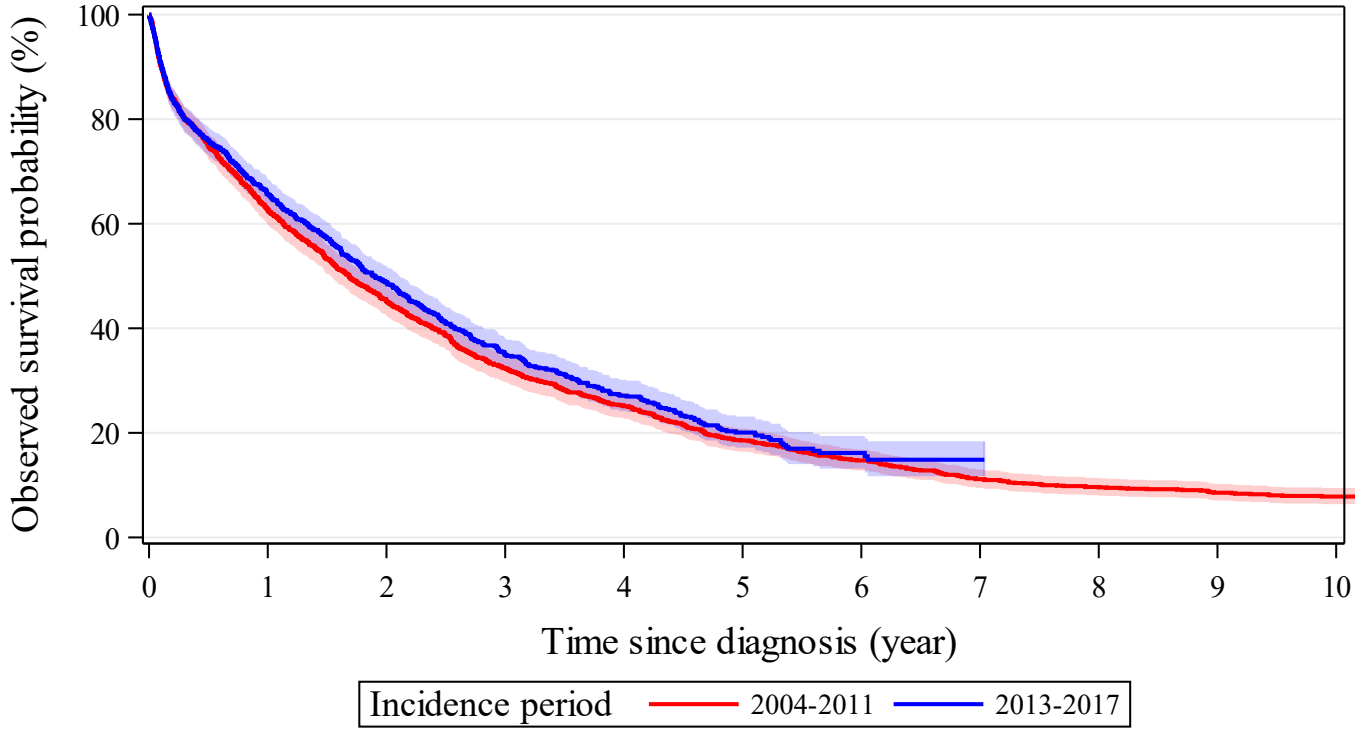
D



Year: Med. ST [95%CI]
2004: N<35
2005: N<35
2006: N<35
2007: 3.0 [2.3, 4.1]
2008: 2.8 [1.9, 3.4]
2009: 3.7 [2.6, 4.6]
2010: 3.8 [2.7, 4.3]
2011: 4.2 [2.7, 5.2]
2012: 3.2 [2.5, 4.4]
2013: 3.0 [2.2, 4.1]
2014: 3.2 [2.5, 4.4]
2015: 4.5 [3.5, NA]
2016: 3.3 [2.9, NA]
2017: 2.9 [2.4, NA]

*Med. ST: median survival time; 3-y OS: 3-year observed survival; * the error bars represent the 95%CI. ** When the upper error is not plotted, the upper limit could not be determined with the available follow-up data. *** 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. Source: BCR.*

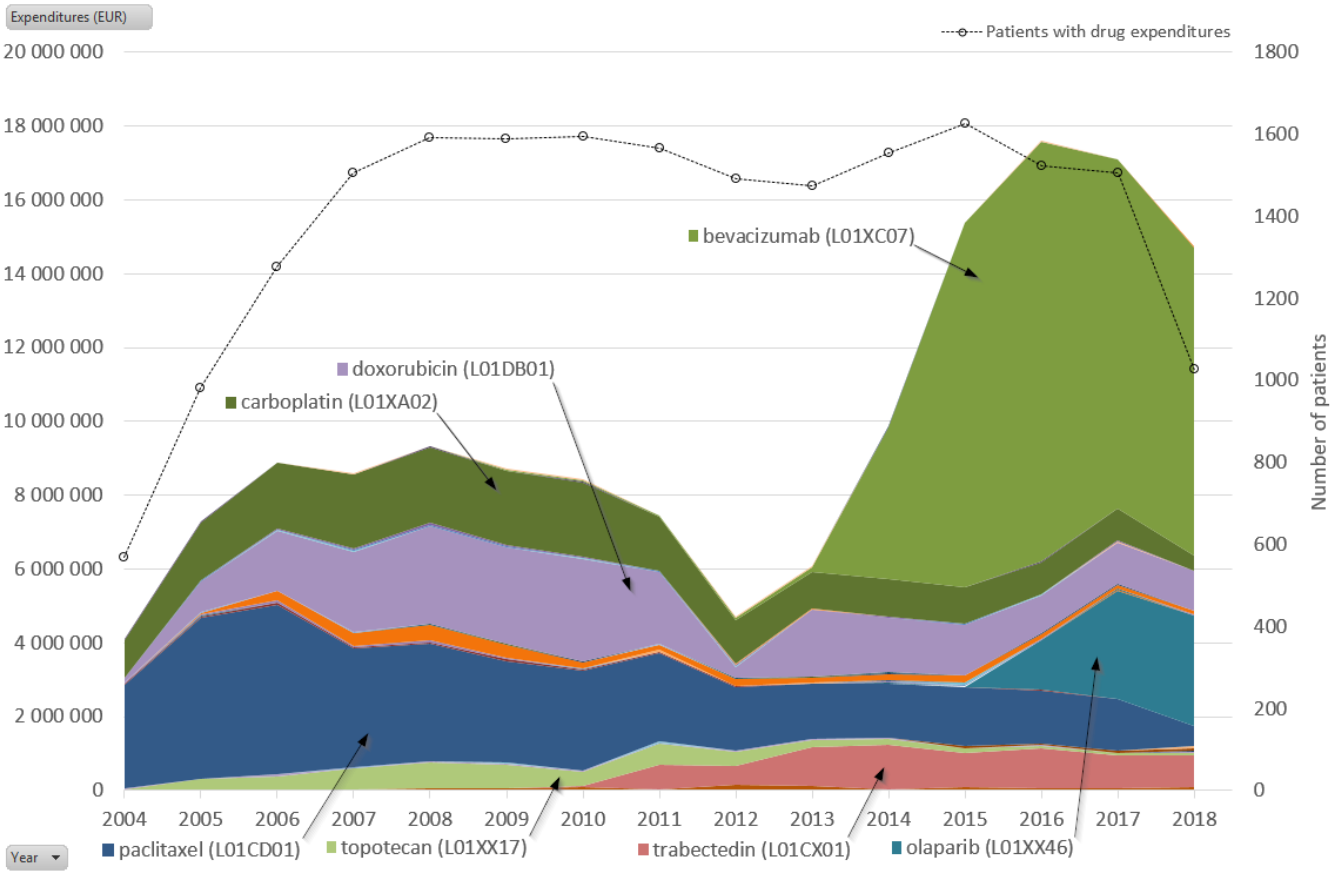
Figure 7 – Epithelial Ovarian Cancer (2004-2017), combined stage IV (observed survival): Kaplan-Meier graph 2004-2011 vs 2013-2017



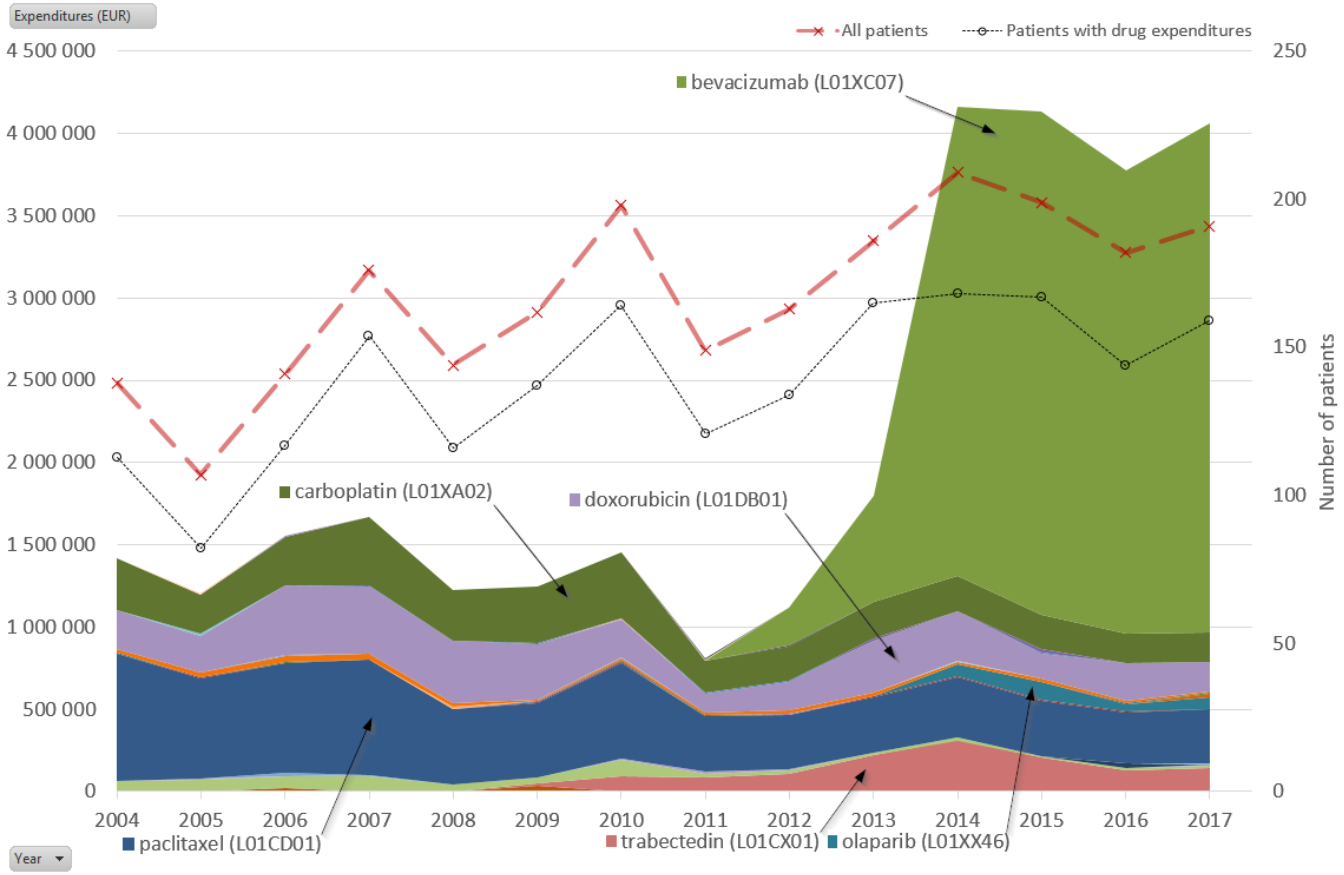
Source: BCR.

Table 55 – epithelial ovarian cancer: drug expenditures

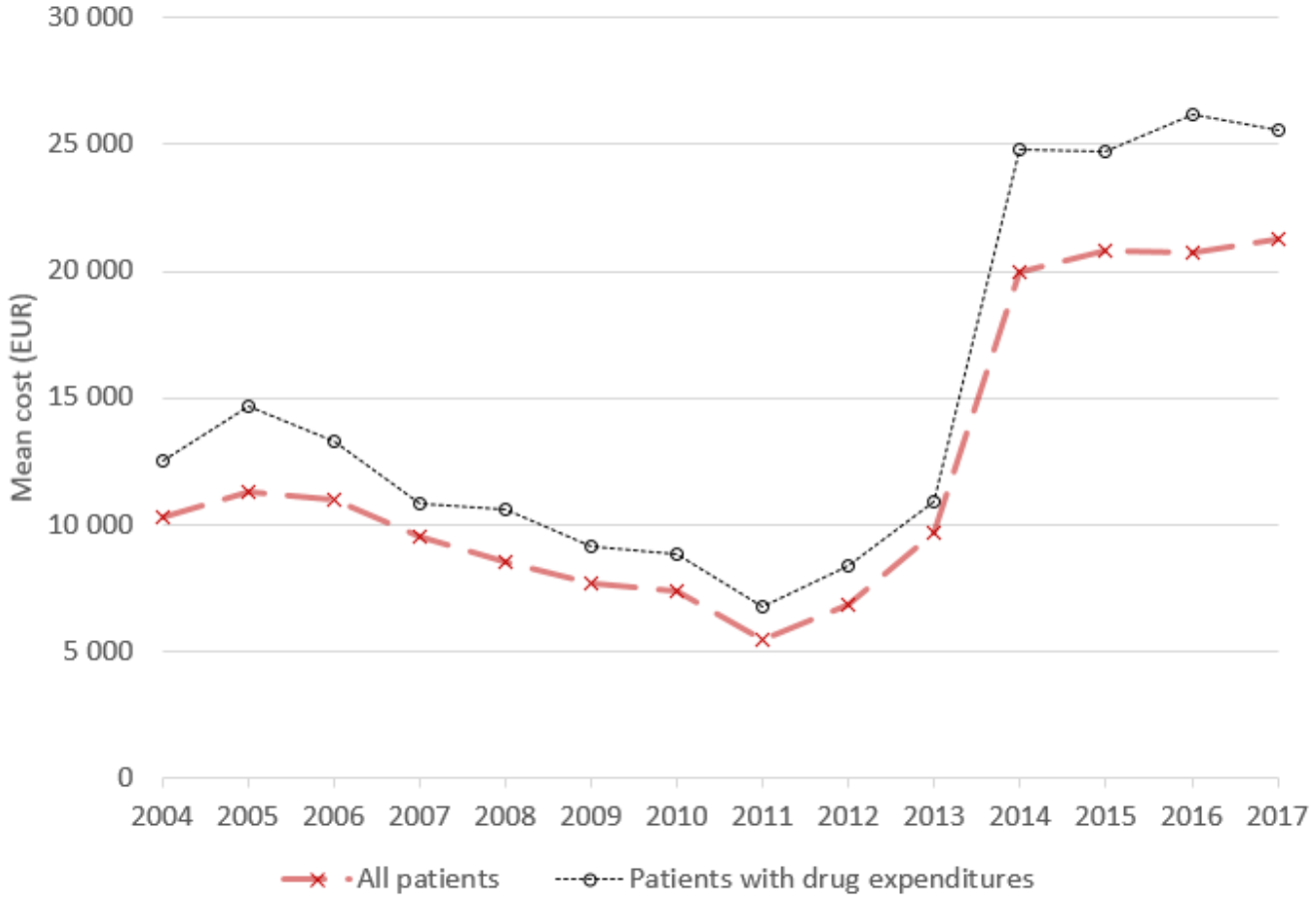
A) Oncological drug expenses per calendar year (all stages)



B) Expenses for the first two years after incidence, per incidence year (stage IV)



C) Mean cost per patient for the first two years after incidence, per incidence year (stage IV)



Source: BCR-IMA.

4.10.2.2 *Drug uptake for a selection of drugs during the first 5 years after diagnosis*

Bevacizumab is reimbursed for ovarian cancer since 2014 in Belgium (Table 56). For stage IV patients, its 5-year uptake progressively rose from 2009 onwards to more than 40% for patients diagnosed in 2014 and reached even 50% in incidence year 2017.

Table 56 – Epithelial ovarian cancer stage IV: uptake of selected drugs

Drug/incidence year (n)	2004 (138)	2005 (107)	2006 (141)	2007 (176)	2008 (144)	2009 (162)	2010 (198)	2011 (149)	2012 (163)	2013 (186)	2014$ (209)	2015 (199)	2016 (182)	2017 (191)
Bevacizumab	0.7%					1.9%	2.5%	6.7%	16.0%	23.1%	42.6%*	47.7%	45.1%	50.3%

** 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, 1.9% of patients received reimbursed bevacizumab during the 5 years after diagnosis. $ IMA data were only available up to the second trimester of 2019 and might have a delay of two years. Five-year follow-up data are thus not 100% complete from incidence year 2012 onwards (see part 3.1.3). Source: BCR-IMA.*

4.10.3 *Medical literature: efficacy*

In a network meta-analysis that included patients with newly diagnosed ovarian cancer treated with cytoreductive surgery, the combination of bevacizumab with chemotherapy and with long-term maintenance by bevacizumab (bevacizumab-initiation and bevacizumab-throughout), did not demonstrate a clear benefit in terms of overall survival when compared to chemotherapy alone.[343]

Subgroups of patients at high risk of recurrence may have better survival with bevacizumab: stage IV patients treated with bevacizumab had better survival in both the GOG28 and the ICON7 study. Results for patients with stage IIIC cancer with residual disease > 1cm after debulking surgery are contradictory in the two studies: a survival benefit was seen in the ICON7 study but not in the GOG28 study.[331]

When the results of both trials GOG-0218 and ICON7 are combined, bevacizumab is associated with a worse quality of life at 18 weeks that withdraw later at weeks 54-60.[331]

In second-line treatment, the combination of bevacizumab with chemotherapy did not improve overall survival when compared with chemotherapy alone.[344] In patients with recurrent platinum-resistant tumour, bevacizumab durably increased the proportion of patients achieving a 15% improvement in patient-reported digestive symptoms during chemotherapy (a score ≥15% being the cut off to define an improvement of symptoms on EORTC QLQ-OV28 instrument).[331]

4.10.3.1 *Bevacizumab in ovarian cancer*

Reference + search date	Intervention and comparator + indication	OS	Quality of life	Other outcomes
Xu 2019[343] Search date: March 2018	Patients with newly diagnosed epithelial ovarian cancer, treated with cytoreductive surgery with or without chemotherapy Intervention: chemotherapy + bevacizumab followed by maintenance bevacizumab Comparator: chemotherapy + placebo followed by maintenance placebo	HR 0.97 (95%CI 0.85-1.09)		
Li 2015[344] Search date: April 2015	Patients with recurrent ovarian cancer (second-line treatment) Intervention: chemotherapy + bevacizumab Comparator: chemotherapy + placebo	HR 0.93 (95%0.78-1.12)		
Neyt 2017[331] Search date: 24 November 2015	Patients with newly diagnosed epithelial ovarian cancer Patients with recurrent ovarian cancer (second-line treatment) Intervention: chemotherapy + bevacizumab Comparator: chemotherapy + placebo	Newly diagnosed: the pooled estimate showed no significant effect HR 0.94 (95%CI 0.84-1.05) Recurrent: The pooled estimate showed no significant effect HR 0.93 (95%CI 0.77-1.12).		
Neyt 2017[331] Search date: 24 November 2015	Patients with high risk of recurrence (FIGO stage IV or FIGO stage IIIC and > 1cm residual disease after cytoreductive surgery). Intervention: first-line chemotherapy + bevacizumab Comparator: first-line chemotherapy	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)"	
Neyt 2017[331] Search date: 24 November 2015	Patients with recurrent ovarian cancer Intervention: chemotherapy + bevacizumab Comparator: chemotherapy		"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."	

4.10.3.2 Discussion

Although a survival benefit is seen in clinical trials for first line treatment in some subgroups such as stage IV ovarian cancer, we observed no better survival for incidence years after the introduction of bevacizumab in 2014, in spite of a maximum uptake of 50% in 2017. The absolute beneft may be very limited. For other reimbursed indications in recurrent disease, no survival benefit was seen in RCTs.

Findings in other countries

To our best knowledge, there is still little evidence on the survival trends after introduction of bevacizumab.

In Spain, an analysis of population based cancer registries compared two incidence periods (1995-1999 and 2000-2007). Age-standardized 5-years relative survival was stable over time: 36.9% (95%CI 35.5–38.4) in the study period 1995-1999 and 36.8% (95%CI 34.7–39.0) in 2000-2007.

In Canada, survival trends were reported in a retrospective cohort study of cases diagnosed during 1992–2011. For the entire cohort during the whole study period, 3-year relative survival was 44.35% (95%CI 42.03-46.64) and no significant time trends in mortality rates were found. Diagnoses of stage IV tumours decreased over time.[345]

Limitations

- We did not discriminate the survival analysis according to the use of bevacizumab as first or second lines therapy.
- Several factors such as extent of debulking surgery, management of local invasion (i.e. diaphragm involvement), hospital volume and adherence to guidelines are factors influencing survival.[346-348] Those data were not available for this report (data on quality of care and hospital volume in Belgium will be published in an upcoming KCE report).
- Tolerance to therapy and subsequent quality of life was not extensively reported in the meta-analysis while bevacizumab can induce many side-effects. In both ICON7 and GOG-0218 phase III clinical trials for first-line therapy, bevacizumab-arms reported a significant but transient altered quality of life when compared with the group with standard chemotherapy.[331]

  In relapsed disease, the main goal of treatment is to control the disease and symptoms. Assessing the quality of life is therefore essential. In patients with platinum-resistant disease, bevacizumab proved to improve the digestive symptoms and ascites.[331]

4.10.4 Economic literature: cost-effectiveness

For more information about the economic evaluations in the identified HTA reports, we refer to the Appendix.

Confidential prices

In the Belgian HTA, the authors mention "the reimbursement of bevacizumab for the treatment of ovarian cancer is based on a confidential contract"[331] The authors performed sensitivity analyses "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."[331]

In the four identified reports from NICE, no reference is made to confidential discounts. In two reports, an assessment was made and, based on the outcomes, bevacizumab was not recommended (see further).[349, 350] In the other two reports, no assessment was made because no evidence submission was received from the company.[351, 352]

Quality of life

In the Belgian report, the researchers note that "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."[331] Furthermore, the authors notice that "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."[353] 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."[354"331]

In TA285, an evaluation of second-line bevacizumab treatment in patients with advanced, recurrent, platinum-sensitive ovarian cancer, "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."[350] "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.,[355] Krasner et al.,[356] Pokrzywinski et al.,[357] Havrilesky et al.,[358] Vergote et al.[359]). The manufacturer notes that Brundage et al.,[355] Pokrzywinski et al.,[357] Havrilesky et al.,[358] and Vergote et al.[359] 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.[356] 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."[360] Finally, "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."[350]

So in general, QoL is most of the times not measured with a generic utility instrument in the underlying trials. Researchers have to make assumptions, including QoL from studies with bevacizumab administered at a lower dose (ICON7 trial) or even from a study with a similar population but a different intervention (trabectedin).

Uncertainty & influential parameters

Since QoL is most of the times not measured with a generic utility instrument in the underlying trials (see previous paragraph), utility values are highly uncertain. In the Belgian HTA report, different QoL scenarios did not have a major impact on results. In this study, there was high uncertainty around the treatment effect, as seen by the wide confidence interval around the incremental effects, and results were most sensitive to the price of bevacizumab and the extrapolation period."[331]

Also in the two identified NICE publications, similar uncertainties and sensitivities are noticed related to survival (or time horizon and extrapolation) and treatment costs (or treatment duration). In TA284, "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."[349] The results of the economic evaluations were also 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.[349] In TA285, "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."[360] "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."[350] In this evaluation, "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."[350] "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."[350] Also in their probabilistic sensitivity analyses, cost and duration of treatment with bevacizumab and the time horizon of the analysis were key drivers of the cost-effectiveness results.[350]

Results

There is no single assessment where the authors conclude an intervention being cost-effective if the official list prices are used. In the Belgian HTA dossiers, results are presented depending on the discount provided (ranging from 0-100%). In the UK dossiers, the intervention is not recommended for reimbursement and no results with confidential prices are discussed.

The ICERs in the identified HTA reports are as follows (see more details in appendix):

- **Bevacizumab**
  - The description of the eligible population reflects the population included in the trials. That is: 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):[331]

    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.
  - Patients with advanced ovarian cancer (Stage III and Stage IV patients):[349]

    Manufacturer's base-case ICER: approximately £144 000 per QALY gained.

    ERG's exploratory analyses: range of ICERs from £128 000 to £161 000 per QALY gained.
  - Patients with advanced, recurrent, platinum-sensitive ovarian cancer:[350]

    Manufacturer's base-case ICER: £149 000 per QALY gained

> "The Committee agreed that [this] was likely to be an optimistic cost-effectiveness estimate and that the most plausible ICER could be much higher than this."[350]

The conclusions of the identified HTA reports were not very favourable. For first-line treatment, the authors of the Belgian HTA report concluded that "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)."[331] Also in the UK analysis, "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."[354] In this assessment, "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."[349] As a result, "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)."[349]

For second-line treatment, the authors of the Belgian HTA report concluded that, "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."[331] Similarly, in the UK assessment, "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."[350] As a result, "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."[350]

4.10.5 Summary

Observational data

- Observational data indicate that overall survival of stage IV ovarian cancer has not clearly improved between 2004 and 2017. The 3-year survival was 29% (95%CI 21.7-36.7) in 2004 and 28.8% (95%CI 19.1-39.2) in 2017. Likewise, the median survival time did not display any meaningful variation throughout the incidence periods with values remaining between 1.3 and 2.3 years throughout all incidence years.
- For all stages of ovarian cancer, total yearly oncology drug expenditures increased from €4.1 million in 2004 to €9.3 million in 2008 and substantially dropped to less than €5 million in 2012. Due to the reimbursement of bevacizumab, expenses considerably rose afterwards from 2014 to reach more than €17 million in 2016 and 2017.
- For stage IV ovarian cancer, oncology drug expenditures during the first two years after diagnosis were low until 2013 and sharply went up to reach more than €4 million. This rise is mainly due to the reimbursement of bevacizumab in 2014.
    - The number of patients with oncology drug expenditures went up from 113 in 2004 to 159 in 2017.
    - The mean cost per stage IV ovarian cancer patient with drug expenses for the first two years after incidence significantly increased from €12 500 in 2004 to €25 000 in patient diagnosed in the years 2014 and later.

Medical literature

- In first-line, there is no evidence that bevacizumab along with chemotherapy and combined with a long-term maintenance by bevacizumab improves overall survival when compared to chemotherapy alone. Subgroups of patients who are at high risk of recurrence may benefit from bevacizumab in terms of survival.
- Quality of life is transiently worse in patients treated with newly diagnosed ovarian cancer who are treated with bevacizumab.
- In second-line treatment, there is no evidence that the combination of bevacizumab with chemotherapy has a significant effect on overall survival in patients with recurrent ovarian cancer in comparison with chemotherapy alone.
- In patients with recurrent platinum-resistant tumour, bevacizumab durably increased the proportion of patients achieving a 15% improvement in patient-reported digestive symptoms occurring with chemotherapy.

Economic literature

- Measuring QoL with a generic utility instrument is not present in four out of five of the underlying trials on which the economic evaluations rely. In one of the evaluations, authors retrieve QoL information from another study with bevacizumab (the ICON7 trial), in which a lower dose of bevacizumab was administered. This approach would not capture AEs caused by the higher dose. In another study, QoL information from a study in ovarian cancer with another product (trabectedin) is included. It is preferable to measure QoL directly in the underlying RCTs with a generic utility instrument and include the results in the economic evaluation.
- The most important uncertainties and sensitivities that impact bevacizumab's cost-effectiveness are related to survival (or time horizon and extrapolation) and treatment costs (or treatment duration).
- In all identified HTA reports, bevacizumab treatment, both in first- and second-line, is not considered a cost-effective treatment option when official list prices are used.

4.11 Prostate cancer

4.11.1 Introduction

Prostate cancer is the most common malignancy in men.[361] In 2018, 9 800 new prostate cancers were diagnosed in Belgium. The majority of patients are diagnosed with stage I or II prostate cancer and about 10% has stage IV at diagnosis.[33]

Castration-resistant prostate cancer is defined as disease progression during androgen-deprivation therapy. Current guidelines recommend apalutamide, darolutamide and enzalutamide as possible treatment options for non-metastatic castration-resistant prostate cancer.

Suppression of testicular androgens by castration is the mainstay of treatment for (primary or recurrent) metastatic disease.[361] For metastatic castration-resistant prostate cancer, abiraterone and enzalutamide or docetaxel are recommended. In the post-docetaxel setting, abiterone and enzalutamide can be considered.[362]

The drug selected for prostate cancer is listed in Table 57.

Table 57 – Selected drugs for prostate cancer

Drug	Year#	Trade Name	Company$	Mechanism of action
Enzalutamide	2014	Xtandi	Astellas Pharma	Enzalutamide is a androgen receptor signalling inhibitor that blocks several steps in the androgen receptor signalling pathway

$ of the originator; # year of start reimbursement first indication in Belgium

4.11.2 Observational data

4.11.2.1 Patient characteristics, survival and expenditures

The number of patients reported to be diagnosed with metastatic prostate cancer (stage IV) increased over the years during the study period (see appendix). Patient characteristics did not change substantially over time (Table 58A). Observed survival (Table 58B) and relative survival (appendix) slightly improved over time. Three-year observed survival was 56.2% (95%CI 52.1-60.1) for patients diagnosed in 2004 and 66.2% (95%CI 63.0-69.2) for those diagnosed in 2017 (Table 58C). Median survival was 3.7 years (95%CI 3.2-4.0) for patients diagnosed in 2004 and 4.6 years (95%CI 4.2-NA) for patients diagnosed in 2015. Median survival was not reached at the time of database closure for patients diagnosed in 2016 and 2017. Additional analysis comparing 2004-2010 with 2012-2017 confirms a small improvement in overall survival over time (Figure 8).

Overall drug expenditures for prostate cancer (all stages) increased between 2004 and 2009 mainly because of an increase of the number of patients treated with oncological drugs (Table 59A). After 2011, overall expenditures started to raise steeply first due to the introduction of abiraterone and later due to the introduction of enzalutamide. In 2004, about €2.2 million was spent on oncological drugs for prostate cancer patients, in 2018 it had increased to about €42 million.

The same steep raise of expenditures is seen for stage IV prostate cancer patients during the first two years after diagnosis from incidence year 2010 onwards, linked to the introduction of abiraterone and enzalutamide as well (Table 59B). Expenditures were about €1 million for incidence year 2004 and about €6.6 million in 2016.

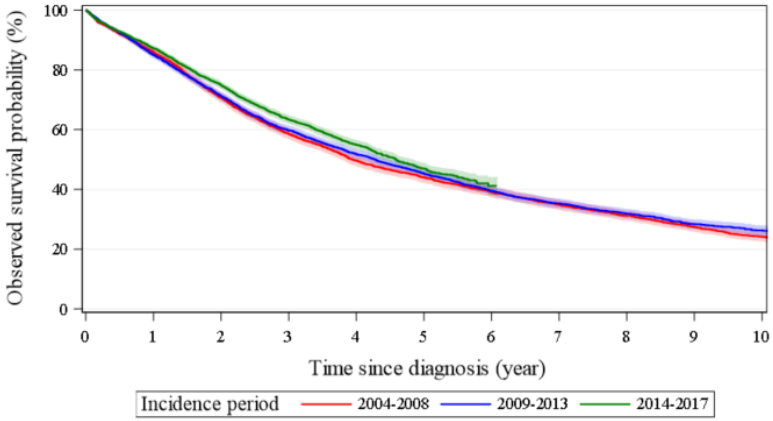
This is also reflected in the mean cost per stage IV patient treated with oncological drugs. Mean cost per patient during the first two years after diagnosis was about €2 300 for incidence year 2004 and reached €9 000 for incidence year 2016.

Table 58 – Prostate cancer (2004-2017), combined stage IV (observed survival): A) Patient characteristics; B) Kaplan-Meier graph per incidence period; C) Time trend with incidence year*; D) Median survival time* **

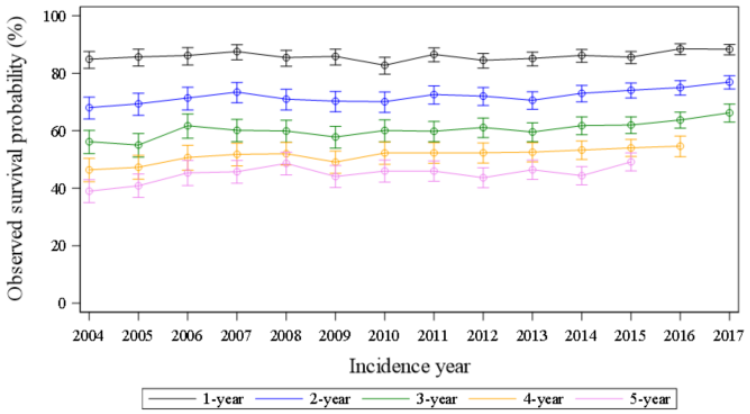
A

Characteristic	Incidence period		
	2004-2008	2009-2013	2014-2017
Overall	2,883	3,687	4,412
Gender			
Male	2,883 (100.0)	3,687 (100.0)	4,412 (100.0)
Age at diagnosis (year)			
<50 years	44 (1.5)	36 (1.0)	55 (1.2)
50-59 years	345 (12.0)	439 (11.9)	452 (10.2)
60-69 years	790 (27.4)	1,083 (29.4)	1,306 (29.6)
70-79 years	1,119 (38.8)	1,235 (33.5)	1,471 (33.3)
80+ years	585 (20.3)	894 (24.2)	1,128 (25.6)
WHO - Performance Status			
0 – Asymptomatic	724 (25.1)	1,117 (30.3)	1,245 (28.2)
1 – Symptomatic but completely ambulatory	1,229 (42.6)	1,906 (51.7)	2,298 (52.1)
2 – Symptomatic, <50% in bed during the day	244 (8.5)	197 (5.3)	334 (7.6)
3 – Symptomatic, >50% in bed, but not bedbound	49 (1.7)	60 (1.6)	68 (1.5)
4 – Bedbound	19 (0.7)	19 (0.5)	20 (0.5)
Not reported	618 (21.4)	388 (10.5)	447 (10.1)

B

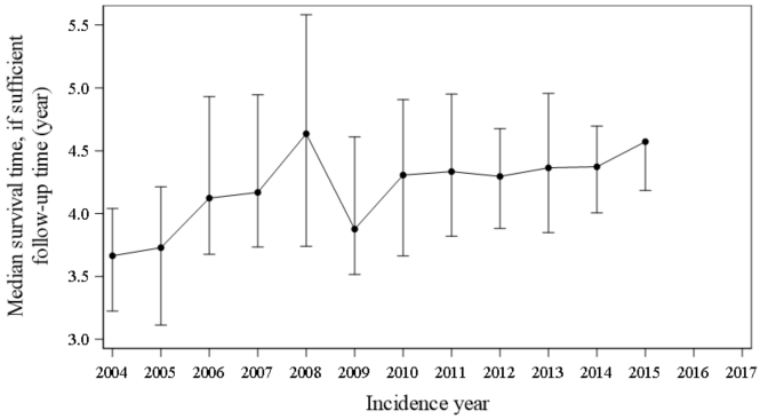


C



Year: 3-y OS [95%CI]
2004: 56.2 [52.1, 60.1]
2005: 55.0 [50.8, 59.0]
2006: 61.7 [57.4, 65.8]
2007: 60.2 [56.2, 63.9]
2008: 59.9 [56.0, 63.6]
2009: 57.8 [53.9, 61.5]
2010: 60.1 [56.2, 63.8]
2011: 59.8 [56.2, 63.2]
2012: 61.1 [57.6, 64.4]
2013: 59.6 [56.2, 62.8]
2014: 61.8 [58.6, 64.8]
2015: 62.0 [59.0, 64.8]
2016: 63.7 [60.9, 66.5]
2017: 66.2 [63.0, 69.2]

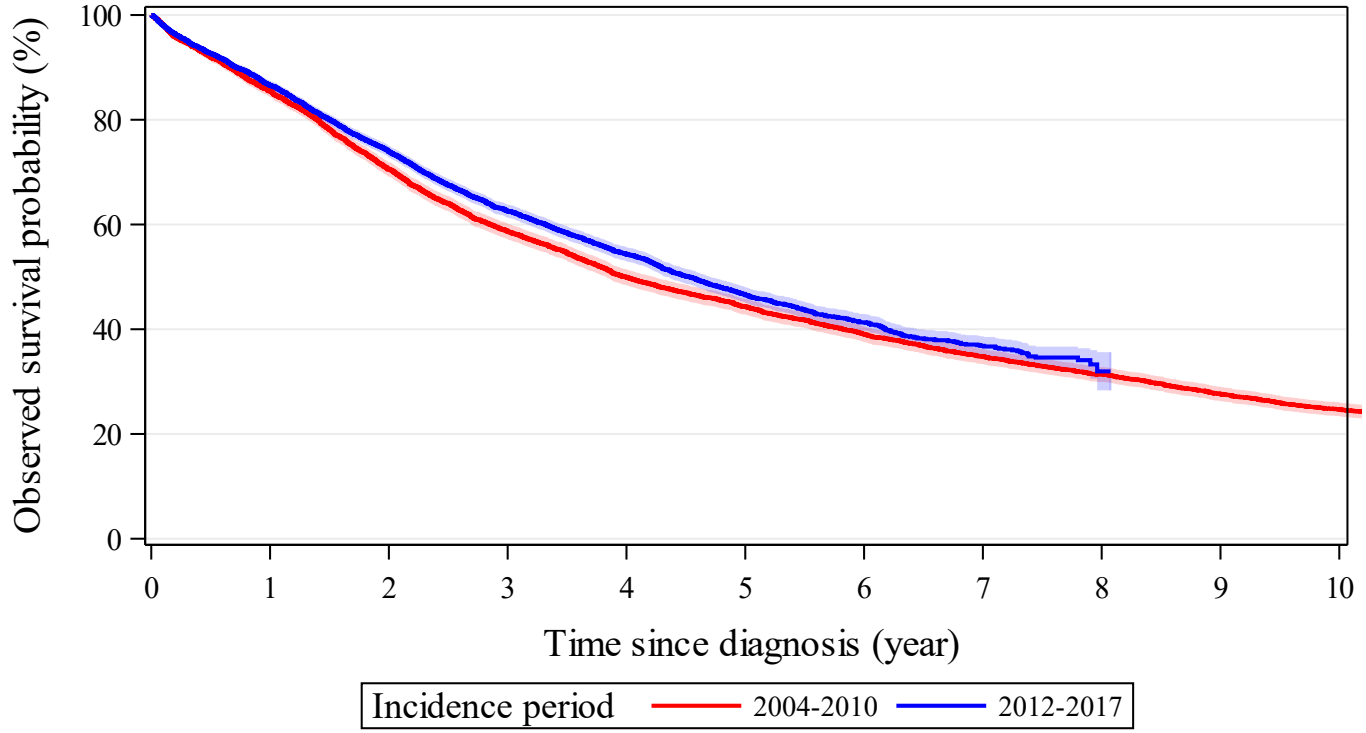
D



Year: Med. ST [95%CI]
2004: 3.7 [3.2, 4.0]
2005: 3.7 [3.1, 4.2]
2006: 4.1 [3.7, 4.9]
2007: 4.2 [3.7, 4.9]
2008: 4.6 [3.7, 5.6]
2009: 3.9 [3.5, 4.6]
2010: 4.3 [3.7, 4.9]
2011: 4.3 [3.8, 5.0]
2012: 4.3 [3.9, 4.7]
2013: 4.4 [3.8, 5.0]
2014: 4.4 [4.0, 4.7]
2015: 4.6 [4.2, NA]
2016: >4
2017: >3

*Med. ST: median survival time; 3-y OS: 3-year observed survival; * the error bars represent the 95%CI. ** When the upper error is not plotted, the upper limit could not be determined with the available follow-up data. Source: BCR.*

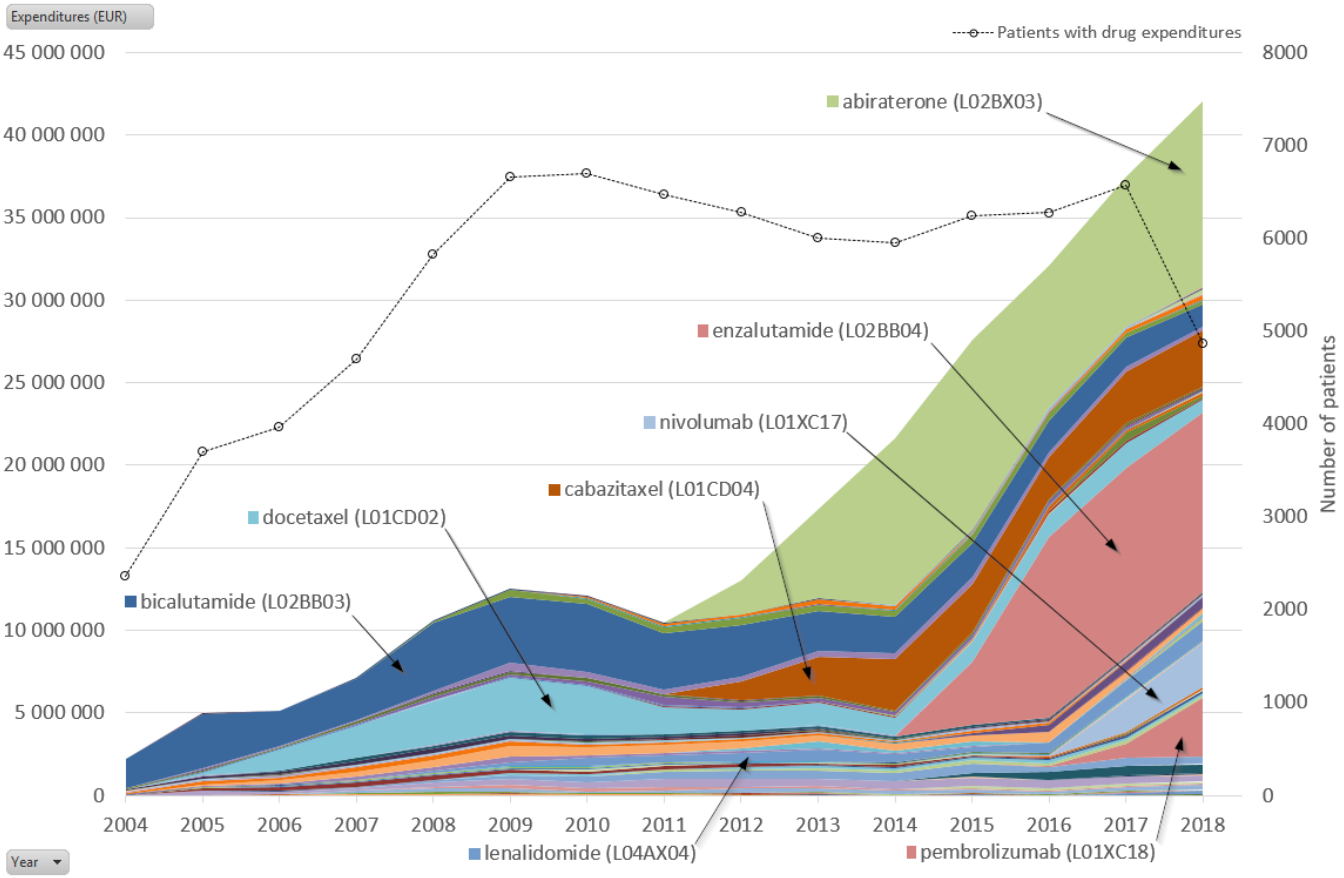
Figure 8 – Prostate cancer (2004-2017), combined stage IV (observed survival): Kaplan-Meier graph 2004-2010 vs 2012-2017



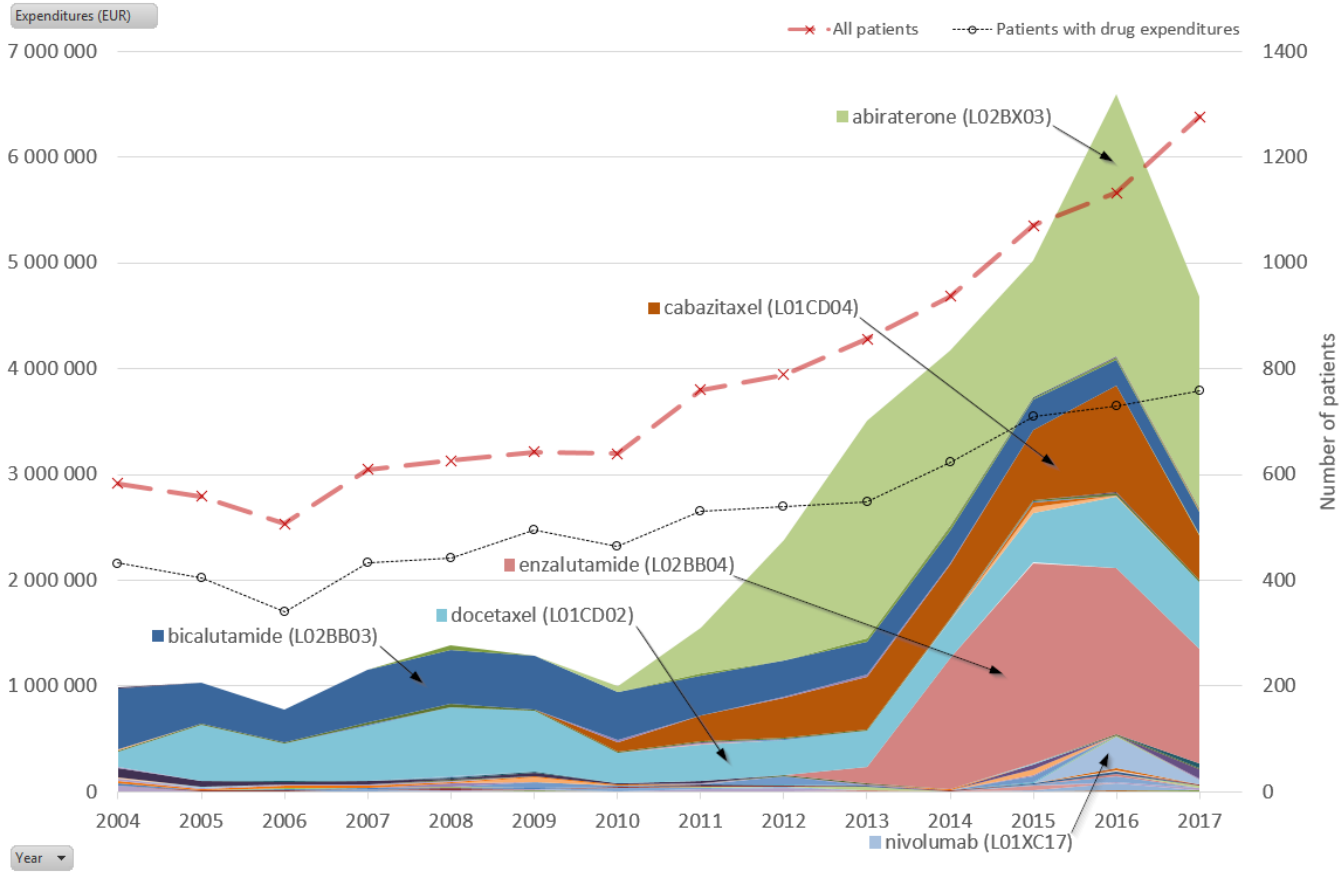
Source: BCR.

Table 59 – Prostate cancer: drug expenditures

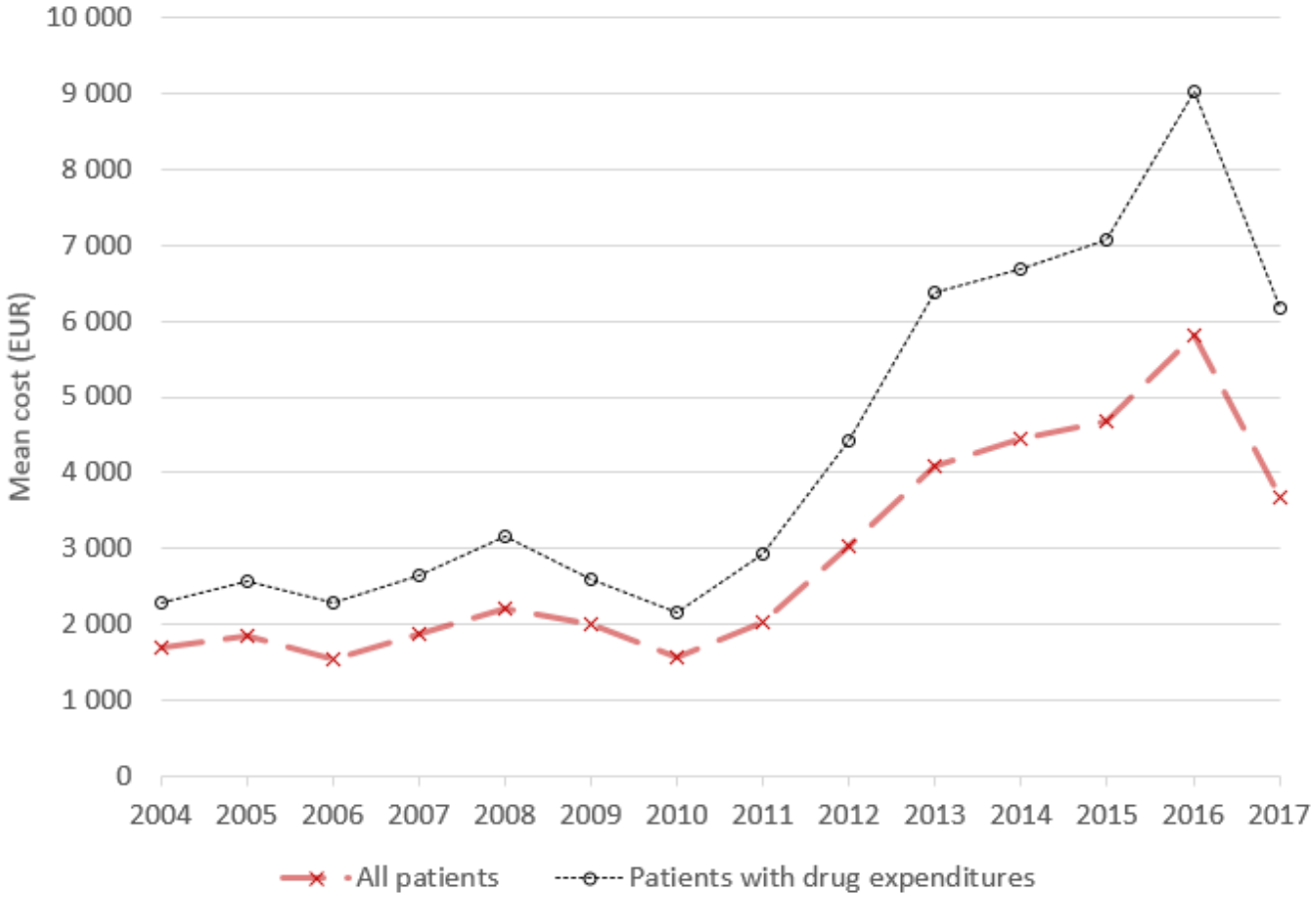
A) Oncological drug expenses per calendar year (all stages)



B) Expenses for the first two years after incidence per incidence year (stage IV)



C) Mean cost per patient for the first two years after incidence per incidence year (stage IV)



Source: BCR-IMA.

4.11.2.2 *Drug uptake for a selection of drugs during the first 5 years after diagnosis*

Enzalutamide is reimbursed for castration resistant prostate cancer since 2014. The first incidence year with a small uptake of enzalutamide during the first five years after diagnosis is 2010. The maximum uptake is seen in 2014, but for the following incidence years, the follow-up period is less than five years.

Table 60 – Prostate cancer stage IV: uptake of selected drugs

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. $ IMA data were only available up to the second trimester of 2019 and might have a delay of two years. Five-year follow-up data are thus not 100% complete from incidence year 2012 onwards (see part 3.1.3). Source: BCR-IMA.

4.11.3 *Medical literature: efficacy*

In non-metastatic prostate cancer with castration resistance, there is no clear proof that enzalutamide improves overall survival compared to placebo.[363] Health-related quality of life appears not to be impacted by the use of enzalutamide.[364]

In patients with asymptomatic or mildly symptomatic metastatic castration resistant prostate cancer, enzalutamide improves overall survival compared to placebo. There is no proof of survival benefit compared to docetaxel-prednisone combinations. There is also no proof of survival benefit compared to the abiraterone/prednisone combination.[365] A benefit in health-related quality of life is seen if compared to placebo.[364]

Patients with castration-resistant disease who were previously treated with docetaxel benefit from enzalutamide in terms of overall survival and quality of life, if compared to placebo.[366]

Reference + search date	Intervention and comparator + indication	OS	Quality of life	Other outcomes
Liu 2020[363] Search date: December 2018	Patients with non-metastatic prostate cancer with castration resistance Intervention: enzalutamide Comparator: placebo	HR 0.80 (0.58-1.11)		
Kretschmer 2020[364] Search date: March 2019	Patients with non-metastatic castration-resistant prostate cancer Intervention: enzalutamide Comparator: placebo		"Study confirmed preservation of HRQoL based on FACT-P total scores." (study in asymptomatic patients)	
McCool 2018[365] Search date: 20 October 2014	Patients with asymptomatic/mildly symptomatic mCRPC who had not received prior chemotherapy Intervention: enzalutamide Comparator: see results	Enzalutamide vs placebo/best supportive care: HR 0.77 (95%CI 0.77-0.88) Enzalutamide vs abiraterone/prednisone: HR 0.95 (95%CI 0.77-1.46) Enzalutamide vs weekly docetaxel + prednisone HR 0.87 (95%CI 0.66-1.13) Enzalutamide vs 3-weekly docetaxel + prednisone HR 1.00 (95%CI 0.76-1.31)		
Kretschmer 2020[364] Search date: March 2019	Patients with metastatic castration-resistant prostate cancer, who received prior chemotherapy Intervention: enzalutamide Comparator: placebo		"The authors found a significant HRQoL benefit for the enzalutamide group compared to the placebo group, observed for the total FACT-P score as well as subdomains of the FACT-P questionnaire."	
Poorthuis 2017[366] Search date: June 2016	Patients with metastatic castration-resistant prostatic cancer who received prior docetaxel therapy Intervention: enzalutamide Comparator: placebo	HR 0.63 (95%CI 0.5-0.75)	"A symptomatic improvement in the study period was found in 42.2% of the enzalutamide group and in 14.5% of the placebo group."	

4.11.3.1 Discussion

We observed only a slight improvement of survival over time for metastatic prostate cancer. For enzalutamide, clinical trials showed only a survival beneft if compared to placebo or best supportive care, but not if compared to docetaxel and prednisone. We note that after 2012, there was also an increase of expenditures for abiraterone and cabazitaxel (not included in our study).

Findings in other countries

In Sweden, based on data from the national cancer registry, a 6-month increase in median overall survival was seen between 1998-2001 and 2010-2015 for men with de novo metastatic prostate cancer, from 2.2 years (95%CI 2.1-2.4) to 2.7 years (95%CI 2.6-2.9).[367]

In the USA, data from population-based cancer registries, show an increase in 5-year relative survival was seen for distant stage prostate cancer, from 28.7% during 2001-2005 to 32.3% during 2011-2016.[368]

No other publications reporting on the evolution in survival over time of metastatic prostate cancer was identified in the recent literature.

Limitations

- No data specific for castration-resistant (metastatic) prostate cancer are available to assess the survival evolution over time after the introduction of new medication in that group. Furthermore, it could not be assessed if patients received docetaxel prior to enzalutamide therapy.
- In the available RCTs, enzalutamide is compared with placebo, not with earlier available treatment, e.g. docetaxel + prednisone. Comparison of available active treatment options is only possible using network meta-analysis.[365]
- Although several studies evaluated quality of life (measured with a generic utility instrument, EQ-5D – see part 4.11.4), this outcome is not reported in the included systematic reviews.

4.11.4 Economic literature: cost-effectiveness

For more information about the economic evaluations in the identified HTA reports, we refer to Appendix.

Confidential prices

All of the four identified technology assessment reports refer to confidential discounts. In one report, the technology was not recommended, but the authors mention that “the company has a commercial arrangement which would apply if the technology had been recommended.”[369] In TA316,[370] the situation is more complex for making cost-effectiveness calculations for enzalutamide since there is also a confidential discount for the comparator (abiraterone). In this case, “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.”[370] Instead, “both the manufacturer and the ERG provided sensitivity analyses varying the discount in the model.”[370]

Quality of life

Concerning the measurement of QoL, both positive and negative observations are made in the identified HTA reports.

First, a positive element is that QoL is measured in the underlying trials with a generic utility instrument (EQ-5D). In the HTA reports, the authors state that EQ-5D data is collected in the three underlying RCTs (PREVAIL, PROSPER and AFFIRM) on which the assessments are based.

Unfortunately, results for the EQ-5D measurements are not transparently presented, i.e. no results are provided for both treatment arms at the different points in time. Results are considered to be confidential in some of the identified HTA reports. For example, in TA316, it is stated that “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).”[370] Also in TA580, mean changes for the EQ-5D visual analogue scale (VAS) scores from baseline to week 97 were presented as confidential in the HTA report.[369]

Next, QoL is not measured after disease progression, while differences in QoL might especially be important when the disease progression is postponed. As stated in one of the report, "the Committee agreed that the benefit of delaying chemotherapy may not have been fully captured by the utility values included in the modelling."[371] In TA580, "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."[372] "The committee noted that data from PROSPER supported this, but that the company did not reflect this benefit in its economic model."[369] Also in TA377, it was "unclear whether the benefit of delaying chemotherapy had been fully captured by the utility values included in the modelling."[371] Including such information in the economic evaluations could have been more straightforward if QoL data would have been gathered also for the full follow-up period of the underlying trials, i.e. also after disease progression.

Furthermore, in TA377, the reviewers state that collecting EQ-5D data was not specified in the study protocol of the PREVAIL study.[371] In TA316,[370] it is mentioned that EQ-5D utility data were not collected at all study sites. Due to the limited number of patients completing the EQ-5D, the result of a disease-specific questionnaire (FACT-P) had to be mapped to EQ-5D data, which introduces another level of uncertainty.

Uncertainty & influential parameters

In the identified reports, the main drivers of results or variables that are linked to a high level of uncertainty are the following: impact on PFS or OS and extrapolation over the longer term, price and or duration of treatment, and utility values.

Already in the first identified report assessing enzalutamide for prostate cancer (TA316), the importance of the impact on survival, treatment duration and impact on QoL was clear: "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')."[370]

In the All Wales Medicines Strategy Group (AWMSG) report, the authors mention that "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."[373] "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."[373] "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"[373]

The immaturity and uncertainty around survival data is also an issue. In the AWMSG report, the authors state that "relatively short-term survival data are extrapolated in the long-term."[373] In TA580, "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."[369] In this assessment, "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."[369] Similarly in TA377, "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."[374] In this study, the key drivers of cost effectiveness are "the data cut-offs from PREVAIL that are used in the modelling and the utility value estimates."[371] Related to the data immaturity, "the Committee was concerned that 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."[371]

Results

The ICERs are as follows (see more details in appendix):

- **Enzalutamide**
  - Metastatic castration-resistant prostate cancer, asymptomatic or mildly symptomatic after failure of androgen deprivation therapy (ADT) in whom chemotherapy is not yet clinically indicated (with PAS):[373]
    - Results are commercial in confidence
    - "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."
  - Hormone-relapsed non-metastatic prostate cancer whose disease is at 'high risk' of metastasis (with PAS):[369]
    - Company's base-case ICER: £28 853 per QALY gained
    - ERG's base-case ICER: £56 168 per QALY gained
  - Metastatic hormone-relapsed prostate cancer, asymptomatic or mildly symptomatic after failure of ADT, before chemotherapy is indicated:[371]

    Without PAS:
    - Company's base-case ICER: £78 587 per QALY gained
    - ERG's base-case ICER: £112 878 per QALY gained

    With PAS:
    - Most plausible ICER: near to £31 600 per QALY gained
  - Metastatic hormone-relapsed prostate cancer previously treated with a docetaxel-containing regimen (with PAS for enzalutamide, but without PAS for the comparator):[370]
    - Enzalutamide compared with abiraterone: £22 604 per QALY gained
    - Enzalutamide compared with best supportive care: £45 898 per QALY gained

In the AWMSG report, results are not very transparent and treated as confidential: "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."[373] Based on a probabilistic analysis, the probability of having an ICER below £20 000 and £30 000 per QALY is presented, being 0% and 57%, respectively.

Also in TA580, incremental costs and effects are confidential. "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"[369] In conclusion, "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. … 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."[369]

In TA377, without 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 £113 000 per QALY."[374] 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."[371] Therefore, the Committee "considered enzalutamide to be a cost-effective use of NHS resources."[371]

In TA316, "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."[370] The Committee "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."[370]

4.11.5 Summary

Observational data

- Observational data indicate that overall survival of stage IV prostate cancer patients improved over time. Three-year observed survival was 56.2% (95%CI 52.1-60.1) for patients diagnosed in 2004 and 66.2% (95%CI 63.0-69.2) for those diagnosed in 2017 (Table 9C). Median survival was 3.7 years (95%CI 3.2-4.0) for patients diagnosed in 2004 and 4.6 years (95%CI 4.2-NA) for patients diagnosed in 2015. Median survival was not reached at the time of database closure for patients diagnosed in 2016 and 2017.
- For all stages of prostate cancer, oncological drug expenditures started to raise steeply after 2011 first due to the introduction of abiraterone and later due to the introduction of enzalutamide. In 2004, about €2.2 million was spent on oncological drugs for prostate cancer patients, in 2018 it had increased to about €42 million.
- Drug expenditures for stage IV prostate cancer during the first two years after diagnosis were about €1 million for incidence year 2004 and about €6.6 million in 2016.
    - The number of patients with stage IV prostate cancer for which oncology drug expenditures were identified went up from 432 in 2004 to 758 in 2017
    - Mean cost per stage IV patient during the first two years after diagnosis was about €2 300 for incidence year 2004 and reached €9 000 for incidence year 2016.

Medical literature

- In non-metastatic prostate cancer with castration resistance, there is no clear proof that enzalutamide improves overall survival compared to placebo.
- In patients with asymptomatic or mildly symptomatic metastatic castration resistant prostate cancer, enzalutamide improves overall

survival compared to placebo, but there is no proof of survival benefit compared to docetaxel-prednisone combinations. A benefit in health-related quality of life is seen if compared to placebo.

- Patients with castration-resistant disease who were previously treated with docetaxel benefit from enzalutamide in terms of overall survival and quality of life, if compared to placebo.

Economic literature

- In the four identified HTA reports of enzalutamide, a confidential price discount was included in the economic evaluations. In one of these evaluations, the calculations were even more complex since there was also a confidential discount for the comparator.
- QoL was measured with a generic utility instrument (EQ-5D) in the three underlying trials (PREVAIL, PROSPER and AFFIRM) on which the assessments are based. Unfortunately, several shortcomings appear: results for the EQ-5D measurement are not transparently presented (no results per treatment arm for the different points in time this outcome is measured), results are considered to be confidential, there is no measurement of QoL after disease progression, collecting EQ-5D data was not specified in the PREVAIL study protocol, and EQ-5D utility data were only collected at a selection of study sites and for a limited number of patients in the AFFIRM trial.
- The most influential parameters for cost-effectiveness calculations are the impact on PFS and/or OS and long-term extrapolations, price and/or duration of treatment, and utility values. The relatively short-term survival data or immaturity of overall survival data are also an issue in the identified evaluations.
- In three out of four identified reports, incremental costs and effects are not transparently published. In one report (TA580), the cost-effectiveness estimates are not within the range that NICE considers a cost-effective use of their resources. In the other NICE reports, ICERs were considered to be acceptable when confidential discounts were taken into account. In a subgroup with higher ICERs, the end-of-life considerations resulted in accepting the ICERs (<£50 000/QALY) as cost-effective use of resources.

4.12 Renal cell carcinoma

4.12.1 Introduction

Kidney cancer is part of the 15 most common malignancies worldwide.[375] In 2018, 1799 patients were diagnosed for renal tumour, in Belgium.[33] Metastatic disease is generally described in one-third of patients and one-quarter of all patients will ultimately undergo a relapse.[376] Although cytoreductive nephrectomy may be proposed in stage IV Renal Cell carcinoma (RCC) patients with limited cancer burden, most of them have generally unresectable disease and require systemic therapy.[377-379]

Kidney cancer encompasses a wide range of histological subtypes.[380] Renal cell carcinoma (RCC) makes up approximately 80 to 90% of all kidney tumours and comprises a highly heterogeneous group that includes clear-cell, papillary and chromophobe tumours.[378, 381] Clear-cell RCC is the most common form, accounting for about 70% of RCC.[377] Stage III corresponds to an involvement of surrounding venous structures (or a smaller tumour mass with lymph node invasion) while stage IV concurs with a marked locoregional tumoral invasion (beyond Gerota fascia) or with a distant metastasis.[378]

Although the underlying molecular features of each group are distinct, recommendations are mainly based on studies that have been conducted in the clear-cell RCC subgroup.[378] The latter is associated with mutations in the VHL gene resulting in disturbances in the angiogenesis. Other molecular impairments involving the m-TOR (mammalian target of rapamycin) pathway or PD-L1 (Programmed Death Ligand-1) overexpression have also been identified.[376, 377, 382]

Formerly, patients with metastatic RCC were treated with interleukine-2 and interferon-alpha. Both molecules have considerably fell out of favour because of their restricted effectiveness.[377] New oncological drugs have been developed and include drugs targeting the downstream tyrosine kinases of VEGF (Vascular Endothelial Growth Factor) and Platelet-

Derived Growth Factor (PDGF) receptors (sunitinib, sorafenib, pazopanib, axitinib, cabozantinib, lenvatinib), mTOR inhibitors (everolimus, temsirolimus), and monoclonal antibodies targeting the PD1/PD-L1 pathway (nivolumab) or the Cytotoxic T Lymphocyte Antigen 4 (ipilimumab).

Therapeutic strategies are guided by classifying patients according to their disease prognostic score, based on performance status and biological markers.[378, 383]

In front-line therapy, antiangiogenic drugs targeting VEGF/PDGF receptor tyrosine kinases represent the standard of care in favourable-risk patients whereas nivolumab plus ipilimumab or tyrosine kinase inhibitors (cabozatinib) are recommended for those with intermediate and poor-risk.[378]

For second-line treatment, in patients previously treated with antiangiogenic tyrosines kinases inhibitors (TKIs), nivolumab (or cabozantinib) in monotherapy is recommended. TKIs (cabozatinib) are also possible for patients who previously received immunotherapy. Therapeutic options for those patients are currently not well defined. In this setting, TKIs are suggested and lenvatinib plus everolimus also remains an option.[378]

For non-clear cell tumours, clinical data are limited. To date, the most robust evidence supports the use of sunitinib, pazopanib and immunotherapy.[378]

Table 61 shows the list of selected drugs for metastatic RCC.

Table 61 – Selected drugs for renal cancer

Drug	Year#	Trade Name$	Company$	Mechanism of action
sunitinib	2007	Sutent	Pfizer	inhibitor of platelet-derived growth factor receptors (PDGFRα and PDGFRβ), VEGFreceptors (VEGFR1, VEGFR2,and VEGFR3), stem cell factor receptor (KIT), Fms-like tyrosine kinase-3 (FLT3), colony stimulating factor receptor (CSF-1R), and the glial cell-line derived neurotrophic factor receptor (RET)
sorafinib	2007	Nexavar	Bayer	inhibitor of C-RAF, B-RAF and the receptor tyrosine kinases for VEGFR-2, VEGFR-3, PDGFβ, c-KIT and FLT3.
pazopanib	2011	Votrient	Novartis	multi-target tyrosine kinase inhibitor (TKI) of vascular endothelial growth factor receptors (VEGFR) -1, -2, and -3, platelet-derived growth factor (PDGFR) -α and –β, and stem cell factor receptor (c-KIT)
axitinib	2013	Inlyta	Pfizer	small molecule ATP-competitive inhibitor of VEGFR-1, 2 and 3
everolimus	2010	Afinitor	Novartis	selective mTOR (mammalian target of rapamycin) inhibitor. mTOR is a key serine-threonine kinase, the activity of which is known to be upregulated in a number of human cancers
temsirolimus	2008	Torisel	Pfizer	selective inhibitor of mTOR (mammalian target of rapamycin)
nivolumab	2016	Opdivo	Bristol-Myers Squibb	monoclonal antibody (HuMAb), which binds to the programmed death-1 (PD-1) receptor

$ of the originator; # year of start reimbursement first indication in Belgium

4.12.2 Observational data

4.12.2.1 Patient characteristics, survival and expenditures

A small increase is observed in the number of stage IV diagnosed RCC in the last incidence periods (Table 62A).[z] Patient characteristics have remained stable throughout the three time periods. Men made up two thirds of reported cases and majority of RCC occur after 60 years, in all time periods. Stage IV RCC accounts for approximately 14% of all reported RCC, in the three cohorts (see Appendix).

For stage IV RCC, an improvement (with overlapping confidence intervals) of observed and relative survival is seen for patients diagnosed between 2014 and 2017 (Table 62B). Three-year observed survival was 22.7% (95%CI 16.6-29.4) in incidence year 2004 and started to rise from the cohort of patients diagnosed in 2014 to reach 34.3% (95%CI 27.3-41.3) in 2017 (Table 62C). Likewise, median survival time grew up from 0.9 year (95%CI 0.6-1.1) in incidence year 2004 to 1.4 year (95%CI 1.1-1.9) in the 2017 cohort (Table 62D). To further investigate a possible change in overall survival after the introduction of anti-VEGF therapy, the period before (2004-2005) and after (2007-2017) were analysed. No difference in survival was observed (Figure 9).

For stage III RCC, overall and relative survival also improved (with overlapping confidence intervals) between 2004 and 2017. Among stage III patients, the 3-year observed relative survival was 69.1% (95%CI 61.8-75.2) in incidence year 2004 and slightly increased in incidence year 2013 to reach its maximum value of 78.9% (95%CI 73.2-83.5) in 2015. It was 75.4% (95%CI 68.1-81.2) in 2017. Median survival time was 7.2 years (95%CI 5.3-8.7) in incidence year 2004 and remained rather constant over time (median survival not reached for incidence year 2013 and after).

For the general RCC population (all stages), yearly oncology drug expenditures were almost non-existing before 2006 (Table 63A). Since then, yearly expenses regularly grew and reached about €14 million in 2016. The introduction of anti-VEGF therapy (sunitinib, sorafenib, pazopanib, everolimus) and an increment of the number of patients for whom oncological drugs were prescribed (from 122 patients in 2004 to 1 077 in 2017), account for this rise. A further sharp increase is observed after 2016, particularly linked to the introduction of nivolumab. Expenditures exceeded €22 million in 2018.

The same trend is observed for stage IV RCC patients. The oncology drug expenditures during the first two years after diagnosis were marginal before 2006 and surged thereafter to reach more than €6 million in 2016 (Table 63B). Apart from a rise in the number of patients with drug expenditures between 2006 and 2008 (from 68 to 150), it was particularly linked to a price-effect related to the uptake of anti-VEGF drugs and later to nivolumab. The mean amount of expenditures for oncological drugs per patient the first two years after diagnosis, was about €3 300 for incidence year 2004 and reached about €32 000 in patients diagnosed in 2011. It further exceeded €46 000 per patient for incidence year 2016, after nivolumab started to be prescribed.

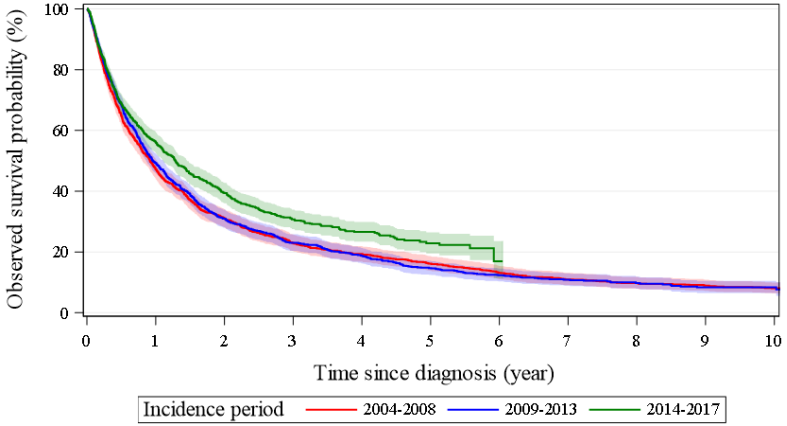
[z] The incidence period 2014-2017 only includes four years, whereas this is five years for the first two incidence periods (2004-2008 and 2009-2013). Taking this difference into account shows an increase in the number of stage IV renal cell carcinoma in the last incidence period in Table 9A.

Table 62 – Renal Cell Carcinoma (2004-2017), combined stage IV (observed survival): A) Patient characteristics; B) Kaplan-Meier graph per incidence period; C) Time trend with incidence year*; D) Median survival time* **

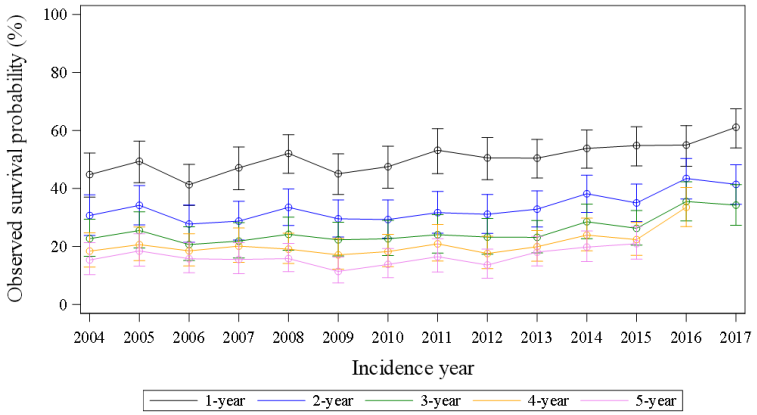
A

Characteristic	Incidence period		
	2004-2008	2009-2013	2014-2017
Overall	926	934	821
Gender			
Male	595 (64.3)	627 (67.1)	552 (67.2)
Female	331 (35.7)	307 (32.9)	269 (32.8)
Age at diagnosis (year)			
<50 years	68 (7.3)	63 (6.7)	44 (5.4)
50-59 years	183 (19.8)	173 (18.5)	140 (17.1)
60-69 years	269 (29.0)	290 (31.0)	266 (32.4)
70-79 years	316 (34.1)	278 (29.8)	251 (30.6)
80+ years	90 (9.7)	130 (13.9)	120 (14.6)
WHO - Performance Status			
0 – Asymptomatic	133 (14.4)	146 (15.6)	123 (15.0)
1 – Symptomatic but completely ambulatory	455 (49.1)	567 (60.7)	490 (59.7)
2 – Symptomatic, <50% in bed during the day	123 (13.3)	83 (8.9)	86 (10.5)
3 – Symptomatic, >50% in bed, but not bedbound	31 (3.3)	32 (3.4)	28 (3.4)
4 – Bedbound	8 (0.9)	11 (1.2)	4 (0.5)
Not reported	176 (19.0)	95 (10.2)	90 (11.0)

B

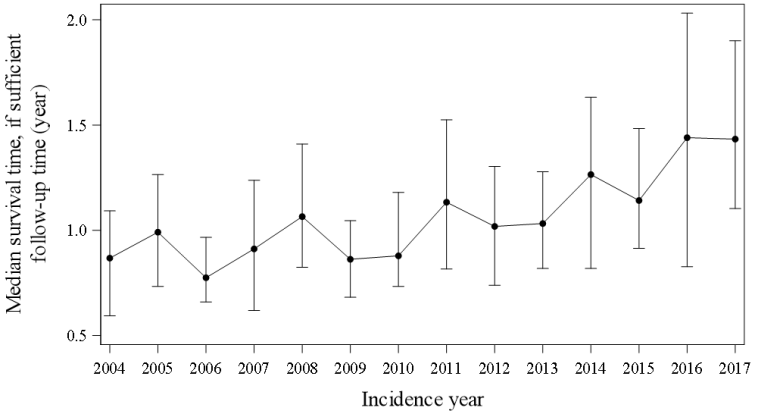


C



Year: 3-y OS [95%CI]
2004: 22.7 [16.6, 29.4]
2005: 25.5 [19.5, 32.0]
2006: 20.7 [15.1, 26.8]
2007: 21.8 [16.0, 28.2]
2008: 24.2 [18.7, 30.1]
2009: 22.3 [16.7, 28.4]
2010: 22.7 [16.9, 29.0]
2011: 24.1 [17.7, 31.0]
2012: 23.2 [17.4, 29.6]
2013: 23.1 [17.8, 29.0]
2014: 28.5 [22.7, 34.6]
2015: 26.3 [20.5, 32.4]
2016: 35.5 [28.8, 42.3]
2017: 34.3 [27.3, 41.3]

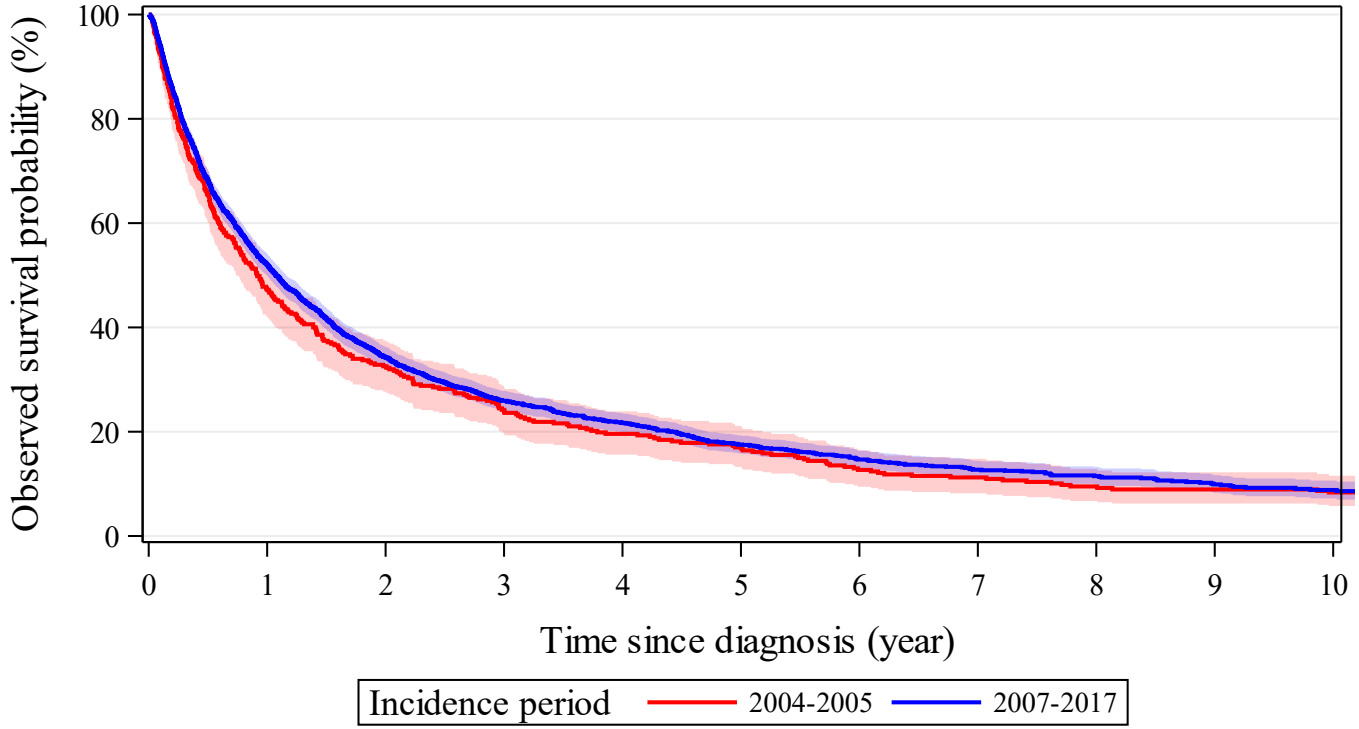
D



Year: Med. ST [95%CI]
2004: 0.9 [0.6, 1.1]
2005: 1.0 [0.7, 1.3]
2006: 0.8 [0.7, 1.0]
2007: 0.9 [0.6, 1.2]
2008: 1.1 [0.8, 1.4]
2009: 0.9 [0.7, 1.0]
2010: 0.9 [0.7, 1.2]
2011: 1.1 [0.8, 1.5]
2012: 1.0 [0.7, 1.3]
2013: 1.0 [0.8, 1.3]
2014: 1.3 [0.8, 1.6]
2015: 1.1 [0.9, 1.5]
2016: 1.4 [0.8, 2.0]
2017: 1.4 [1.1, 1.9]

*Med. ST: median survival time; 3-y OS: 3-year observed survival; * the error bars represent the 95%CI. ** When the upper error is not plotted, the upper limit could not be determined with the available follow-up data. Source: BCR.*

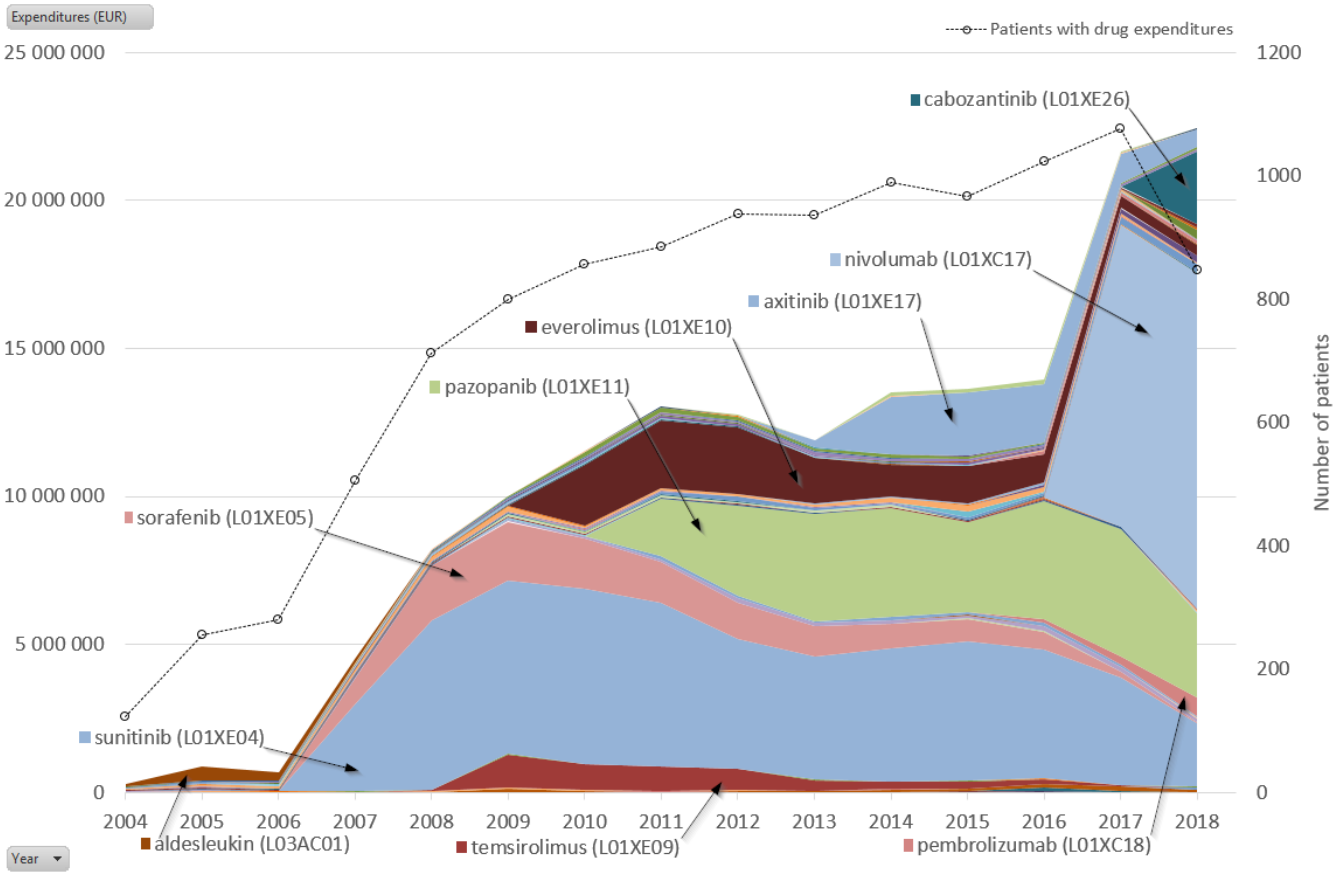
Figure 9 – Renal Cell Carcinoma (2004-2017), combined stage IV (observed survival): Kaplan-Meier graph 2004-2005 vs 2007-2017



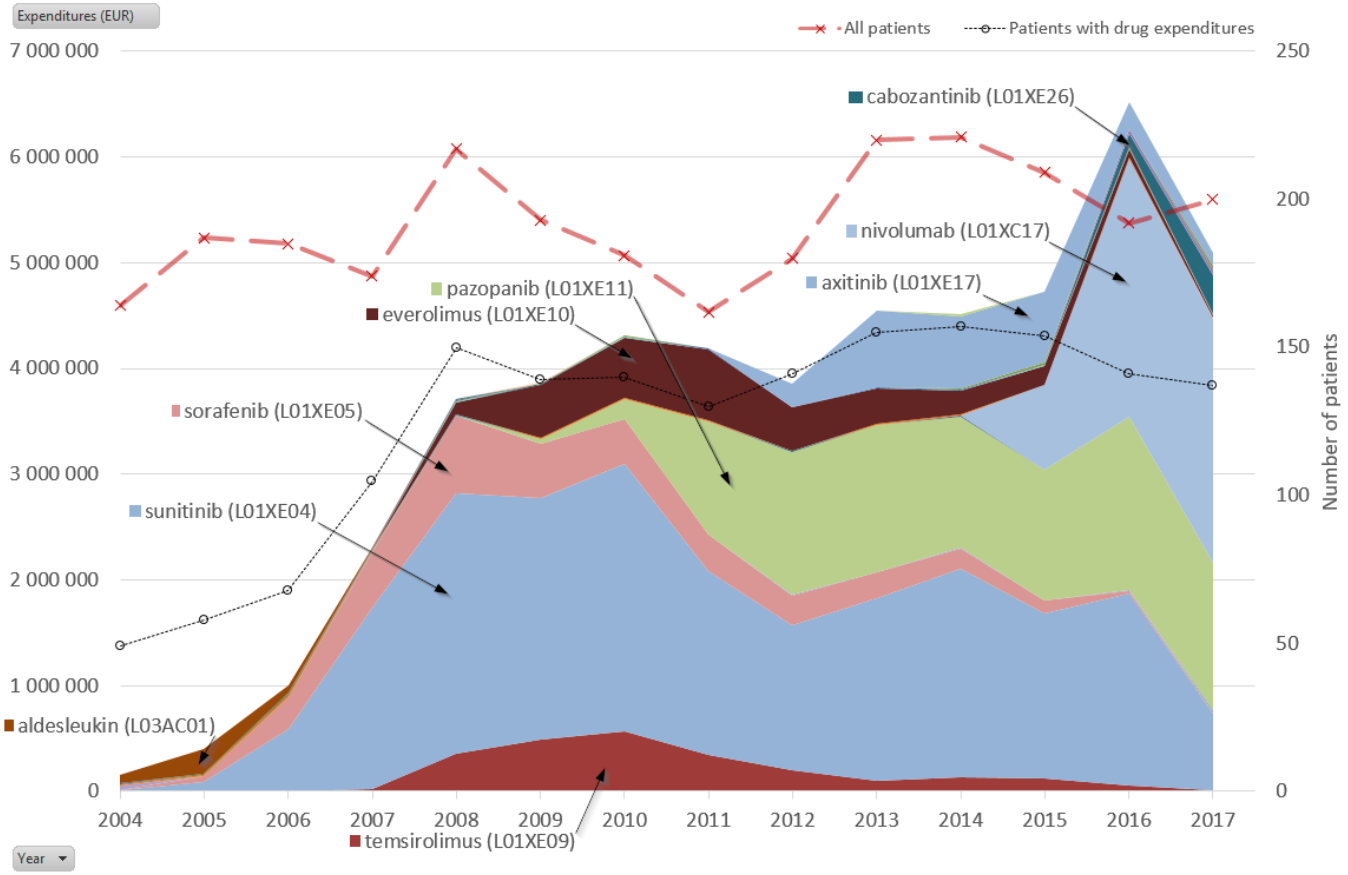
Source: BCR.

Table 63 – Renal Cell Carcinoma: drug expenditures

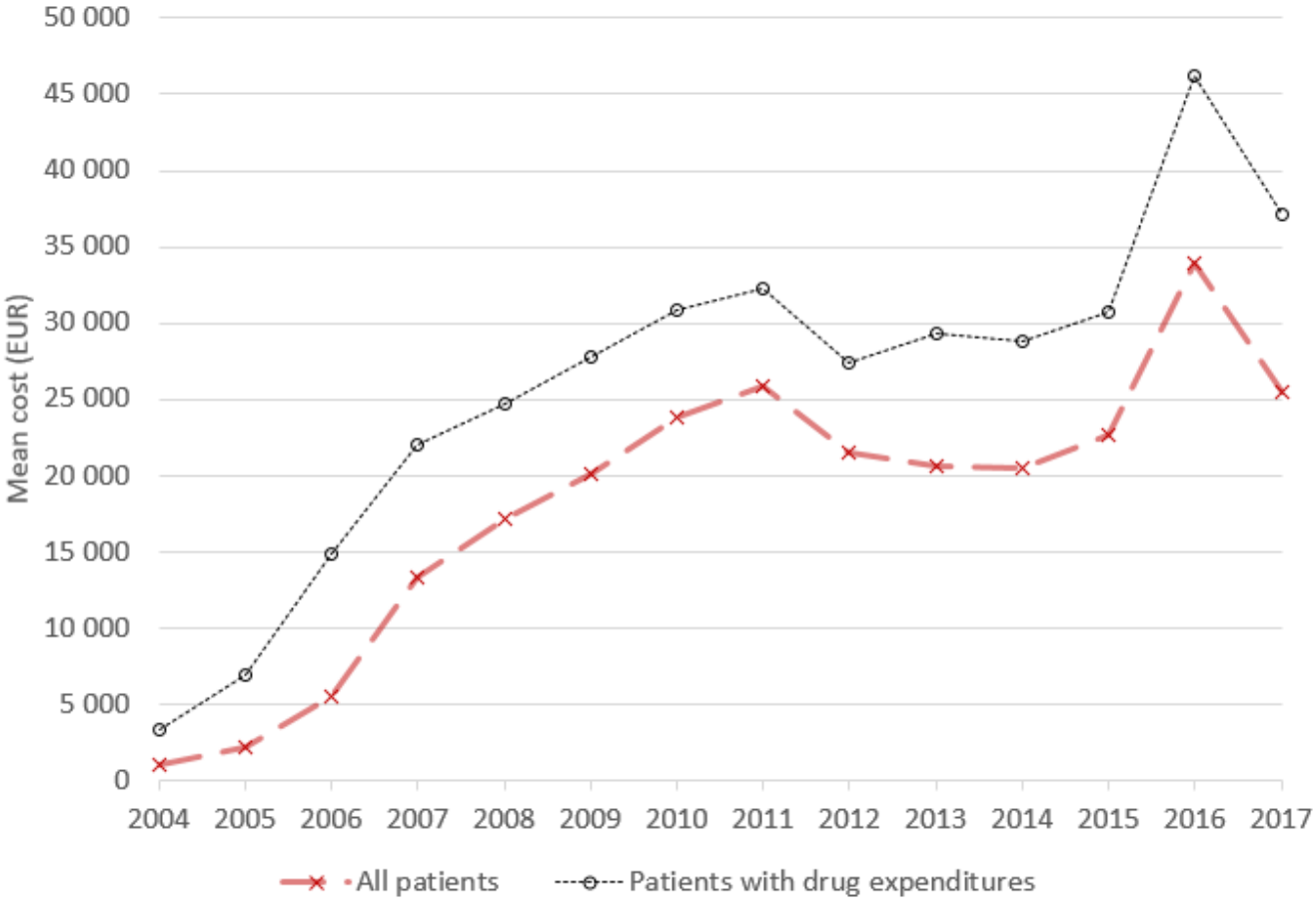
A) Oncological drug expenses per calendar year (all stages)



B) Expenses for the first two years after incidence, per incidence year (stage IV)



C) Mean cost per patient for the first two years after incidence, per incidence year (stage IV)



Source: BCR-IMA.

4.12.2.2 *Drug uptake for a selection of drugs during the first 5 years after diagnosis*

- Sunitinib is reimbursed since 2007. Among stage III RCC patients, 6.6% of patients who were diagnosed in 2004 received sunitinib during the first five years after diagnosis (Table 64). Its uptake peaked in the incidence year 2007 and levelled out, over the next incidence years, at percentages between 12 and 19%. Minimum uptake value was 8% for patients diagnosed in 2015 but this value is underestimated since we do not have the five year follow-up data for this incidence year. For those diagnosed in 2017, the uptake was 7.9% but the follow-up period is less than 5 years for 2017. Among stage IV RCC patients, its uptake during the first five years after diagnosis was below 7% for patients diagnosed in 2004 and then steeply rose to reach maximum values of 55.8% for patients diagnosed in 2010. Its uptake declined subsequently and was between 30 and 39% in incidence years 2012-2016.
- Sorafenib is also reimbursed since 2007. In both stage III and IV RCC patients, its uptake went up from incidence years 2004 to 2007. In 2007, it reached 12.6% and 25.3% in stage III and IV RCC patients, respectively. It was followed by a marked decline from the 2008 cohorts onwards. Uptake was less than 1% in stage III patients diagnosed in 2016 and stage IV patients diagnosed in 2017 but these values are undervalued since we do not have the five-year follow-up data for this incidence year.
- Pazopanib is reimbursed since 2011. Its uptake during the first five years after diagnosis was marked by a constant increase in stage III RCC patients diagnosed from 2006 to 2011, from 1.6% to 17.9%, respectively. It slightly went down and remained fairly constant afterwards. Its uptake was 12.5% in 2016. The trend observed for stage IV RCC patients is globally similar with a maximum uptake at 38.3% for patients diagnosed in 2012 and values rather constant over time. In incidence year 2017, pazopanib uptake was still 37.5%.
- Axitinib is reimbursed since 2013. Its uptake grew steadily in the cohorts of patients diagnosed from 2009 to 2013, for both stage III and IV RCC patients. In incidence year 2013, the uptake was 9.7% and 26.8% for stage III and stage IV patients, respectively. Uptake during the first five years after diagnoses decreased from incidence year 2014 onwards and was 2.3% in incidence year 2016 for stage III RCC patients and 3.5% in 2017 for stage IV group (incomplete five-year follow-up for the last incidence years).
- Inhibitors of m-TOR are reimbursed since 2006 (everolimus) and 2008 (temsirolimus). Altogether, both drugs uptakes underwent an ongoing rise from very low uptake in 2004-2005 to maximum uptake in incidence years 2010-2011 and substantially decreased thereafter. For stage III group, everolimus uptake peaked at 12.8% for patients diagnosed in 2011 while temsirolimus uptake reached its maximum at 5.3% for the 2010 cohort. Both drugs were more frequently used in stage IV group. Maximum everolimus uptake was 34% in incidence year 2011 whereas temserolimus uptake peaked at 22.7% in patients diagnosed in 2010.
- Nivolumab is reimbursed since 2016. Overall, an upward trend is observed in both stage III and IV RCC patients. Among stage III RCC patients, 5.6% of patients who were diagnosed in 2012 received nivolumab during the first five years after diagnosis. Uptake was 11.4% in 2016 and 9.6% in 2017 (5-year follow-up not yet achieved for these cohorts). Among stage IV RCC patients, its uptake during the first five years after diagnosis considerably rose. For patients diagnosed in 2012, uptake was 3.3 % and it reached 34.5% in those diagnosed in 2017 (5-year follow-up incomplete).

Table 64 – Renal cell carcinoma stage III: uptake of selected drugs

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. $ IMA data were only available up to the second trimester of 2019 and might have a delay of two years. Five-year follow-up data are thus not 100% complete from incidence year 2012 onwards (see part 3.1.3). Source: BCR-IMA.*

Table 65 – Renal cell carcinoma stage IV: uptake of selected drugs

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. $ IMA data were only available up to the second trimester of 2019 and might have a delay of two years. Five-year follow-up data are thus not 100% complete from incidence year 2012 onwards (see part 3.1.3). Source: BCR-IMA.*

4.12.3 Medical literature: efficacy

- Cytokine therapy (Interferon-alpha, Interleukine 2) was the most commonly used treatment prior to targeted therapies (antiangiogenic dugs and m-TOR inhibitors) and immunotherapy.

  In first-line therapy (see 4.12.3.1), systemic reviews clearly indicated that targeted therapy drugs have provided survival benefits. In treatment-naïve metastatic patients presenting clear-cell tumour, oral sunitinib demonstrated an improvement of overall survival when compared with interferon-alfa.[384, 385]

  In metastatic RCC patients without prior therapy or with previous cytokine-therapy, pazopanib versus placebo demonstrated improvement of progression-free survival[385, 386] but no significant improvement of overall survival.[387] Nevertheless, since crossover from placebo to pazopanib was possible, the post hoc analysis that took into account the crossover, demonstrated a decrease of mortality HR 0.504 (95%CI, 0.315–0.762).[387]

  In untreated patients with poor prognosis metastatic RCC, intravenous temsirolimus was associated with longer survival. Severe adverse reactions were more common in the interferon alpha group.[385, 388]

  In previously untreated patients, a meta-analysis demonstrated that interferon-alpha increases one-year mortality when compared to targeted therapies including sunitinib or temserolimus. Although quality of life was similar between both groups, serious adverse effects were more frequent in the patients treated with interferon alpha.[389]

- In second-line-treatment (see 4.12.3.2), among patients with cytokine therapy failure, no clear benefit on overall survival has been proven with sorafenib in comparison with placebo. In order to assess the impact of crossover on survival, a secondary analysis that censored placebo patients at the time of crossover observed a difference of overall survival in favour of sorafinib. However, patients who crossed-over were different from patients who did not and had a lower risk profile.[385]

  For those treated with sunitinib or sorafenib and experiencing a disease progression, everolimus uptake did not result in a survival benefit in comparison with placebo: 14.8 months for everolimus versus 14.4 months for placebo (HR, 0.87; P = 0.162).[390]

  A network meta-analysis, focused on patients with advanced or metastatic RCC previously treated with VEGF-targeted drugs, showed that everolimus did not improve overall survival if compared with axitinib. However, everolimus may be more effective than sorafinib. Authors mentioned, nonetheless, that heterogeneity of included studies was high and could bring a certain degree of uncertainty around the estimate of the relative effect.[391] In patients with progressive RCC after one approved systemic treatment, second-line regimen drugs were compared. Overall survival was not different between patients for whom axitinib was used as second-line therapy versus those who received sorafenib.[392]

- The effects of immunotherapy (see 4.12.3.3) as frontline and second-line therapy were compared with targeted therapy in meta-analysis. In first-line, immunotherapy showed a significant survival benefit in comparison with sunitinib. The included studies used several immune checkpoint inhibitors. Overall survival was better with checkpoint inhibitors.[393] Specifically, a significant difference in overall survival favouring the combination nivolumab-ipilimumab versus sunitinib was reported in the intention-to-treat population of advanced intermediate and poor-risk patients.[394] In second-line strategy, nivolumab was shown superior to everolimus in metastatic patients who were initially treated with anti-VEGF drugs. In addition, serious adverse events were less frequently reported in patients treated with nivolumab.[389]

4.12.3.1 Targeted therapy – first line treatment

Reference + search date	Intervention and comparator + indication	OS	Quality of life	Other outcomes
Coppin 2008[385] Search Date: June 2010	Renal cancers with a clear cell component, systemically untreated Intervention: sunitinib Comparator: interferon-α	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		
Coppin 2008[385] Search Date: June 2010	Patients with metastatic RCC with no prior therapy or with prior cytokine therapy Intervention: pazopanib Comparator: placebo	"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"	
Coppin 2008[385] Search Date: June 2010	RCC patients with three or more six adverse prognostic factors for survival Intervention: temsirolimus Comparator: interferon-alfa	Median OS was 10.9 months for temsirolimus versus 7.3 months for interferon-α. HR 0.73 (95%CI 0.58-0.92)		"severe adverse reactions were more common in the interferon arm (78% versus 67%; p=0.02)"
Unverzagt 2017[389] Search date: November 2016	Patients diagnosed with all types of histologically confirmed metastatic RCC including stage IV (T4 any N M0, any T any N M1) Intervention: interferon-α Comparator: sunitinib or temsirolimus	RR for mortality within 1 year after randomisation: 1.30 (95%CI 1.13-1.51) (higher mortality with interferon-α)	"Summarizing these results, the treatment options may lead to similar QoL"	adverse events, grade 3 or greater: RR 1.17 (95%CI 1.03-1.32) (more frequent with interferon-α)

4.12.3.2 Targeted therapy – second line treatment

Reference + search date	Intervention and comparator + indication	OS	Quality of life	Other outcomes
Coppin 2008[385] Search Date: June 2010	Patients with metastatic RCC after cytokine failure Intervention: sorafinib Comparator: placebo	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 sorafinib over placebo on formal QoL assessment with validated QoL measures."	

Coppin 2008[385] Search Date: June 2010	Patients with metastatic RCC with progression on or within 6 months of sunitinib and/or sorafenib Intervention: everolimus Comparator: placebo	"overall survival was essentially the same in both arms"
Karner 2019[391]* Search date: January 2018	Patients with advanced or metastatic RCC who had previous treatment with a VEGF-targeted treatment Intervention: axitinib, sorafinib or best supportive care Comparator: everolimus	Axitinib vs everolimus: HR 1.14 (95%CI 0.95-1.37) Sorafinib vs everolimus: HR 1.38 (95%CI 1.12-1.68)
Motzer 2013[392]*	Patients with advanced RCC who failed one previous systemic treatment. Intervention: axitinib Comparator: sorafinib	HR 0.969 (95%CI 0.800-1.174)

**The network meta-analysis contains observational studies to be able to construct the network. The only identified RCT evaluating axitinib is reported separately (Motzer 2013).*

4.12.3.3 Immunotherapy

Reference + search date	Intervention and comparator + indication	OS	Quality of life	Other outcomes
Roviello 2019[393] Search date: 1 February 2019	Patients with first line metastatic renal cell carcinoma Intervention: an immune checkpoint inhibitor alone or in combination treatment Comparator: sunitinib	Checkpoint-inhibitors: HR 0.65 (95%CI 0.54-0.79) Nivolumab + ipilimumab: HR 0.68 (99.8%CI 0.49-0.95)		
Unverzagt 2017[389] Search date: November 2016	Patients with advanced or metastatic RCC who had prior therapy with sunitinib, pazopanib or axitinib Intervention: nivolumab Comparator: everolimus	RR for mortality within 1 year after randomisation: RR 0.70 (95%CI 0.56-0.87) (higher mortality with everolimus) The median overall survival was 25.0 months with nivolumab and 19.6 months with everolimus.	"Clinically relevant differences in improvements were more frequently observed in patients treated with nivolumab."	adverse events, grade 3 or greater: RR 0.51 (95%CI 0.40-0.65) (less frequent with nivolumab)

4.12.3.4 Discussion

The introduction of anti-VEGF therapy was not associated with a survival benefit, inspite of a rather high uptake reaching for sunitinb even more than 50%. Indeed, RCTs show no or only a limited survival benefit for sunitinib, sorafenib, pazopanib and exitinib, and their introduction was not associated with a detectable change in survival in our observational data. Also, for the mTOR inhibitors everolimus and temsirolimus no or a limited survival benefit was seen in the Belgian observational data.

For patients diagnosed during the last observation period, a better survival is seen. It can be hypothesised that this can be explained by the introduction of nivolumab, as RCTs show a survival benefit for nivolumab both in the first line and in the recurrent setting.

Findings in other countries

Many population-based studies suggest an improvement of survival after the introduction of targeted therapy (TT).

- In Sweden, the impact of TT was analysed on 4 217 metastatic patients, by comparing survival data from national cancer registries throughout three time-periods from 2002-2005 (pre-TT era) to 2006-2008 (early-TT era) and 2009–2012 (late-TT era). Uptake of TT increased over time from 5.6% of patients in 2002-2005 to 32.6% (2006-2008) and 31% (2009-2012), respectively. Administered drugs were mainly sunitinib, sorafenib, pazopanib and everolimus. Overall survival improved progressively over the three periods: median overall survival was 10 (95%CI 8.9-11.1), 13 (95%CI 11.8-14.2), and 18 (95%CI 16.2-19.8) months, respectively. Multivariate regression analyses indicated a decreased risk of mortality in patients of the 2009-2012 cohort versus those from 2002-2005 (adjusted HR:0.76; 95%CI 0.69-0.82).[395]
- In Denmark, the effect of targeted therapy was assessed within the first 5 years after its implementation, in 1049 metastatic RCC patients treated in four centres. The proportion of patients receiving targeted therapy as first line treatment significantly increased, from 22% in 2006 to 75% in 2010. The proportion of patients for whom a second-line treatment was given increased over time. Overall survival increased significantly (p=0.0435) from 11.5 months (95%CI 9.1-14.8) in 2006 to 17.2 months (95%CI 13.5-23.1) in 2010.[396]
- In a population-wide retrospective study from national registries in Norway, survival rates of 5 463 RCC patients were analysed over three periods between 2002 and 2011. Approximately one third of patients had metastatic RCC. Among those, 41.6% received at least a targeted therapy with TKIs. Use of targeted therapies increased from 22.6% to 70.7% between 2006 and 2011. The most common drug was sunitinib. Median overall survival displayed a significant increasing trend over time and was 9 months (2002-2005), 12 months (2006-2008) and 14 (2009-2011) months, respectively.[397]
- In US, data from the Surveillance, Epidemiology and End Results (SEER) database were used to examine survival differences between the periods prior targeted therapy (2000-2005) and after its introduction (2006-2010), in 13 670 advanced RCC patients. Median overall (OS) and cancer specific survival (CS) were significantly higher in patients diagnosed in the targeted therapy era (OS 9 months, CS 11 months) compared to those diagnosed in the pre-targeted therapy period (OS 7 months, CS 9 months). Overall 3-year survival probability significantly improved from 11.9% in 2000-2005 period to 16.5% in 2006-2010. Adjusted Hazard ratio for patients diagnosed in 2006–2010 relative to the reference category of patients diagnosed in 2000–2005 was 0.86 (95%CI 0.82-0.90). However, data on treatments regimen were not provided.[398]
- Another large population-based study in the US evaluated temporal trends of tumour characteristics and survival during two time periods ranging from 2004-2009 to 2010-2015 through SEER database. Among T3-4 N0-1 (stages III and IV) clear-cell RCC patients, five year cancer specific mortality was 20% in the 2004-2009 period and 18% in 2010-2015 period (p<0.001). Cancer specific mortality decreased in T3-4 N0-1 (stages III and IV) non-clear cell RCC patients from 29% in the first period to 21% in the second one (p=0.008). Among clear-cell histology group, systemic therapy was administered in 5.5% of patients from the whole 2004-2009 cohort (all stages) and in 6.9% of

patients from the 2010-2015 one. Among non-clear cell group, the proportion of patients was 5.4% in both periods.[399]

- In Latvia, data from the national population-based cancer registry analysed survival trends of 7 893 patients with newly diagnosed RCC between 1997 and 2016. Stage IV and unknown stage made up 20.7% and 19.2% of the whole cohort, respectively. Distribution remained rather constant over time with stage IV accounting for 18.5% and unknown stage for 19.6% in the 2012-2016 cohort. The 5-year overall survival probability (all stages) improved overtime from 46% (95%CI 43.6-48.4) in 1997-2001 to 52.7% (95%CI 50.3-55.1) in 2002-2006 and to 56.4% (95%CI 54.2-58.7) in 2012–2016. Treatment schedules were not reported.[400]

Limitations

- Due to crossover after progression of patients in the placebo arm to the active arm, evidence on possible gains in overall survival is not robust. Furthermore, absolute difference in overall survival appears to be small.
- The regular classification based on tumour characteristics have a restricted prognosis value for patients with metastatic disease. As such, prognostic scores, including amongst others performance status, are preferentially used. International Metastatic RCC Database Consortium (IMDC) score has been validated for clear cell and non-clear cell histology tumours, in first and second-line strategy.[401-403] In our analysis, no separate survival curves could be obtained based on this score. Such a classification could possibly have allowed to refine the assessment of oncological drugs on survival, to assess a possible impact of new drugs.
- We don't have information on whether new oncological drugs were used in the first-line or second-line (or later) setting, or whether a watchful waiting approach was applied. In addition, not all types of TKIs were analysed in our study (lenvatinib and cabozatinib were not selected for analysis).
- The effectiveness of surgical resection of distant metastasis (brain, liver, lung) on stage IV patients survival is still controversial. A systematic review suggested, in 2014, that metastasectomy may have a beneficial impact on overall survival.[404] However, authors mentioned that the risk of bias was high. In our analysis, this information was not available. Besides, whether cytoreductive nephrectomy was performed or not was not reported. Nevertheless, this technique is recommended for patients with good performance status with favourable or intermediate risk and limited burden disease[378] but its effectiveness remain matter of debate.[405]
- There is probably still limited data on the impact of treatment schedules based on immunotherapy on overall survival since it came later to the market. Even though the combination nivolumab and ipilimumab has proved to be shown superior over anti-VEGF therapy.[394] Ipilimumab is only recently reimbursed in this indication.
- Comparing the efficacy of treatment schedules remains complex for some reasons. First, the number of available molecules is high and head-to-head comparisons are not tested for all comparisons. Second, assessment of efficacy is sometimes difficult due to survival censoring after crossover between treatment and control groups.
- Although statistically significant results on survival are shown, the absolute survival gain appears to be limited to a few months.

4.12.4 Economic literature: cost-effectiveness

For more information about the economic evaluations in the identified HTA reports, we refer to Appendix.

Confidential prices

The search identified eight NICE Technology appraisals (TAs) and one recent HTA report[406] (funded by the National Institute for Health Research) assessing the effectiveness and cost-effectiveness of treatments against advanced renal cell carcinoma (RCC).

In all NICE TAs, the interventions and/or the included comparators were provided under a patient access scheme (PAS) in which discounts to the list prices of the drugs were negotiated with the companies. In five TAs the discounts were commercial in confidence. This was the case for axitinib,[407] the combination lenvatinib plus everolimus,[408] everolimus alone,[409] the combination nivolumab plus ipilimumab[410] and nivolumab alone.[411] In three TAs, the oldest ones published in 2009[412, 413] and 2011,[414] the negotiated discounts were disclosed (i.e. for pazopanib, sorafenib and sunitinib). The PAS consisted in the first pack of sorafenib (TA178[413]) or the first treatment cycle of sunitinib (TA169[412]) to be free to the NHS, and was a 12.5% discount on the list price of pazopanib.[414] As an exception to this, also in TA178,[413] there was no discount on the price of temserolimus that was assessed at its official list price.

In the 2018 HTA by Edwards et al.,[406] ICERs were derived based on list prices, while confidential PAS existed for the drugs considered. This illustrates the difficulty for external researchers to derive exact ICERs when they do not have access to the confidential discounts for the NHS, as stated in the conclusion by Edwards et al.:[406] "*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.*"

Quality of life

Good quality of life (QoL) estimates measured with a generic utility instrument administered alongside the underlying head-to-head trial were most often not available.

First, in most studies, a head-to-head comparison of the scope interventions and comparators used in the economic evaluations was lacking. This was the case for the following comparisons: axitinib versus best-supportive care (BSC);[407] lenvatinib plus everolimus versus axitinib, nivolumab or cabozantinib;[408] everolimus versus axitinib,[409] nivolumab versus axitinib or BSC;[411] pazopanib versus BSC, interferon-α or sunutinib;[414] and in the HTA by Edwards et al.[406] that performed an incremental analysis of BSC, everolimus, axitinib, cabozantinib and nivolumab altogether. In those cases, usually the manufacturer/authors carried out a systematic review to identify health state utility value (HSUV) studies relevant to the health states considered in the model. QoL estimates came then from previous studies done within the same population (advanced RCC) but for a different intervention (e.g. QOL values in TA333[407] were used by Edwards et al.[406]).

Second, in TA432[409] the underlying head-to-head RECORD-1 trial did well compare the interventions in scope (i.e. everolimus versus BSC) but no generic measure of health-related quality of life (such as the EQ-5D) was collected in the RCT and utilities were obtained indirectly from another HSUV study. This was also the case for the comparison sorafenib versus BSC in TA178.[413]

This lack of direct evidence to measure the impact on quality of life gives rise to uncertainty in the results of the economic evaluations.

Four TAs directly measured utility estimates with a generic instrument (in all cases the EQ-5D) administered alongside their underlying head-to-head trial. In TA581[410] EQ-5D data were collected from the CheckMate 214 trial comparing nivolumab plus ipilimumab with sunitinib.[410] Likewise, in TA178[413] and in TA169[412] EQ-5D data were obtained from the underlying "Temserolimus" (temserolimus versus interferon-α[413]), and "Sunitinib" (sunitinib versus Interferon-α[412]) trials, respectively. In those TAs, however, QoL results were not modelled per treatment arm and for all moments in time they were measured, but were used indirectly by converting them to mean utility values for the progression-free survival (PFS) and progressed-disease (PD) health states. In TA417[411] EQ-5D data were collected from the CheckMate 025 trial comparing nivolumab with everolimus. However, it is not clear how the QoL data were used to populate the health economic model, i.e. directly per treatment arm and for each collection time, or indirectly by transferring them to mean values for each health state modelled.

QoL input data were usually transparently reported, except in one TA of nivolumab where this information was not available.[411]

Uncertainty and influential parameters

The greatest uncertainty in all identified evaluations was the relative impact of the treatments on overall survival (OS), which further generated uncertainty in the estimated QALYs and incremental cost-effectiveness ratios (ICERs). Several reasons led to this uncertainty.

First, there was the problem of a lack of head-to-head trials in most evaluations (for at least one comparison in 6 out of the 9 identified studies).[406-409, 411, 414] In the absence of direct evidence, indirect comparisons of the scope treatments were performed (for example network meta-analyses,[408, 411] mixed-treatment comparisons[406] or matched indirect comparisons[409]). Unfortunately indirect comparisons are subject to inherent uncertainty due to e.g. the limited number of studies, their poor quality, the treatment comparison method used… as illustrated in this example (TA417[411]): "*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.*"[411]

Second, there was the problem of the immaturity of the available data that affected most analyses when a head-to-head trial was available.[410-413] In these TAs, the clinical uncertainty about the long-term treatment effectiveness was due to premature termination of the underlying trials (each time in favour of the study interventions) for nivolumab versus everolimus in TA417,[411] for sorafenib versus BSC in TA178,[413] for sunitinib versus interferon-α in TA169[412] and for nivolumab plus ipilimumab versus sunitinib in TA581.[410] In this last TA[410] for example, "*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.*" Also related to the immaturity of the data, there was the difficulty to model and extrapolate OS in the absence of long-term trial data to appropriately inform the OS curve in the economic model.[410-413] In TA581, the committee reports that "*To estimate parameters beyond the end of the trial, the company extrapolated survival outcomes (…) 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. (…) 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.*"[410] This problem of immaturity of the trial data and uncertainty in the extrapolation results is also clearly illustrated in the Committee's comments in TA417[411] about the CheckMate 025 trial comparing nivolumab with everolimus: "*Because the trial data were immature, 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.*"[411]

Third, there was the problem of treatment crossover, which occurred in the sole analysis for which longer-term OS data from the underlying head-to-head trial was available.[409] For the comparison everolimus with BSC in TA432,[409] "*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 <u>any estimate of overall survival obtained using statistical modelling would be subject to uncertainty</u>.*" Crossover was further allowed in two RCTs after early termination of the trials (see above).[412, 413]

To sum-up, there was no single economic evaluation in which the benefits in OS could be clearly demonstrated. All studies further stated that the estimates of treatment effectiveness (impact on OS, extrapolation methods…) were the key drivers affecting the ICERs.

Further when QoL was not measured with a generic utility instrument in the underlying trials (see previous section), utility values were uncertain, as illustrated in the evaluation of sunitinib (TA169): "*In particular, the Assessment Group highlighted a paucity of data surrounding accurate health-state utility values and best supportive care costs.*"[412] Related to this, TA498 referred to the uncertainty in the estimation of the QoL decrements reflecting the treatments' adverse events: "*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.*"[408]

Also, logically, the price of the treatment (and hence the discounts) were key drivers of the cost-effectiveness results.

Results

The ICERs supporting the committee's conclusions are (see more details in Appendix):

First-line treatment

- **Sunitinib**
  - First-line treatment of advanced RCC (including PAS for sunitinib, not confidential):[412]

    Sunitinib versus interferon-α: "*The Committee was persuaded that the ICER for sunitinib could be less than £50 000 per QALY gained*"[412] (ICER from the Decision Support unit: £49 300 per QALY gained, ICER from the Assessment Group: £54 400)
- **Temsirolimus**
  - First-line treatment of adults with advanced RCC and a poor prognosis who are suitable for immunotherapy:[413]

    Temsirolimus versus IFN-α (list prices): £102 000 per QALY gained
- **Pazopanib**
  - First-line treatment of adults with advanced RCC (including PAS for pazopanib, not confidential):[414]
    - Pazopanib versus BSC: £33 000 per QALY gained
    - Pazopanib versus interferon-α: £38 900 per QALY gained
    - Pazopanib versus sunitinib: £1 790 per QALY gained
- **Nivolumab plus ipilimumab**
  - First-line treatment of adults with intermediate- or poor-risk advanced RCC:[410]
    - Without managed access agreement for nivolumab (and including confidential PAS for ipilimumab)

      Nivolumab plus ipilimumab versus pazopanib or sunitinib: between £35 000 and £40 000 per QALY gained
    - With managed access agreement for nivolumab (and including confidential PAS for ipilimumab)

      Nivolumab plus ipilimumab versus pazopanib or sunitinib: between £20 000 to £30 000 per QALY gained

Second-line treatment

- **Sorafinib**
  - Second-line treatment of adults with advanced RCC (including PAS for sorafenib, not confidential):[413]
    - Suitable for immunotherapy: £65 900 per QALY gained for sorafenib versus BSC
    - Unsuitable for immunotherapy: £72 500 to £74 900 per QALY gained for sorafenib versus BSC
- **Axitinib**
  - Second-line treatment of advanced RCC (including PAS for axitinib):[407]

- Prior-cytocine group: between £36 500 and £55 300 per QALY gained for axitinib versus BSC
- Prior-sunitinib group: between £33 500 and £52 900 per QALY for axitinib versus BSC

- **Everolimus**
  - Second-line treatment of adults with advanced RCC (including revised PAS for everolimus):[409]
    - Everolimus versus BSC: below £30 000 per QALY gained
    - Everolimus versus axitinib: everolimus is equally effective but less costly than axitinib
- **Lenvatinib plus everolimus**
  - Second-line treatment of adults with advanced RCC (including PAS for all drugs):[408]
    - Lenvatinib plus everolimus versus cabozantinib: lenvatinib plus everolimus dominates
    - Lenvatinib plus everolimus versus nivolumab: lenvatinib plus everolimus dominates
    - Lenvatinib plus everolimus versus axitinib: between £20 000 and £30 000 per QALY gained
- **Axitinib, everolimus, nivolumab**
  - Second-line treatment of adults with advanced RCC (all drugs at list prices):[406]
    - Axitinib and nivolumab are dominated options, i.e. they are more costly and less (or equally) effective than their respective comparators
    - Everolimus versus BSC: £45 000 per QALY gained
    - Cabozantinib versus everolimus: £126 000 per QALY gained
- **Nivolumab**
  - Second-line treatment of adults with advanced RCC:[411]

    Nivolumab versus axitinib, everolimus or BSC (including PAS for nivolumab and axitinib): "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."[411]

In the five TAs where negotiated discounts for the interventions (and/or comparators) were confidential, exact ICERs used for decision-making (and incremental costs and incremental effects) were not transparently presented. Instead, a range of ICERs was reported or an indication of the relative position of the decision-making ICER with respect to the official NICE threshold (i.e. £20 000 - £30 000 per QALY gained, or £50 000 in case of an end-of-life treatment[aa]). This was the case for the assessments of nivolumab plus ipilimumab[410] for the first-line treatment of advanced RCC; and for axitinib,[407] everolimus,[406, 409] lenvatinib plus everolimus[408] and nivolumab[411] for the second-line treatment of advanced RCC.

In the three older TAs (2009[412, 413] and 2011[414]) where discounts were disclosed, exact ICERs were transparently reported: for sunitinib[412] and pazopanib[414] used first-line, and for sorafenib[413] used second-line. ICERs were also transparently reported when list prices were used in the economic evaluations, as was the case for temserolimus used first-line,[413] and in the HTA by Edwards et al.[406] assessing axitinib, everolimus and nivolumab for the second-line treatment of advanced RCC. Despite this transparency in the ICERs, information on incremental costs and effects was reported in only 2 of these assessments, i.e. in TA215[414] and in Edwards et al.[406]

[aa] To qualify as an "end-of-life' treatment, the following two criteria must be fulfilled: 1) the treatment is indicated for patients with a short life expectancy, normally less than 24 months; 2) there is sufficient evidence to indicate that the treatment has the prospect of offering an extension to life, normally of a mean value of at least an additional three months, compared with current NHS treatment.

There was no single assessment where the authors concluded that a treatment was cost-effective at its official list price.

Of the nine studies identified, only two recent evaluations of the same drug (everolimus) reported ICERs below the usual NICE threshold of £20 000 - £30 000 per QALY gained when the confidential (revised) discounts were included. This was the case in TA432[409] assessing everolimus alone and in TA498[408] evaluating the combination everolimus plus lenvatinib, both used second-line against advanced RCC and for all the comparators considered (BSC and axitinib for everolimus alone, axitinib, cabozantinib and nivolumab for the combination everolimus plus lenvatinib). Without the confidential PAS, everolimus alone was valued at £51 700 per QALY compared with BSC and was not considered as good value for money.[409]

For some other interventions, higher ICERs were reported (above £30 000 but lower than £50 000 per QALY gained) but were still accepted by NICE as the treatments met the end-of-life criteria.[aa] This was the case in the assessments of sunitinib[412] and pazopanib[414] for the first-line treatment of advanced RCC, and for axitinib[407] and nivolumab[411] for the second-line treatment of advanced RCC. In all these cases, discounts were negotiated and included in the assessments. Further, if the ICER was too high to recommend an intervention for routine use, and more evidence was needed to address clinical uncertainties, the intervention could be recommended as an option for use within the Cancer Drugs Fund. This was the case in the evaluation of the combination nivolumab plus ipilimumab[410] for the first-line treatment of advanced RCC: "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."[410] The Committee concluded that "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."[410]

Two of the nine identified studies reached negative reimbursement decisions due to a lack of demonstration of cost-effectiveness of the drugs. In TA178,[413] despite meeting the end-of-life criteria (for those suitable to immunotherapy) and despite taking discounted prices into account, sorafenib was associated with ICERs varying from £65 900 (immunotherapy suitable) to £74 000 (immunotherapy unsuitable) per QALY gained compared with BSC. This led the Committee to conclude that "sorafenib as second line-treatment for people (…) with advanced RCC would not be a cost-effective use of NHS resources."[413] In the same TA,[413] temserolimus (administered first-line to people with advanced RCC and a poor prognosis, and who are suitable for immunotherapy) also met the end-of-life criteria but was not recommended for routine use because its ICER was very high (£102 000 per QALY gained compared with interferon-α). No price discount was taken into account and temserolimus was valued at list price. Finally, in the incremental cost-effectiveness analysis by Edwards et al.[406] none of the drugs investigated for the second-line treatment of advanced RCC was cost-effective at the usual UK threshold: everolimus (versus BSC) and cabozantinib (versus everolimus) were associated with ICERs of £45 000 and £126 000 per QALY gained, respectively; while both axitinib and nivolumab were dominated options. The authors did not have access to the confidential discounts negotiated for the drugs considered and had to use list prices, which limited the accuracy of the results and their applicability to UK practice. Their economic evaluation showed indeed 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."[406] It is striking indeed to note that when confidential discounts were taken into account by NICE in the assessments of everolimus (used alone[409] or in combination therapy[408]), ICERs were all below £30 000 per QALY and everolimus was recommended for routine use. This illustrates the difficulty for external researchers to provide ICERs relevant for decision-making when confidential discounts are negotiated for the interventions in scope.

4.12.5 Summary

Observational data

- Observational data indicate that overall survival and relative survival improved (confidence intervals overlapping) for stage IV RCC patients diagnosed in 2014-2017, compared to earlier time periods. Three-year observed survival was 22.7% (95%CI 16.6-29.4) in incidence year 2004 and started to rise from the cohort of patients diagnosed in 2014 to reach 34.3% (95%CI 27.3-41.3) in 2017. Likewise, median survival time increased from 0.9 year (95%CI 0.6-1.1) in incidence year 2004 to 1.4 year (95%CI 1.1-1.9) in the 2017 cohort.
- For the general RCC population (all stages), yearly oncology drug expenditures were almost non-existing before 2006. Since then, yearly expenses regularly grew and reached about €14 million in 2016. With the introduction of nivolumab, this increased further to more than €22 million in 2018.
- For stage IV renal cancer, oncology drug expenditures during the first two years after diagnosis were marginal before 2006 and surged thereafter to reach more than € 6 million in 2016.
    - The number of patients with oncology drug expenditures went up from 49 in 2004 to 157 in 2014 (and 137 in 2017).
    - The mean cost per stage IV renal cell cancer patient with drug expenses for the first two years after diagnosis increased from €3 266 in 2004 to €46 236 in patient diagnosed in the years 2016.

Medical literature

- First line
    - In treatment-naïve metastatic patients presenting clear-cell tumour, oral sunitinib demonstrated an improvement of overall survival when compared with interferon-alfa.
    - In metastatic RCC patients without prior therapy or with previous cytokine-therapy, there is no clear proof that pazopanib improves overall survival compared to placebo.
    - In untreated patients with poor prognosis metastatic RCC, intravenous temsirolimus is associated with longer survival and better quality of life than interferon alfa.
    - Immunotherapy (checkpoint inhibitor alone or in combination treatment) improves overall survival in newly diagnosed RCC patients compared to sunitinib.
- Second line
    - There is no clear proof that sorafinib improves overall survival in patients with RCC that have been treated with cytokines, compared to placebo.
    - Everolimus does not improve overall survival compared to placebo, in patients with RCC who have been treated with sunitinib or sorafenib.
    - Everolimus may be more effective compared to axitinib, sorafenib or best supportive care in patients who have received previous treatment with VEGF-targeted treatment, but quality of the evidence is low.
    - In patients who had prior treatment with VEGF-targeted therapy, nivolumab improves overall survival compared to everolimus.

Economic literature

- In the economic evaluations of the 9 studies identified against advanced renal cell carcinoma, discounts to the list prices of the interventions considered were negotiated. In most cases the discounted prices were confidential implying that exact decision-making ICERs were not transparently reported. Instead, a range of ICERs was reported or an indication of the relative position of the decision-making ICER with respect to the official NICE threshold. Negotiated PAS and discounts (and hence the resulting ICERs) were transparently reported in the three oldest TAs (2009 –

2011).[412-414] A study performed by external researchers did not have access to the negotiated discounts and conducted its analysis based on list prices.[406] This limited the applicability of results.

- QoL input data were mostly obtained from indirect sources because of a lack of head-to-head trial. Only few TAs directly measured utility estimates with a generic instrument (in all cases the EQ-5D) administered alongside their underlying head-to-head trial. Unfortunately, the impact on QoL was always modelled by assuming a mean utility value for each health states modelled (e.g. progression-free survival, progressed disease, death) irrespective of the treatment administered, instead of directly using the utilities observed in the clinical trials (i.e. utilities per treatment arm and for all scheduled measurement times). QoL input data for the health states modelled were usually transparently reported.
- In all economic evaluations, the greatest uncertainty relates to the estimation of the treatment effect on overall survival. This was mainly due to the absence of head-to-head comparisons or, when such a trial was available, to the immaturity of the trial data and the difficulty to extrapolate overall survival data. In one study with longer OS data, crossover biased the intention-to-treat analyses and corrections for this were subject to uncertainty.
- There was no single assessment where the authors concluded that a treatment was cost-effective at its official list price.
- Everolimus (alone or combined with lenvatinib, both for second line treatment) was the only drug considered cost-effective at the usual £20 000 - £30 000 per QALY threshold. Interventions with higher ICERs were recommended for routine use when they met the end-of-life criteria (i.e. for sunutinib and pazopanib used first-line and for axitinib and nivolumab used second-line) or when the drug was a promising new treatment for which further evidence was needed to address clinical uncertainty (i.e. interim funding via the Cancer Drugs Fund for the combination nivolumab plus ipilimumab used first-line). Two studies based on list prices reached negative reimbursement decisions due to a lack of demonstration of cost-effectiveness of the drugs.

5 USE OF ANTICANCER DRUGS AT THE END OF LIFE

Apart from the price and the therapeutic effect seen in clinical trials, the usage pattern and appropriateness of prescribing in daily practice will determine the real-world cost-effectiveness of an anticancer drug. The use of chemotherapy and other anticancer drugs is often to be considered futile if the chance of achieving clinical improvement that justifies the burden and toxicity to patients is very low. As a proxy for inappropriate use of anticancer drugs, we measured the proportion of patients who received anticancer drugs 7, 14 and 30 days before death in the population included in this report and evaluated possible changes over time.[415, 416]

Findings are summarised in Table 66-Table 69. The proportion of patients receiving anti-cancer drugs during the last 30 days of life per cancer type varied between 11.6 and 46.3% for the whole study period. Proportions decreased over time for the majority of indications, with exception of SCC of the H&N, melanoma, RCC and mesothelioma. In the most recent time period (2014-2018), for many indications, the proportion of patients receiving cancer drugs 30 days before death was still above 20%.

In a recent population-based study in Denmark, the proportion of patients receiving anticancer drugs 30 days before death was 15-17% in the period from 2010 to 2015. Within 14 days before death, the proportion was only 6%. Only in breast cancer patients and melanoma patients, the proportion receiving anticancer drugs was above 20%.[417]

We did not perform an in depth analysis on, for example, which drugs were used, indications to start therapy, time since diagnosis or number of lines of therapy received. Use of anticancer drugs at the end of life may sometimes be justified and inevitable, for example in young patients who undergo highly toxic treatment schemes with curative intent but a certain mortality rate. However, the use of anticancer drugs near the end of life has been associated with reduced quality of life, less use of palliative care and even shortened survival.[418, 419] Other studies have found that a proportion of the anticancer drugs that were used near the end of life, was started within 30 days of dying, that the mean duration of the last treatment was 61 days, pointing at limited efficacy, and the use of chemotherapy near the end of life is associated with less satisfaction of patients and the family.[415]

In conclusion, using anticancer drugs near the end of life in 20% of patients or more can probably not be considered appropriate and efficient use of the often expensive drugs.

Table 66 – Proportion of patients with stage IV (/non-stageable) cancer who received systemic therapy within 7 days, 14 days and 30 days of death

	7 days			14 days			30 days		
	Denominator*	Numerator	Proportion (%)	Denominator*	Numerator	Proportion (%)	Denominator*	Numerator	Proportion (%)
Cancer type									
Chronic myeloid leukaemia	503	85	16.9	503	156	31.0	503	233	46.3
Mantle cell lymphoma	869	87	10.0	869	153	17.6	869	294	33.8
B-cell chronic lymphocytic leukaemia/small lymphocytic lymphoma (CLL/SLL)	3 053	140	4.6	3 053	279	9.1	3 053	515	16.9
Diffuse Large B-cell Lymphoma (DLBCL)	4 896	300	6.1	4 896	695	14.2	4 896	1 275	26.0
Multiple myeloma	5 644	472	8.4	5 644	893	15.8	5 644	1 712	30.3
Colorectal cancer, adenocarcinoma	15 908	510	3.2	15 908	1 419	8.9	15 908	3 321	20.9
Female breast cancer	5 879	837	14.2	5 879	1 430	24.3	5 879	2 511	42.7
Squamous cell carcinoma of the head and neck	7 935	387	4.9	7 935	830	10.5	7 935	1 478	18.6
Malignant melanoma of the skin	457	18	3.9	457	41	9.0	457	97	21.2
Non-small-cell lung cancer	29 680	1 655	5.6	29 680	3 755	12.7	29 680	7 743	26.1
Epithelial Ovarian Cancer	1 816	108	5.9	1 816	216	11.9	1 816	475	26.2
Renal cell carcinoma	2 180	93	4.3	2 180	231	10.6	2 180	529	24.3
Prostate cancer	5 741	416	7.2	5 741	751	13.1	5 741	1 391	24.2
Malignant epithelioid mesothelioma of pleura	320	6	1.9	320	15	4.7	320	37	11.6

*Source: BCR-IMA; *Patients who died until 30/06/2018 were taken into account*

Table 67 – Proportion of patients with stage IV (/non-stageable) cancer who received systemic therapy within 7 days of death, time trend

Year of death:	2004-2008			2009-2013			2014-2018*		
	Denominator	Numerator	Proportion (%)	Denominator	Numerator	Proportion (%)	Denominator	Numerator	Proportion (%)
Cancer type									
Chronic myeloid leukaemia	107	26	24.3	178	27	15.2	218	32	14.7
Mantle cell lymphoma	177	23	13.0	313	33	10.5	379	31	8.2
B-cell chronic lymphocytic leukaemia/small lymphocytic lymphoma (CLL/SLL)	498	31	6.2	1 120	54	4.8	1 435	55	3.8
Diffuse Large B-cell Lymphoma (DLBCL)	1 194	88	7.4	1 791	114	6.4	1 911	98	5.1
Multiple myeloma	1 082	102	9.4	2 192	188	8.6	2 370	182	7.7
Colorectal cancer, adenocarcinoma	3 744	156	4.2	6 233	197	3.2	5 931	157	2.6
Female breast cancer	1 145	227	19.8	2 277	293	12.9	2 457	317	12.9
Squamous cell carcinoma of the head and neck	1 763	72	4.1	2 947	152	5.2	3 225	163	5.1
Malignant melanoma of the skin	115	3	2.6	185	8	4.3	157	7	4.5
Non-small-cell lung cancer	7 163	455	6.4	11 242	663	5.9	11 275	537	4.8
Epithelial Ovarian Cancer	401	29	7.2	682	33	4.8	733	46	6.3
Renal cell carcinoma	595	10	1.7	810	43	5.3	775	40	5.2
Prostate cancer	937	83	8.9	2 050	169	8.2	2 754	164	6.0
Malignant epithelioid mesothelioma of pleura	59	2	3.4	113	3	2.7	148	1	0.7

*Source: BCR-IMA; *Patients who died until 30/06/2018 were taken into account*

Table 68 – Proportion of patients with stage IV (/non-stageable) cancer who received systemic therapy within 14 days of death, time trend

Year of death:	2004-2008			2009-2013			2014-2018*		
	Denominator	Numerator	Proportion (%)	Denominator	Numerator	Proportion (%)	Denominator	Numerator	Proportion (%)
Cancer type									
Chronic myeloid leukaemia	107	44	41.1	178	58	32.6	218	54	24.8
Mantle cell lymphoma	177	45	25.4	313	50	16.0	379	58	15.3
B-cell chronic lymphocytic leukaemia/small lymphocytic lymphoma (CLL/SLL)	498	59	11.8	1 120	109	9.7	1 435	111	7.7
Diffuse Large B-cell Lymphoma (DLBCL)	1 194	215	18.0	1 791	247	13.8	1 911	233	12.2
Multiple myeloma	1 082	184	17.0	2 192	375	17.1	2 370	334	14.1
Colorectal cancer, adenocarcinoma	3 744	389	10.4	6 233	571	9.2	5 931	459	7.7
Female breast cancer	1 145	355	31.0	2 277	531	23.3	2 457	544	22.1
Squamous cell carcinoma of the head and neck	1 763	165	9.4	2 947	330	11.2	3 225	335	10.4
Malignant melanoma of the skin	115	10	8.7	185	15	8.1	157	16	10.2
Non-small-cell lung cancer	7 163	956	13.3	11 242	1 507	13.4	11 275	1 292	11.5
Epithelial Ovarian Cancer	401	59	14.7	682	65	9.5	733	92	12.6
Renal cell carcinoma	595	27	4.5	810	95	11.7	775	109	14.1
Prostate cancer	937	158	16.9	2 050	292	14.2	2 754	301	10.9
Malignant epithelioid mesothelioma of pleura	59	4	6.8	113	6	5.3	148	5	3.4

*Source: BCR-IMA; *Patients who died until 30/06/2018 were taken into account*

Table 69 – Proportion of patients with stage IV (/non-stageable) cancer who received systemic therapy within 30 days of death, time trend

Year of death:	2004-2008			2009-2013			2014-2018*		
	Denominator	Numerator	Proportion (%)	Denominator	Numerator	Proportion (%)	Denominator	Numerator	Proportion (%)
Cancer type									
Chronic myeloid leukaemia	107	61	57.0	178	92	51.7	218	80	36.7
Mantle cell lymphoma	177	90	50.8	313	81	25.9	379	123	32.5
B-cell chronic lymphocytic leukaemia/small lymphocytic lymphoma (CLL/SLL)	498	126	25.3	1 120	205	18.3	1 435	184	12.8
Diffuse Large B-cell Lymphoma (DLBCL)	1 194	405	33.9	1 791	452	25.2	1 911	418	21.9
Multiple myeloma	1 082	372	34.4	2 192	696	31.8	2 370	644	27.2
Colorectal cancer, adenocarcinoma	3 744	825	22.0	6 233	1 394	22.4	5 931	1 102	18.6
Female breast cancer	1 145	574	50.1	2 277	966	42.4	2 457	971	39.5
Squamous cell carcinoma of the head and neck	1 763	290	16.4	2 947	569	19.3	3 225	619	19.2
Malignant melanoma of the skin	115	19	16.5	185	39	21.1	157	39	24.8
Non-small-cell lung cancer	7 163	1 907	26.6	11 242	3 020	26.9	11 275	2 816	25.0
Epithelial Ovarian Cancer	401	116	28.9	682	167	24.5	733	192	26.2
Renal cell carcinoma	595	77	12.9	810	232	28.6	775	220	28.4
Prostate cancer	937	277	29.6	2 050	517	25.2	2 754	597	21.7
Malignant epithelioid mesothelioma of pleura	59	6	10.2	113	14	12.4	148	17	11.5

*Source: BCR-IMA; *Patients who died until 30/06/2018 were taken into account*

6 SUMMARY

In Table 70 we provide simplified figures presenting an overview of the observational results for the 12 selected cancer indications. For incidence years 2004-2017, the following four figures are presented: 1) one- to five-year observed survival probability, 2) median survival time, 3) oncology drug expenditures for the first two years after incidence, and 4) mean drug expenditures per patient for the first two years after incidence. More detailed figures, including details of the figure axes, are presented per cancer indication in this report (and appendix). More details on the patient characteristics, observed and relative survival probabilities (per incidence period) are available in the report and underlying appendix. With regard to the cancer drug expenditures, we have presented both the general gross expenditures (i.e. without refunds, see part 7.5), as well as the average expenditures per patient for the first two years after incidence. The latter provides a better picture of the increased average treatment costs per patient, while the general expenditure is also influenced by the number of patients treated. We note that the increase of the average treatment cost usually has a much greater impact on the increased expenditures than the number of patients being treated. Before giving an overview of the main findings, we also would like to remember the reader that observed expenditure information for the last years is not always 100% complete and might include an underestimation (see part 1.1.1.1).

Based on the observational data, in about half of the included indications, (slight) improvements[bb] in observed and relative survival are noticed, almost always accompanied by large increases in gross drug expenditures and mean treatment costs:

- In CML, an improvement in overall survival and relative survival over the years was seen. Gross expenditures doubled (from about €4.8 million in 2004 to €10 million in 2015). Mean treatment costs per patient were already above €40 000 in 2004 and increased further to about €64 500 in 2015.
- In multiple myeloma, observed and relative survival has remained stable between 2004 and 2013 while it tends to be higher for the last incidence period 2014-2017. Nevertheless, gross expenditures and mean treatment costs have increased steadily over time from less than €2.5 million (2004) to more than €40 million (2017) and from about €5 300 (2004) to about €59 200 (2017), respectively.
- In Non-Hodgkin lymphoma we get a mixed picture. In the CLL/SLL subgroup, overall and relative survival slightly improved over the years while gross expenditures increased fivefold over time (less than

[bb] The inclusion of an indication in the 'positive' or 'non-positive' list is not a black and white exercise. The assessment is based on a joint review of the evolution of survival over the reported incidence periods, 3-year survival probability and median survival. The magnitude of the difference in these outcomes is also taken into account. In some cases, the positive evolution is only noticeable for a specific period. For example, in NSCLC and RCC, we notice a positive evolution in the last incidence period, while this was not the case over the first two reported incidence periods while there was already an increase in drug use and expenditures.
There is also no algorithm to determine whether an observation can be considered sufficiently positive or not. In multiple myeloma, the KM curves for the three incidence periods are similar in the first 2 years, but thereafter a positive difference is noticeable mainly for the last incidence period, which is also observed in the 3-year survival probability and median survival. Prostate cancer is also on the 'positive' list. While the KM curves for the three incidence periods show an improvement only to a limited extent, we consider the evolution of the 3-year survival probability and the evolution and size of the improvement in the median survival to be sufficient to include this indication in this 'positive' list.
We included colorectal cancer in the 'non-positive' list. However, the 3-year survival probability in 2004 is significantly different from that in 2017. However, this was not the case for subsequent years, the KM curves for the three incidence periods are very close to each other and the absolute improvement in median survival over time is also limited. Head and neck is also in the 'non-positive' list. The change in median survival looks positive at first glance, but we consider the absolute differences to be too small to include this in the 'positive' list. Also the 3-year survival and the KM-curves for the 3 incidence periods show no great improvements while the evolution in use and expenditure of medicines was significant.

€1 million in 2004 to about €5 million in 2015). Average treatment costs increased from about €3 300 (2004) to about €19 200 (2016) per patient. In the DLBCL subgroup, overall and relative survival slightly increased between 2004-2008 and 2009-2013; no further improvement was seen for the period 2014-2017. Increases in gross expenditures were relatively modest (from about €6 million (2004) to about €7.7 million (2016)) and the average treatment cost remained stable at around €12 000 per patient. Unfortunately, in the Mantle cell lymphoma subgroup, overall and relative survival have not clearly improved over the years while gross expenditures increased from about €0.8 million (2004) to about €4 million (2016) and average treatment costs raised form about €8 800 to more than €30 000 per patient.

- In stage IV NSCLC, compared to earlier incidence years, observed and relative survival of patients diagnosed in 2014-2017 seems to have improved. While the median survival time was not positively influenced, improvements in the one- to five-year observed survival probability were clearly present. Up to 2014, gross expenditures already increased from about €5.1 million in 2004 to about €23.6 million in 2013 without any observed improvement in survival. In the last incidence period, gross expenditures increase steeply to more than €77 million. The same trend is seen in mean treatment costs: from about €4100 in 2004, to about €13 200 in 2013 and €36 000 in 2017.
- For stage IV prostate cancer, observed and relative survival slightly improved over time coinciding with an increase in gross expenditures (from about €1 million in 2004 to about €6.6 million in 2016) and mean treatment costs from about €2 300 in 2004 to about €9 000 in 2016.
- Finally, for stage IV RCC, an improvement of observed and relative survival is seen for patients diagnosed between 2014 and 2017. However, also here, already before 2014 there was a sharp increase in gross expenditures (from almost non-existing in 2004 to about €4.5 million in 2013) and mean treatment costs (from about €3 300 in 2004 to €29 300 in 2013). In the last incidence period, these expenditure increased further to about €6.5 million and €46 200 in 2016, respectively.

The results for the other half of the examined indications is not very positive when looking both at the evolution of survival and gross drug expenditures:

- In stage IV breast cancer, there is a large increase in gross expenditures (almost times four up to about €16 million) and average drug expenditures (times three up to about €24 500 per patient) over the period 2004-2017, without any noticeable improvement in observed or relative survival.
- In stage IV colorectal cancer, observed and relative survival did not change substantially over time, while drug expenditures increased from less than €10 million in 2004 to €20-24 million yearly in 2009 and the following years. Average drug expenditures per patient similarly increased from about €10 600 to more than €18 000 over the same period.
- Also for stage IV head and neck cancer, observed overall survival and relative survival did not change significantly over time. In contrast, gross expenditures and mean treatment cost per patient substantially increased from about €420 000 (2004) to about €5.5 million (2016) and less than €1 000 (2004) per patient to more than €8 000 (2016), respectively.
- For stage IV melanoma, no clear positive trend observed and relative survival was observed over the years. Nevertheless, expenditures increased sharply. Drug expenditures were almost non-existing before 2011 and went up to more than €3.2 million in 2016. Average treatment costs per patient, which were less than €1000 before 2011, reached almost €100 000 per patient in 2016. We note that for stage NA melanoma, an improvement in observed and relative survival was seen in the last incidence period.
- In mesothelioma (stage III/IV/X), no clear improvement in observed and relative survival is noticeable over the incidence years. Also data for Flanders starting from incidence year 2000 show no positive evolution in survival. Also for this indication, a significant increase in gross expenditures (from about €103 000 (2004) to about €1.6 million

(2015)) and average treatment costs (from about €2 500 (2004) to more than €16 000 (2015)) is observed.

- And finally, for stage IV ovarian cancer, no clear improvement in observed and relative survival is perceptible over the incidence periods while gross expenditures more sharply increased from less than €1.5 million before 2013 to about €4 million since 2014 and average treatment costs more than doubled from about €12 500 in 2004 to €26 200 in 2016.

In indications and time periods where there is a (strong) increase in gross expenditures/mean treatment costs, and no clear improvements in overall survival, the effectiveness on survival (and therefore also the cost-effectiveness) can be questioned. An important remark is that overall survival is not the only important outcome measure for assessing (cost-)effectiveness. The (impact on) quality of life is also of great importance in cancer treatments and this impact is not at all reflected in these observational survival data. This is correct, however, the impact on quality of life is also very uncertain as measuring and reporting of quality of life in the clinical trials is often severely flawed (see part 7.3).

Furthermore, we should point out that the above findings are based on observational real-world data and should be interpreted with the necessary caution (see part 7.1). Based on these observational data, a causal relationship cannot be demonstrated. An improvement cannot specifically be linked to the use of certain cancer drugs because, for example, other aspects of care have also improved. Vice versa, if no improvement is noticeable, this can also be related to other factors related to the composition and co-morbidities present in the underlying population obscuring the treatment effect. Where staging is present, we focused on stage IV cancers. This is because innovative drugs are first introduced in this group and we assume that other changes besides drug expenditures would be neutral or mainly benefit survival and not the other way around. Other factors like screening policies and stage migration effects probably will also have less influence in stage IV cancers. If we do not see an improvement while new cancer drugs are introduced, then we can also question the impact on the overall survival in the real-world setting of these cancer drugs without claiming that these observations provide hard evidence.

One of the arguments to explain some of the disappointing observations in some indications is that we might not see the impact because it is only a limited part of the population that receives the treatment, as shown in the uptake tables, and therefore only a small part of the patients can experience positive effects. Or similarly, that a larger group receives treatment while the positive treatment effect is limited to a small proportion of these patients. For example, in NSCLC we see an improvement in the 1- to 5-year observed survival probability in the last period, while no improvement is visible in the median survival time. Indeed, only a limited part of the population may experience a clinically relevant positive impact on survival. Nevertheless, it is an observation that the (cumulative) extra gross expenditures for the cancer treatments is clearly visible, and that we only observe (slight) improvements in overall survival in a limited number of the 12 cancer indications. It might thus indeed be true that benefits on survival are rather limited in absolute number (see part 7.2). An important but difficult question policy makers can pose is whether society should allocate (large) extra expenditures from the limited health care budgets to cancer drugs for which the added value for the patient might be limited or is unknown.

Linked to the above, we must also stress that the expenditures presented in this report are gross expenditures. Confidential refunds and taxes could not be taken into account in our figures since we cannot assign them to a specific drug within the selected cancer indications. Nevertheless, there are substantial refunds and taxes which of course reduces the actual net cancer drug expenditures (see part 7.5).

Another limitation that can be cited is that we have not included the most recent cancer drugs in our data. The development of such cancer drugs is evolving very fast with new targeted therapies and immunotherapies coming up. The impact on overall survival and QoL of these newer drugs may be much more prominent. Our observational figures are indeed limited to incidence year 2017 with (incomplete) follow-up data up to mid 2019. It is correct that we will always run somewhat behind. However, also for the included cancer drugs, stakeholders probably have hoped for clear improvements in survival and/or QoL. On the basis of this report, we therefore wish to transfer the message 1) not to assume that all new cancer drugs, so-called ‘innovations’, provide a (large) added value to patients at

the population level, 2) to be aware that it is important to collect the necessary reliable evidence to assess an innovation's added value or make sure this information is gathered in due time (see part 7.6). We also observe the relatively strong increases in gross cancer drug expenditures during the last years of our observations in some cancer indications. Various stakeholders have also reported on the use of even more expensive interventions, like CAR T-cell therapy. In combination with the enormous pressure on the available resources, this will only increase the need to identify the interventions with a clear added value. In addition, it is also important to reinvest the resources of interventions with an unfavorable cost-effectiveness ratio to those that create a relatively large added value in relation to the extra resources needed.

As far as cost-effectiveness is concerned, we mainly relied on data from UK analyzes. We do not consider this to be a major problem for formulating our conclusions and recommendations given 1) the underlying evidence that is used in Belgian or UK HTA reports refers to the same international RCTs and there is the same problem of confidential prices in both countries (see part 7.7), and 2) we do not explicitly formulate conclusions about the cost-effectiveness of an individual cancer drug in a particular indication as in a classic HTA, but rather focus on general findings and problems in estimating the cost-effectiveness of cancer drugs based on the assessments of independent experts. In general, on the basis of the HTA-based economic evaluations we identified for the selected drugs in the 12 cancer indications, we notice the following:

- In almost all recent evaluations confidential prices are involved. Evaluations identified without confidential price discounts are usually older reports. In the more recent evaluations, we are not only confronted with discounts for the intervention itself, but also for one or more comparators or for the follow-up treatment if the disease is progressing. It makes the impact on incremental costs and ICERs difficult to calculate. This applies in the first place to independent researchers who have no insight into the individual discounts. However, this also becomes problematic for company calculations as they cannot receive information about the discounts other companies received for their comparators and/or follow-up treatments. The ICER based on the company's submission is thus not always the ICER used for decision making.
- There is almost no single assessment where the authors conclude an intervention is cost-effective if the official list prices are used. One of the exceptions was e.g. the evaluation of bortezomib in multiple myeloma. If interventions are recommended, it is most often under the condition that the confidential price discounts are applied.
    - Based on the UK analyzes, we note that often higher ICERs are accepted than the normal ICER threshold that applies in the UK. The exceptions then refer to the so-called "end-of-life" criteria[cc]. In other cases, interventions with relatively high ICERs above the range that NICE considers a cost-effective use of resources, even under the end-of-life criteria, are recommended for the Cancer Drugs Fund.
    - It is rather exceptional that reviewers explicitly refer to lower ICER threshold values because of the uncertainty in the clinical evidence and cost-effectiveness. For example, one of these exceptions was TA569 (2019), in which the researchers state that "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."[83]
- Due to the confidentiality, the results are usually not transparent and we cannot verify whether the policymakers paid a "correct" price for these drugs in relation to their added value. Together with this lack of

[cc] ICERs exceeding the NICE cost-effectiveness threshold of £30 000 per QALY gained may be considered as an effective use of NHS resources provided that: 1) the treatment is indicated for patients with a short life expectancy, normally less than 24 months; 2) there is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment, and 3) the treatment applies to small patient populations.[420]

transparency about the decision-making ICERs, the accountability of policy makers also largely disappears. We cannot longer see, for example, whether no additional price is paid for a product without added value or when the added value is limited/unknown, whether this is also reflected in the price paid.

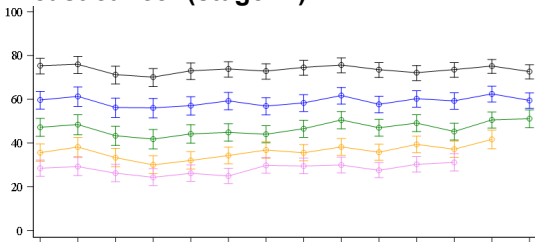
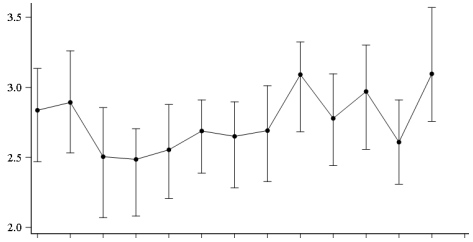
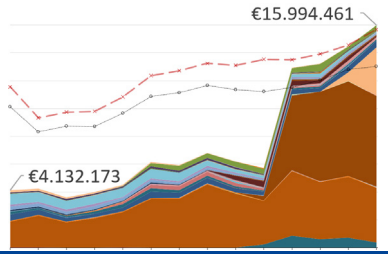
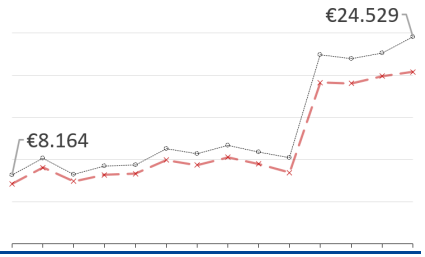
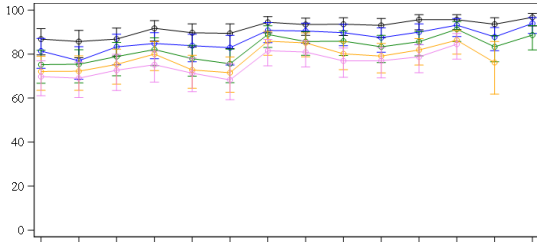
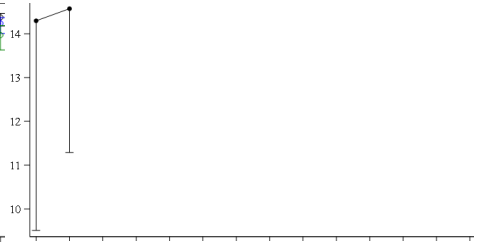
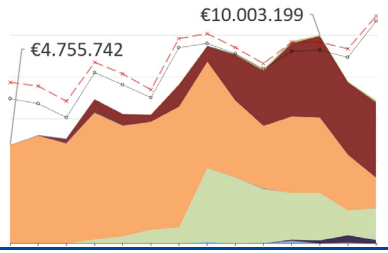
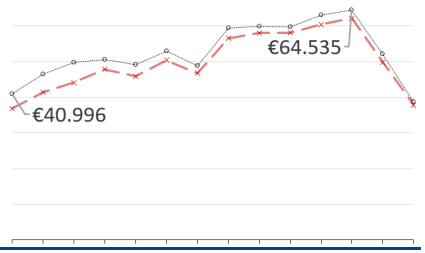
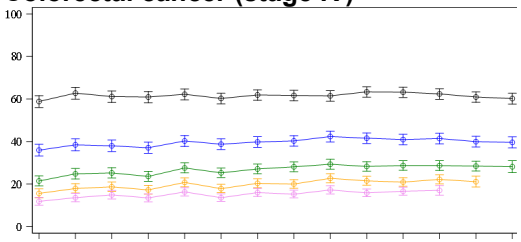
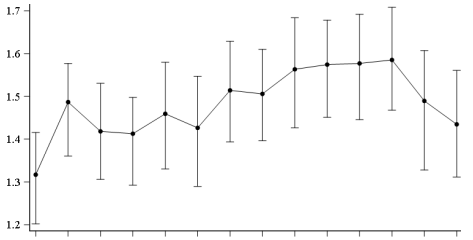
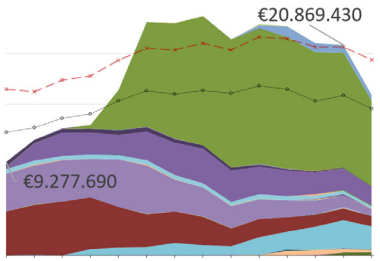
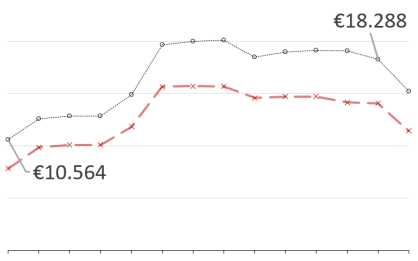
- In all economic evaluations, the greatest uncertainty relates to the estimation of the treatment effect on overall survival. This was mainly due to the following reasons:
  - The absence of a head-to-head trial comparing the intervention with the appropriate comparator(s).
  - When such a head-to-head trial was available, to the immaturity of the trial data and the difficulty to extrapolate overall survival data.
  - The link between the surrogate endpoints (e.g. PFS) and the final outcomes (OS & QoL) that is strongly questioned (see part 7.4)
  - In a number of cases, explicit reference is also made to the problems surrounding cross-over that biased the intention-to-treat analyses.
- The impact on quality of life is also associated with great uncertainty. There are problems with the calculations of QALYs (gained) since quality of life measurements with a generic utility instrument is often lacking in the underlying trials (see part 7.3).
- Not surprisingly, in addition to the impact on survival, the price of the intervention is also one of the most determining variables for an intervention's cost-effectiveness. This makes the results very sensitive to the discount awarded. Discounts on the intervention will improve it's cost-effectiveness. In contrast, we note that the (confidential) discount applied for the comparator also has a major influence on the cost-effectiveness: discounts for the comparator will have a negative impact on the intervention's cost-effectiveness.
- The choice of the comparator can have a very big impact on the calculated incremental costs, incremental effects and ICERs (see part 7.8).

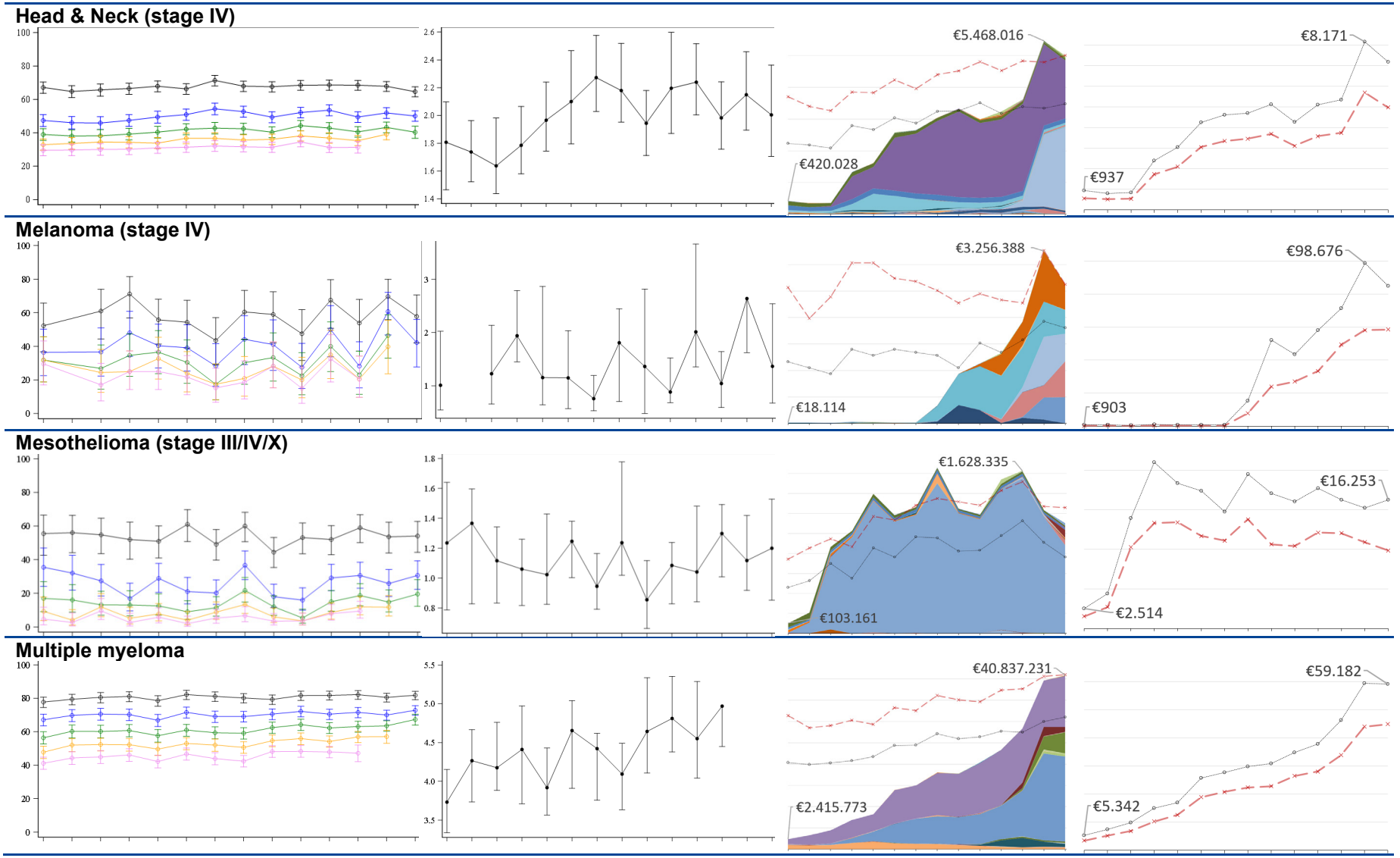
Finally, we would like to highlight that our report is not a classic HTA report. We have not focused on a specific cancer treatment in a specific cancer indication. We have not performed a separate search strategy for the most recently published RCTs. No up-to-date meta-analysis was performed. Nor has a separate specific search strategy been carried out to analyze the impact on adverse events. No context-specific economic evaluation has been carried out for the Belgian situation. Instead, we focus on presenting the Belgian observational data and results from previous systematic reviews for overall survival and QoL and HTA-based economic evaluations. This approach has methodological shortcomings compared to an individual HTA report. The big advantage, however, is that we are able to show a broad picture: observational survival data, gross expenditures, information from economic evaluations from independent bodies, etc. was collected and presented for a wide range of cancer drugs in 12 cancer indications.

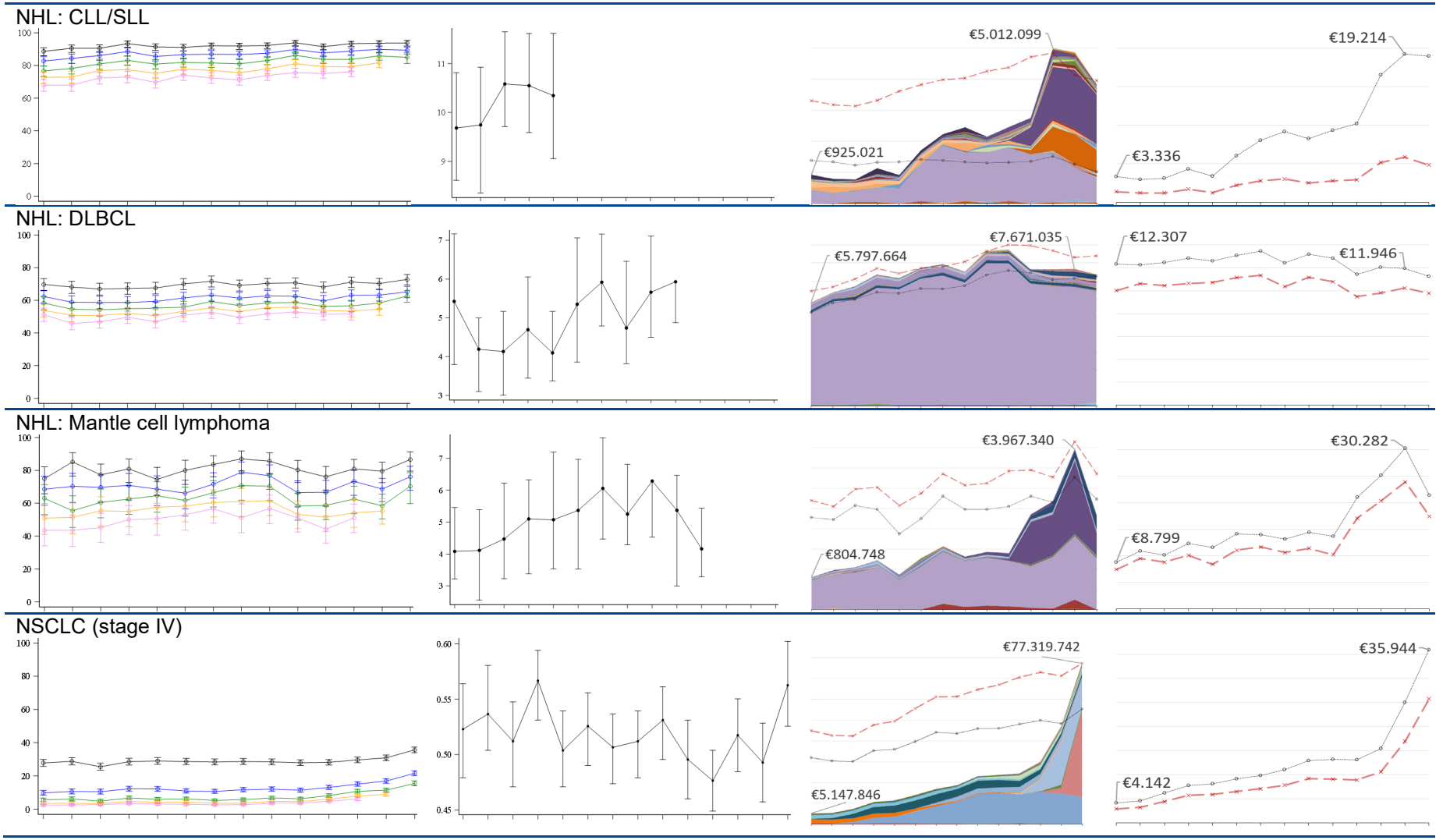
As summarized above, there is a red line in the observations regarding expenditure and impact on overall survival, as well as in the problems identified in the economic evaluations. We hoped to be able to present more positive examples with a more clear improvement in overall survival, as was seen after the introduction of imatinib (Glivec®) for CML. We also explicitly stated this in our call for examples that was mailed to a large group of external experts at the beginning of the project, as a first look at the results did not identify many similar examples.

Different stakeholders will approach the results of this study with their own arguments. We wish to discuss some of these arguments (see part 7.9) and emphasize that 'the health care market' is not just any market after all, to allow for a balanced discussion and formulate constructive policy recommendations (see synthesis of the report).

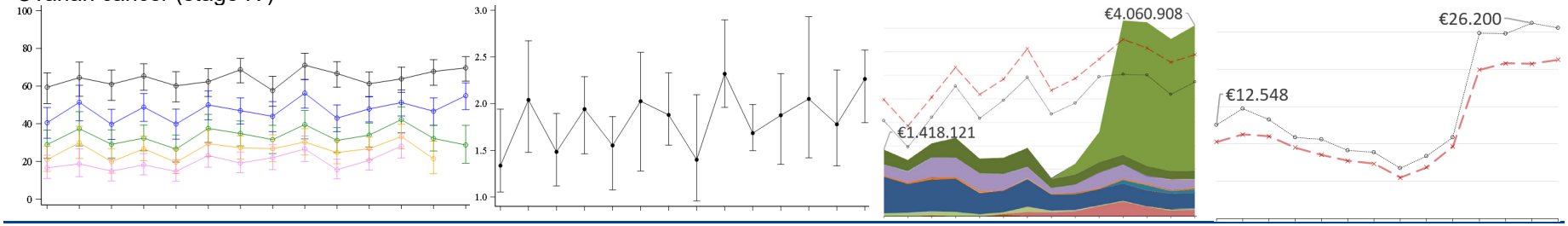
Table 70 – Overview of observational results for 12 cancer indications (2004-2017, information per incidence year): simplified figures of Time trend (1- to 5-year observed survival probability (%) – 1st column), Median survival time (2nd column), Oncology drug expenditures for the first two years after incidence (3rd column), Mean drug expenditures per patient for the first two years after incidence (4th column)

Tumour type				
Breast cancer (stage IV)				
CML				
Colorectal cancer (stage IV)				

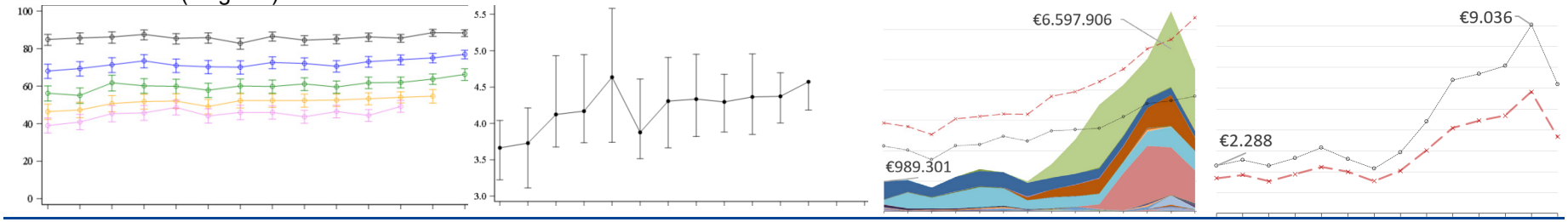

Head & Neck (stage IV)
€5.468.016
€420.028
€8.171
€937
Melanoma (stage IV)
€3.256.388
€18.114
€98.676
€903
Mesothelioma (stage III/IV/X)
€1.628.335
€103.161
€16.253
€2.514
Multiple myeloma
€40.837.231
€2.415.773
€59.182
€5.342


NHL: CLL/SLL
€5.012.099
€925.021
€19.214
€3.336
NHL: DLBCL
€7.671.035
€5.797.664
€12.307
€11.946
NHL: Mantle cell lymphoma
€3.967.340
€804.748
€30.282
€8.799
NSCLC (stage IV)
€77.319.742
€5.147.846
€35.944
€4.142

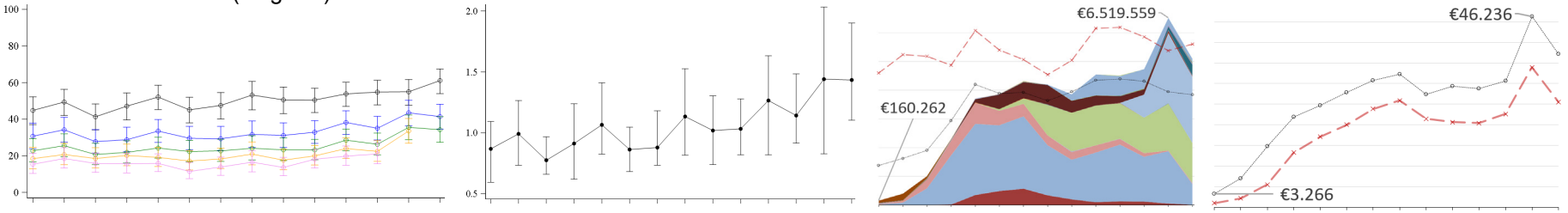
Ovarian cancer (stage IV)



Prostate cancer (stage IV)



Renal Cell Carcinoma (stage IV)



In this table, we provide simplified figures without details of the axis, what the lines present, etc.. For full details, we refer to these figures in the full report.

Key points

Belgian observational data:

- **The increase of the average treatment cost usually has a much greater impact on the increased expenditures than the number of patients being treated**
- **In about half of the included indications,[dd] (slight) improvements in observed and relative survival are noticed, almost always accompanied by large increases in gross drug expenditures and mean treatment costs. These indications are the following: CML, multiple myeloma, NHL, NSCLC (st.IV), prostate cancer (st.IV) and RCC (st.IV).**
- **The results for the other half of the examined indications is not very positive when looking both at the evolution of survival and gross drug expenditures. This is the case for the following indications: breast cancer (st.IV), colorectal cancer (st.IV), head and neck cancer (st.IV), melanoma (st.IV), mesothelioma (st.III/IV/X) and ovarian cancer (st.IV).**
- **In indications and time periods where there is a (strong) increase in gross expenditures/mean treatment costs, and no clear improvements in overall survival, the effectiveness on survival (and therefore also the cost-effectiveness) can be questioned. In line with findings in international literature, the observational findings indicate it is inappropriate to automatically associate 'innovative' oncology drugs with a (large) added value for patients.**
- **Our observational data do not reflect the impact on QoL. Unfortunately, the impact on quality of life is also very uncertain in clinical trials as measuring and reporting of quality of life is often severely flawed.**

Economic evaluations:

Most identified economic evaluations are UK-based analyses.[ee] In general, we notice the following:

- **In almost all recent evaluations confidential prices are involved (for the intervention, comparator and/or following treatments). In such cases, the incremental costs and/or ICERs cannot be published transparently. In cases where there is a confidential price discount for treatments of other companies, even the ICER based on the company's submission is not the one used for decision making.**
- **There is almost no single assessment where the authors conclude an intervention is cost-effective if the official list prices are used.**
- **The greatest uncertainty relates to the estimation of the treatment effect on overall survival. This was mainly due to the following reasons: lack of head-to-head trials comparing the intervention and the appropriate comparator(s), immaturity of trial data, use of surrogate endpoints and uncertain association with final endpoints (OS & QoL), and in some cases also cross-over of patients that biased the intention-to-treat analyses.**

[dd] We summarized the results of the observational data in a 'positive' and 'non-positive' list. The inclusion of a specific indication in one of these two categories is no black and white decision but based on the joint review of the evolution of survival over the three reported incidence periods, 3-year survival probabilities and median survival. The magnitude of the difference in these outcomes is also taken into account.

[ee] This is not a problem since the underlying RCT-based evidence used in these economic evaluations is not different from the RCTs used in Belgium. Furthermore, we focus on general findings and problems in estimating the cost-effectiveness of cancer drugs based on the assessment of independent experts.

- **The impact on quality of life is also associated with great uncertainty. Problems with QALY calculations are especially related to not measuring the impact on QoL with a generic utility instrument and/or not transparently reporting results for these estimates.**
- **Finally, not surprisingly, both the price and the choice of the comparator also have a big impact on the calculated incremental costs, incremental effects and ICERs.**

7 DISCUSSION

7.1 Real-world observational data

7.1.1 Data from the Belgian Cancer Registry (BCR) and Intermutualistic Agency (IMA) – strengths/limitations and nuance needed

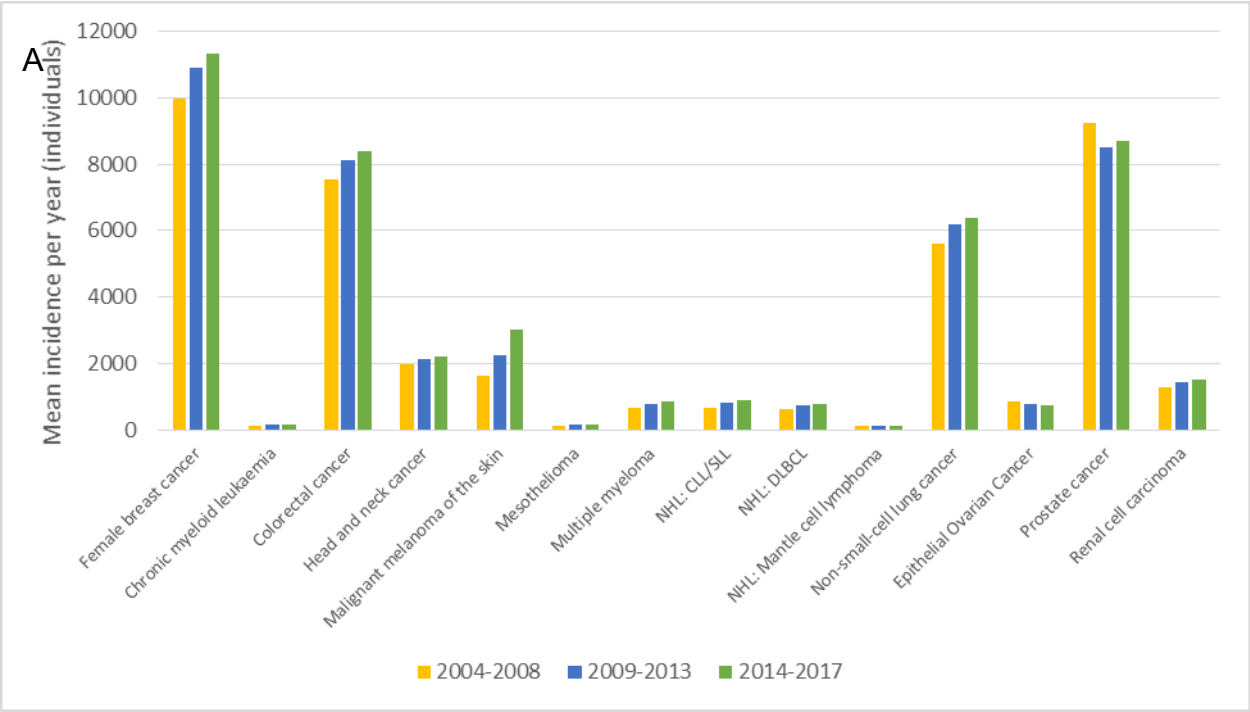
The data used in this report are also subject to strengths and limitations. The strengths are linked to the large sample size of the database, they reflect the real-world situation, the availability of information over a long time period, the possibility to link the information from the BCR to IMA data (see methodology), etc. It is also a legal obligation to register, and thus BCR data are almost completely in registering new cases for the whole of Belgium. In addition, linkage with the National Number allows to update for the vital status of each patient. We also have information on the stage of the disease at time of diagnosis (where applicable). This is very important since e.g. screening or improved diagnosis of diseases might influence the underlying composition of the population within a specific cancer indication. Looking at survival data for all stages combined might be very difficult to interpret. Therefore, all figures are presented separately by disease stage at diagnosis.

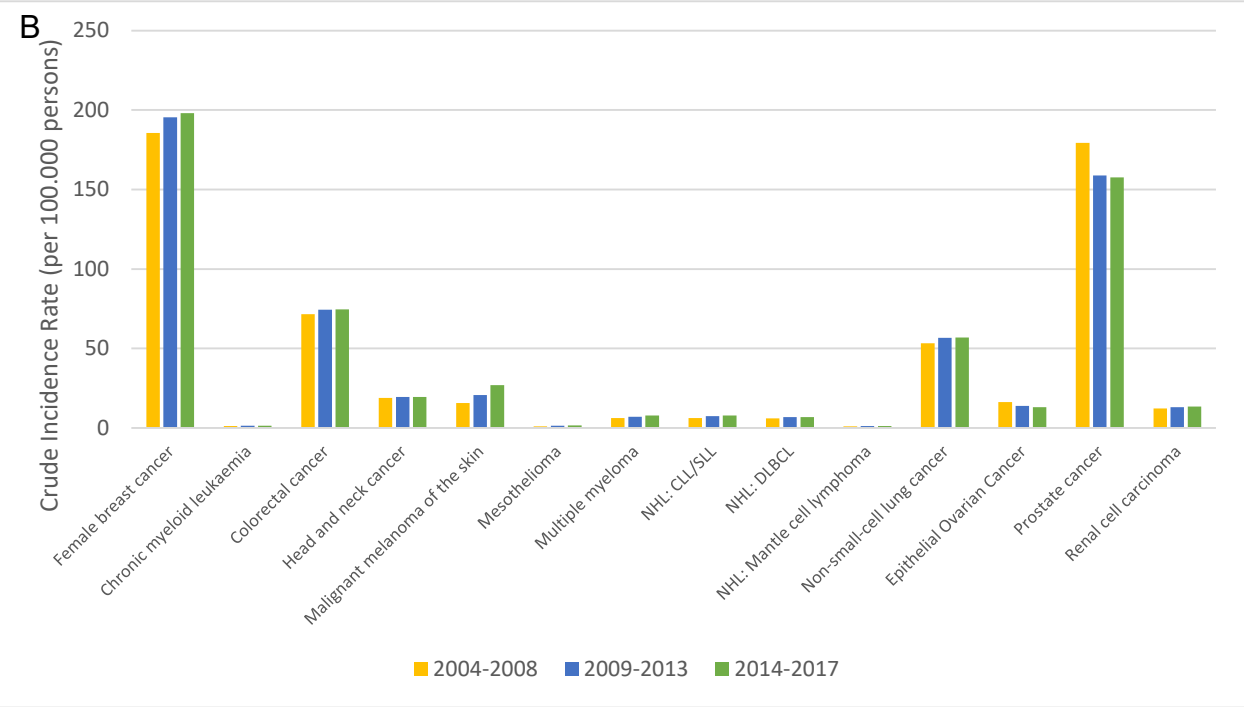
Concerning limitations of such real-world data, we wish to stress that the necessary nuance is needed when interpreting the results of the presented figures and tables. The underlying population does not necessarily reflect exactly the same population as described in the reimbursement criteria. When the reimbursement of cancer drugs is limited to specific subgroups, those subgroups could not be selected if the specific information is not available in the BCR data. For example, at this moment, it was not possible to make a distinction between the HER2-positive or –negative breast cancer population. This might be possible in the (near) future. Furthermore, the underlying population in the selected cancer indications is also not necessarily comparable over time. For example, introduction of screening and/or improvement in available diagnostic procedures may result in earlier detection of specific cancers but also may be accompanied with overdiagnosis. For most of the selected cancer types, we notice an

increase in the average yearly cancer incidence over the three time periods in absolute numbers (see panel A in Figure 10). However, crude incidence rates per 100 000 persons (see panel B in Figure 10) show rather stable figures over the last two incidence periods. In addition, changes in non-cancer related mortality, e.g. due to ischemic heart disease, stroke, chronic obstructive pulmonary disease (COPD), diabetes, etc. might impact the observed survival. This is partly compensated for by displaying the relative survival figures in appendix. However, also the interpretation of these figures needs nuance, since matching to the general population is performed for a limited number of variables (gender, age, calendar year and region). Other potential important factors as tobacco and alcohol consumption, obesity, diabetes, socioeconomic status, etc. are not available. Lastly, a change/improvement in e.g. stage classification is also possible over time with stage migration effects over time. For example, since 2017, the new TNM-8 classification is used in the BCR data.

Another limitation is that BCR does also not have information related to subsequent disease progression/recurrence, and thus we could not further differentiate between e.g. first- or second-line treatment. Also the underlying cause of death is not registered in the available databases.

Figure 10 – Average yearly cancer incidence for the three incidence periods (panel A: absolute numbers; panel B: crude incidence rate (per 100 000 persons)





CLL/SLL: B-cell chronic lymphocytic leukaemia/small lymphocytic lymphoma. Source: BCR.
For female breast cancer and epithelial ovarian cancer, crude incidence rates are expressed versus the total female population. For prostate cancer, this is versus the total male population. For other cancer, the total Belgian population was taken into account.

On top of the above, when linking the evolution in the survival figures with the evolution in drug use and expenditures, changes in cancer-related mortality due to non-drug interventions (e.g. improvement in radiotherapy techniques and surgical procedures) should also be taken into account. The impact of these elements is also not included in this report. The graphs only show the observed and relative survival (in the main report and/or in appendix). This does not comprise other relevant outcomes, such as the patient's quality of life (see 7.3). In other words, the figures we present are based on purely observational data which coincides with the limitations when interpreting such data.

Finally, as mentioned in the methodology section, the IMA data for the last years are not always 100% complete; IMA-data until mid 2019 could be taken into account for this report, but since a delay of 2 years is possible before IMA-data are 100% complete, expenditure as from mid 2017 are incomplete. Though, expenditures for 2017 are far less incomplete than those from 2019. Another limitation is that within the scope of this project, we only selected cancer drug expenditures excluding other cancer-related costs (e.g. for diagnosis, surgery, radiotherapy, hospitalisation etc.). Furthermore, drugs that are not classified under L01 (and additional included categories, see 1.1.1.1), such as e.g. bisphosphonates (M05B), are not included in our observed drug expenditures. Finally, the expenditures are also gross expenditures not taking into account the impact of confidential discounts and taxes (see part 7.5).

7.1.2 Limitations inherent to the use of observational data – no good estimate of treatment effect

(Meta-analyses of) well performed randomized controlled trials are the golden standard and provide the highest level of evidence to establish the treatment effect of different therapeutic approaches. Some of the criticism towards RCTs is that they are expensive and only reflect the treatment effect in ideal circumstances.

However, real-world observational studies have important flaws for identifying the treatment effect. “Nonrandomized observational analyses of large electronic patient databases are being promoted as an alternative to randomized clinical trials as a source of “real-world evidence” about the efficacy and safety of new and existing treatments.[421-423”424] Regarding safety, “For drugs or procedures that are already being used widely, such observational studies may involve exposure of large numbers of patients. Consequently, they have the potential to detect rare adverse effects that cannot plausibly be attributed to bias, generally because the relative risk is large … .”[424] Regarding efficacy/effectiveness, “Nonrandomized clinical observation may also suffice to detect large beneficial effects when good outcomes would not otherwise be expected … .”[424]

“However, because of the potential biases inherent in observational studies, such studies cannot generally be trusted when – as is often the case [see part 7.2] – the effects of the treatment of interest are actually null or only moderate (i.e., less than a twofold difference in the incidence of the health outcome between using and not using the treatment).[425-427] In those circumstances, large observational studies may yield misleading associations of a treatment with health outcomes that are statistically significant but noncausal, or that are mistakenly null when the treatment really does have clinically important effects.”[424]

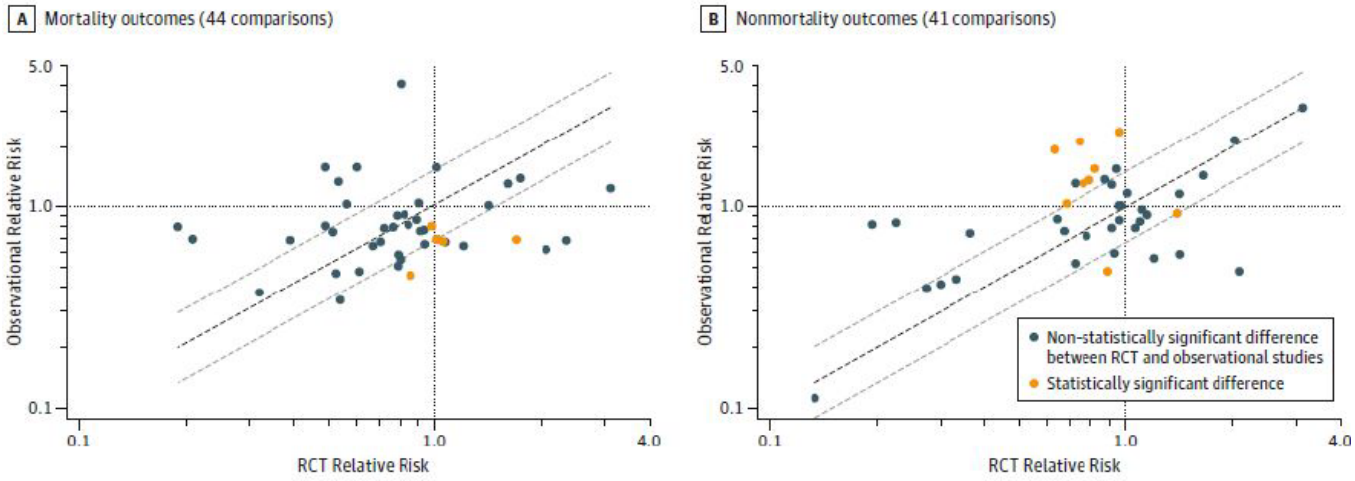
“Indeed, that is what would be expected in medical practice, since both the severity of the disease being treated and the presence of other conditions may well affect the choice of treatment (often in ways that cannot be reliably quantified). Even when associations of various health outcomes with a particular treatment remain statistically significant after adjustment for all the known differences between patients who received it and those who did not receive it, these adjusted associations may still reflect residual confounding because of differences in factors that were assessed only incompletely or not at all (and therefore could not be taken fully into account in adjusted analyses).”[424]

Banerjee and Prasad mention that “an aggressive therapy that looks favorable in observational data turns out to be beneficial less than half the time. Confounding by indication, a type of selection bias that means that we reserve aggressive therapies for the healthiest candidates, likely explains this finding. Aggressive therapies often look favorable in observational data not because they usually work, but because we preferentially deploy them in patients who are healthier than average.”[428]

“Neither propensity score nor instrumental variable approaches can correct for the risk of confounding from variables that were not measured or those that researchers do not completely understand.”[428] “The overall findings by Kumar et al[429] [see further] make it clear that even the most well-designed CER [comparative effectiveness research] study will not necessarily deliver results similar to RCT-based research.”[428]

If we look at evidence comparing RCT- and observational-based evidence, results are rather disappointing. Individual cases both in favor or disfavor can be presented. However, it is more interesting to look at the results of studies investigating the agreement/differences between RCTs and observational studies on a larger scale. In a EUnetHTA guidance document,[430] the authors refer to a viewpoint published in 2014 by Dahabreh and Kent in which there is concern that inferences from observational data can lead to poor health care decisions by misrepresenting association for causation.[431] In their article, they present the combined results of 3 studies contrasting the results of propensity score analyses and RCTs, comparing the effect of the same interventions in similar patient populations (Figure 11).[432-434] The figures show no clear pattern of agreement and the authors indicate there is no way of knowing when observational study results are reliable.[431] Methods to analyze the treatment effect based on observational data might improve in the near future. However, at this moment, evidence shows it often provides misinformation.

Figure 11 – Comparison of propensity score analyses and RCT results from 3 empirical assessments

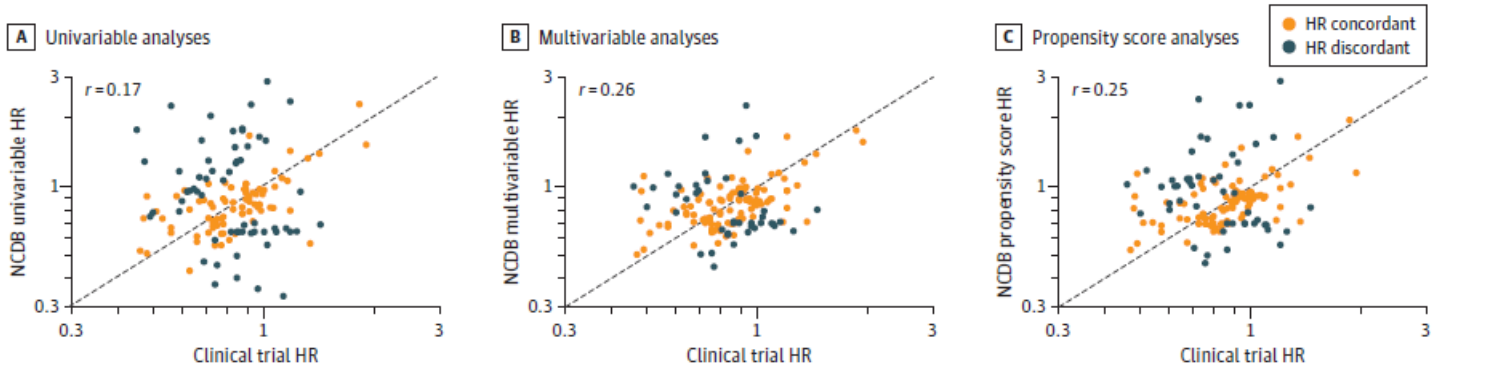


Scatter plots of results from empirical comparisons of propensity score analyses (y-axis) and corresponding randomized clinical trial (RCT) results (x-axis). Markers denote comparisons between observational and randomized study estimates for the same research question (similar populations, interventions, and outcomes); statistically significant differences ($P < .05$) are shown in orange. The dotted lines indicate lack of effect in RCTs (vertical lines) and observational studies (horizontal lines). Values lower than 1 indicate that the new treatment evaluated in the trial was more effective than the more established treatment; observational study results are expressed in the same way as the corresponding trial results. Markers in the top-right and bottom-left quadrants in each panel indicate agreement between randomized and observational results with respect to the direction of effects. Markers in the top-left and bottom-right quadrants indicate discordant direction of effects between designs. Black dashed diagonal lines indicate the line of identity (perfect agreement) between RCT and observational study results; gray dashed lines demarcate observational study relative risks that are between 0.67 and 1.5 times those produced by the corresponding RCT results. The term "relative risk" is used to denote risk, odds, or hazard ratio estimates, as reported in the 3 empirical analyses contributing data to this figure.

Source: Dahabreh and Kent (2014)[431]

More recently, in 2020, a study by Kumar et al. was published examining the extent to which comparative effectiveness analyses using observational cancer registry data produced results concordant with those of randomized clinical trials. “In this comparative effectiveness study, a total of 141 randomized clinical trials referenced in the National Comprehensive Cancer Network Clinical Practice Guidelines for 8 common solid tumour types were identified. Data on participants within the National Cancer Database (NCDB) diagnosed between 2004 and 2014, matching the eligibility criteria of the randomized clinical trial, were obtained.”[429] This study is thus also looking at oncology indications over a time window similar to the present report. In contrast, it only included patients with no previous diagnosis of cancer, while in our report patients with multiple tumours are included. A major limitation of this study is that owing to a lack of available data on specific systemic agents, they were unable to include randomized clinical trials comparing single-agent with multiagent systemic regimens or randomized clinical trials evaluating 2 different systemic agents. Furthermore, RCTs often have specific eligibility criteria, which are not available in the observational database. “The trials addressed an array of clinical questions (e.g., addition of radiotherapy, 18 [13%] and addition of surgery, 6 [4%]), and nearly half evaluated the utility of adding systemic therapy to surgery or radiotherapy (67 [48%]).”[429] “The trials included 85 118 patients, and the corresponding NCDB analyses included 1 344 536 patients. Three Cox proportional hazards regression models were used to determine hazard ratios (HRs) for overall survival, including univariable, multivariable, and propensity score–adjusted models. Multivariable and propensity score analyses controlled for potential confounders, including demographic, comorbidity, clinical, treatment, and tumor-related variables.”[429] “Analyses using the NCDB-produced HRs for survival were concordant with those of 141 randomized clinical trials in 79 univariable analyses (56%), 98 multivariable analyses (70%), and 90 propensity score models (64%) [see Figure 12].”[429] For calculated p-values, the results were even less concordant. The conclusion of the authors is that “the findings of this study suggest that comparative effectiveness research using cancer registry data often produces survival outcomes discordant with those of randomized clinical trial data. These findings may help provide context for clinicians and policy makers interpreting observational comparative effectiveness research in oncology.”[429]

Figure 12 – Comparison of Hazard Ratios (HRs) From Randomized Clinical Trials and Analyses With Data From the National Cancer Database (NCDB)



Hazard ratios shown for univariable analyses (A), multivariable analyses (B), and propensity score analyses (C). Each point on the scatter plot represents the HR for overall survival from 1 of the 141 randomized clinical trials in this study and the corresponding analysis within the NCDB. Yellow dots represent NCDB analyses in which the NCDB HR falls within the 95% CI of the HR in the clinical trial (concordant), and blue dots represent HRs from the NCDB analyses that fall outside the 95% CI of the HR in the clinical trial (discordant). The gray dashed line shows where clinical trial HRs equal NCDB HRs. The intersection of the axes represents an HR equal to 1.

Source: Kumar et al. (2020)[429]

"Multiple factors could potentially explain the observed differences between comparative effectiveness research with registry data and randomized clinical trials, although selection bias represents a key factor. The lack of randomization in observational research suggests the possibility of selection bias, which represents an imbalance in known or unknown confounding factors between treatment groups. Variables such as body mass index, tobacco use, or performance status, which are not recorded in cancer registry data, could be factors in treatment decisions and independently affect survival regardless of the treatment chosen."[429]

"The holy grail of medicine is to develop a system where we can make reliable inferences regarding the effectiveness of therapies as fast as possible, as cheaply as possible, with the least number of patients exposed to less effective regimens. Although many believe observational, real-world data will someday fill this niche, the work of Kumar and colleagues[429] reminds us that for the time being randomization remains the reference standard in cancer research."[428] As stated by Banerjee et al.: "Is there a role for retrospective CER studies in oncology in light of these findings? We believe the answer is yes. Observational studies may clarify issues of prognosis, patterns of real-world usage, rare adverse events, and glaring disparities in cancer care delivery. However, when it comes to establishing the fundamental efficacy of therapeutic interventions, caution is warranted, and propensity score matching is not a panacea."[428] "Part of the drive toward using nonrandomized observational studies to assess the effects of treatment comes from the current costs and complexity of conducting randomized trials.[435, 436]"[424] However, "Promotion of nonrandomized analyses of databases as a rapid source of "real-world evidence" about the effects of treatments is a false solution …"[424]

Key points

- **The strengths of the observational data used in this report are linked to the large sample size of the database, they reflect the real-world situation, the availability of information over a long time period, and the possibility to link the information from the BCR (~cancer diagnosis) to IMA data (~expenditures) and the National Number (~survival).**
- **The Belgian data presented are purely observational, which coincides with the limitations when interpreting such data.**
- **Evidence shows observational data often provide misinformation for estimates of the treatment effect. Current statistical approaches cannot correct for the risk of confounding from variables that were not measured or those that researchers do not completely understand.**
- **RCTs remain the gold standard to estimate an intervention's comparative treatment effect. As mentioned by Collins et al. "promotion of nonrandomized analyses of databases as a rapid source of "real-world evidence" about the effects of treatments is a false solution."[424]**

7.2 Limited benefits in overall survival

It is interesting to place our findings next to those of Davis et al.,[21] which looked at the available evidence of benefits on overall survival and quality of life of cancer drugs approved by the European Medicines Agency (EMA).

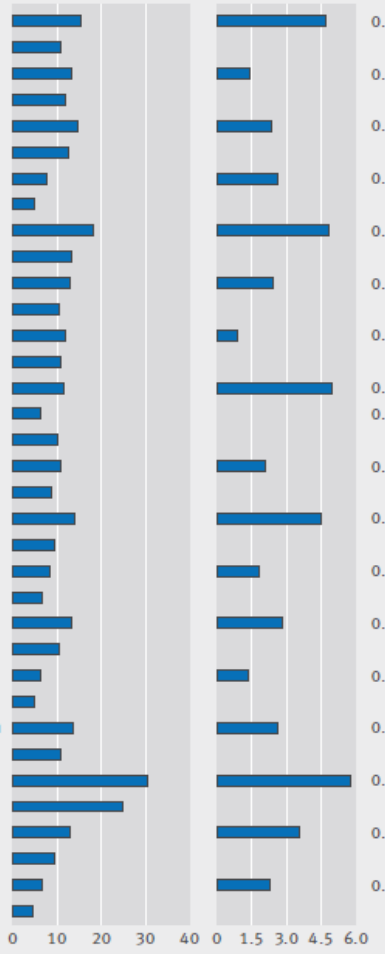
The authors of this study state "there is growing concern that the benefits offered by many new treatments for cancer—often discussed and promoted as "breakthroughs"[418, 437-439]—are marginal and might not be clinically meaningful to patients, despite rapidly escalating costs.[6, 440-443] Consequently, there have been calls to raise the evidence bar for market authorisation of new cancer drugs.[418, 440, 441, 444-446]"

According to the study results of Davis et al., "at time of market approval, according to the European public assessment report (EPARs), there was significant prolongation of survival in just over a third (24/68, 35%) of all drug indications (including 3/17 drugs to treat haematological malignancies and 21/51 drugs to treat solid tumours). There were gains in survival for seven compared with an active comparator, eight compared with placebo, one compared with best supportive care, and eight as add on treatment."[21] The results of 17 of these 24 studies with a statistically significant prolongation of survival is presented by the authors in Figure 13. Results for the other seven indications were not included because median overall survival could not be estimated at time of marketing authorization. "The magnitude of the overall survival benefit ranged from 1.0 to 5.8 months (median 2.7 months)."[21] "For the 44 (65%) remaining drug indications, there was no conclusive evidence at time of market authorisation that the drugs offered survival benefits, either as add on treatment or compared with placebo or existing treatment options in their authorised use."[21] Survival gains in most studies were thus inconclusive, and for studies with a significant improvement, the absolute survival benefit was rather limited.

Our findings in the medical literature (see overview table in appendix 13) are in line with the findings of Davis et al. Often meta-analysis of available RCTs could not show a clear survival benefit for the selected drugs and if a positive effect was proven, the effect was often limited in absolute terms. For example, for trastuzumab emtansine in HER(+) breast cancer and bortezomib in multiple myeloma, a beneficial effect on survival has not been shown in clinical trials (results inconclusive). In colorectal cancer, for example cetuximab and bevacizumab had a 'statistically significant' positive effect on overall survival in the first-line setting, but effect was small with an estimated hazard ratio of 0.89 (95%CI 0.80-0.98) and 0.85 (95%CI 0.78-0.94) respectively.

Figure 13 – Magnitude of overall survival benefit at the time of EMA approval (of interventions where a significant improvement of survival was proven).

Agent	Cancer site	Indication	Intervention and control groups	Median OS benefit (months)	Difference between groups (months)	Hazard ratio (95% CI)
Abiraterone acetate	Prostate	After chemo mCRPC (+pred)	Group 1: Abiraterone acetate + pred			0.74 (0.64 to 0.86)
			Group 2: PBO + pred			
Aflibercept	Colorectal	2nd line mCRC (+FOLFIRI)	Group 1: Aflibercept followed by FOLFIRI			0.82 (0.71 to 0.94)
			Group 2: PBO followed by FOLFIRI			
Cabazitaxel	Prostate	Hormone refractory mPC (+pred) previously treated with docetaxel	Group 1: Cabazitaxel + pred			0.70 (0.59 to 0.83)
			Group 2: Mitoxantrone + pred			
Decitabine	Haematological	1st line AML in chemo ineligible adults aged ≥65	Group 1: Decitabine and/or supportive care			0.82 (0.68 to 0.99)
			Group 2: Cytarabine and/or supportive care			
Enzalutamide	Prostate	mCRPC previously treated with docetaxel	Group 1:MDV3100 – enzlutamide			0.63 (0.53 to 0.75)
			Group 2: PBO			
Eribulin	Breast	3rd line mBC	Group 1: Eribulin			0.81 (0.66 to 0.99)
			Group 2: Physician's choice			
Erlotinib	Lung	Maintenance therapy in mNSCLC (previously platinum based chemo)	Group 1: Platinum based chemo + erlotinib			0.81 (0.70 to 0.95)
			Group 2: Platinum based chemo + PBO			
Ipilimumab	Haematological	2nd line unresectable or metastatic melanoma	Group 1: Ipilimumab + gp 100			0.68 (0.55 to 0.85)
			Group 2: gp 100 + PBO			0.66 (0.51 to 0.87)
			Group 3: Ipilimumab + PBO			
Ipilimumab	Haematological	1st line unresectable or metastatic melanoma	Group 1: Dacarbazine + ipilimumab			0.72 (0.59 to 0.87)
			Group 2: Dacarbazine + PBO			
Lapatinib	Breast	HER2+ HR- mBC (+trastuzumab) Previous trastuzumab + chemo	Group 1: Lapatinib + trastuzumab			0.74 (0.57 to 0.97)
			Group 2: Lapatinib			
Paclitaxel (nab-paclitaxel)	Pancreas	1st line (+gemcitabine) metastatic pancreatic adenoca	Group 1: Abraxane (paclitaxel) + gemcitabine			0.72 (0.62 to 0.84)
			Group 2: Gemcitabine			
Pemetrexed	Lung	Maintenance for mNSCLC (non-squam) after platinum based doublet chemo (with gemcitabine or taxane)	Group 1: Pemetrexed + BSC			0.79 (0.65 to 0.95)
			Group 2: Placebo + BSC			
Regorafenib	Colorectal	mCRC either after previous therapy with or eligible for 5-FU based chemo or VEGFi or EGFRi therapy	Group 1: Regorafenib + BSC			0.79 (0.66 to 0.93)
			Group 2: PBO + BSC			
Trastuzumab	Stomach	1st line HER2+ mGC or mGOJ adenoca	Group 1: Trastuzumab + (5-FU or capecatebine) and cisplatin			0.74 (0.60 to 0.91)
			Group 2: (5-FU or capecatebine) and cisplatin			
Trastuzumab emtansine	Breast	HER2+ unresectable or mBC after trastuzumab and/or taxane therapy	Group 1: Trastuzumab emtansine			0.68 (0.55 to 0.85)
			Group 2: Lapatinib + capecatebine			
Vemurafenib	Haematological	Unresectable or metastatic melanoma (BRAFV600 mut)	Group 1: Vemurafenib			0.62 (0.49 to 0.77)
			Group 2: Dacarbazine			
Vinflunine	Urinary	Advanced or metastatic TCC or urothelial tract previous platinum regimen	Group 1: Vinflunine + BSC			0.78 (0.61 to 0.96)
			Group 2: BSC			



Source: Davis et al., BMJ, 2017[21] For further details, we refer to the original publication.

The authors of this study also looked for potential reasons for the paucity of drug approvals with demonstrated survival advantages over existing treatments. In first instance, they mention that "only 18 (26%) indications for use in our cohort were supported by trials in which extension of life was the primary outcome, and trials that evaluated survival as a secondary endpoint might not have been powered to detect differences between groups with and without the experimental treatment."[21] Secondly, they refer to crossover from the control to the experimental treatment arm as a commonly cited reason for the lack of demonstrated survival benefits. However, they also note "that for some indications for use in [their] cohort there were no survival gains even in the absence of crossover.[65, 353, 447-449]"21

On the other hand, the authors also indicate they might even have overestimated the treatment effect: "we did not consider the appropriateness of clinical trial design, including whether a treatment administered in the control arm of a study was optimal or even informative. This is an important study limitation, which again means we might have overestimated the benefits offered by the drugs in our sample. For example, the control arm of the pivotal trial to support approval of ipilimumab for metastatic melanoma was an experimental treatment. Similarly, the pivotal trial to support lapatinib in combination with trastuzumab for patients with metastatic breast cancer used lapatinib monotherapy as the comparison—a treatment acknowledged in the EPAR to be "without established efficacy."[450] Although this trial design failed to isolate the effects of the test drug, the EMA nevertheless concluded that the reported benefit in survival was clinically relevant and could be attributed to the combination."[21]

In their conclusion, Davis et al. state that "when expensive drugs that lack clinically meaningful benefits are approved and paid for within publicly funded healthcare systems, individual patients can be harmed, important societal resources wasted, and the delivery of equitable and affordable care undermined."[21] The observations based on the Belgian overall survival data and drug expenditures in the twelve selected cancer indications seem to be in line with this statement.

Key points

- **Most of the cancer drugs enter the market without conclusive evidence whether the drug offers survival benefits. According to the study results of Davis et al., "at time of market approval, according to the European public assessment report (EPARs), there was significant prolongation of survival in just over a third (24/68, 35%) of all drug indications. … "The magnitude of the overall survival benefit ranged from 1.0 to 5.8 months (median 2.7 months)."[21] "For the 44 (65%) remaining drug indications, there was no conclusive evidence at time of market authorisation that the drugs offered survival benefits , either as add on treatment or compared with placebo or existing treatment options in their authorised use."[21] Survival gains in most studies were thus inconclusive, and for studies with a significant improvement, the absolute survival benefit was rather limited.**
- **As mentioned by Davis, and in line with the findings in this report, "there is growing concern that the benefits offered by many new treatments for cancer—often discussed and promoted as "breakthroughs"[418, 437-439]—are marginal and might not be clinically meaningful to patients, despite rapidly escalating costs."[21]**
- **David et al. conclude that "when expensive drugs that lack clinically meaningful benefits are approved and paid for within publicly funded healthcare systems, individual patients can be harmed, important societal resources wasted, and the delivery of equitable and affordable care undermined."[21]**

7.3 QoL as an important endpoint

7.3.1 A patient-relevant endpoint in clinical trials

Davis et al. also noted that "none of the pivotal studies supporting oncology drug approvals from 2009 to 2013 included quality of life as a primary outcome measure. This is perhaps unsurprising as the EMA does not require marketing authorisation holders to evaluate quality of life, even when drugs are intended for late line palliative care.[451] Of the 68 study indications, 37 (54%) were supported by a pivotal trial in which quality of life was evaluated as a secondary endpoint, and for only seven (10%) was there a significant improvement in quality of life at time of market entry. Neither the EPARs nor the published studies were consistent in reporting whether significant improvements for specific quality of life outcomes were also clinically relevant. These are particularly troubling findings as many of the drugs in our sample were approved to treat advanced metastatic disease, when the purpose of treatment is palliative – that is, to improve quality of life – or to extend life while ensuring that any survival gains are not outweighed by a deterioration in quality of life from adverse events or other negative factors related to treatment.[452, 453]"[21]

Furthermore, Davis et al. noted "there was also considerable variation in the reporting of quality of life endpoints in both the EPARs and the medical literature. Significant results might have been shown for isolated parameters or single subscales only, and it was not clear whether a net quality of life benefit had been shown. Nor was it consistently reported whether or not the magnitude of improvement was such that it would be considered clinically meaningful for patients. Consequently, we [the study of Davis et al.] might have overestimated the proportion of drugs that offer benefits on survival or quality of life and the clinical meaningfulness of these. Our findings, however, are consistent with recent findings from the US.[454, 455]"[21]

We noted that data on quality of life are often missing in systematic reviews on the efficacy of innovative oncology drugs.

7.3.2 Measuring QoL with a generic utility instrument

In our report, when going through the more than hundred selected HTA reports, we focused on the measurement of QoL with a generic utility instrument, as this is an important outcome for economic evaluations since the results of such instruments can be translated in utilities to enable the calculation of (differences in) quality-adjusted life years (QALYs). The EUnetHTA guidelines on health-related quality of life (HRQoL) generally recommend both the complementary use of disease- or population-specific and a generic HRQoL measure to adequately capture the impact of a disease on daily life. Both context and purpose are important to determine how QoL should be measured. The EUnetHTA guideline states it as follows:[456]

- "the purpose of the REA [relative effectiveness assessment] and the policy context determine the best practice guidelines for HRQoL measurement in the context of REA."

  "HRQoL can be measured for different purposes. The choice of the HRQoL instrument (generic versus disease-specific, utility versus profile measure) used will depend on the objective of the measurement. For cost-utility analyses, for instance, a utility measure is needed. For informing patients or clinicians, disease-specific HRQoL measures may be preferred over generic measures because they might capture better the specific impact of the disease and its intervention."

As mentioned in the EUnetHTA guidance document:[430] "The EUnetHTA guideline for methods for health economic evaluations recommends that:

- Results should be presented in terms of both a cost-effectiveness analysis (CEA) and a cost-utility analysis (CUA).[457]
- the primary outcome measure(s) should be presented where appropriate as natural units (including life-years) and as QALYs.[457]

The health-related quality of life (HRQoL) aspects of the QALY are captured in a HRQoL weight, expressed as utilities. Based on the review of guidelines used by EUnetHTA partners, the EuroQoL-5 dimension (EQ-5D) questionnaire is the most commonly recommended [generic utility]

instrument for the derivation of HRQoL weights, although other instruments are also mentioned (e.g. Health Utility Index (HUI), Short Form-6 dimension (SF-6D) or 15 Dimension instrument (15D)).[457]"

If we look at the national guidelines for economic evaluations, then EQ-5D is explicitly recommended in several national guidelines. For example, in Belgium, "in order to stimulate the use of generic utility instruments and to promote consistency, the Belgian guidelines explicitly encourage the use of the EQ-5D instrument." "Health-related quality-of-life weights should be based on empirical data, obtained in patients with a descriptive system for health status for which corresponding preference values exist from the general public such as the EQ-5D."[458] In the UK, "for the cost-effectiveness analyses health effects should be expressed in QALYs. For the reference case, the measurement of changes in health-related quality of life should be reported directly from patients and the utility of these changes should be based on public preferences using a choice-based method. The EQ-5D is the preferred measure of health-related quality of life in adults."[420] Also in the Dutch guidelines for economic evaluations, the EQ-5D-5L is explicitly recommended for measuring QoL. Furthermore, "alternative questionnaires and other methods for measuring QoL may be used in addition to the standard analysis. These alternatives do not replace the standard analysis, but may be necessary to give an image of the full effect. This means that even if it is expected that the EQ-5D-5L is not sensitive, the EQ-5D-5L must still be administered."

As for all applied questionnaires, the EUnetHTA guidelines also state that "documentation of the validity, reliability, responsiveness and acceptability of the HRQoL instruments used in REA should be provided."[456] It has already been stated a long time ago that a substantial and growing body of literature using the EQ-5D in cancer has emerged that supports the validity and reliability of EQ-5D in cancer.[459] It is not that this is a perfect instrument (as none of the instruments is). For example, in a study looking at the ability of cancer-specific and generic preference-based instruments to discriminate across clinical and self-reported measures of cancer severities, it was mentioned that the usefulness of the generic instruments may be limited if they are not able to detect small changes in health status within cancer patients.[460] A review across disease areas shows that "the EQ-5D was found to be responsive in 25 conditions (45%) with the magnitude of responsiveness varying from small to large depending on the condition. There was mixed evidence of responsiveness in 27 conditions (48%). Only four conditions (7%) (i.e., alcohol dependency, schizophrenia, limb reconstruction, and hearing impairment) were identified where the EQ-5D was not responsive."[461] The authors conclude that "in conditions with mixed evidence of responsiveness, researchers should consider using the EQ-5D with other condition-specific measures to ensure appropriate estimates of effectiveness. These conditions should be a main focus for future research using the new EQ-5D version with 5 response levels."[461] Indeed, a difference should be made between the EQ-5D-3L and 5L version. The EQ-5D-3L is so brief with only 3 response levels for the questions posed, which relates to the responsiveness concern. A new version of the EQ-5D with 5 levels (EQ-5D 5L) was developed to address this concern.[462] A recently published study, however in Chinese cancer patients, concluded that "with greater discriminatory power, convergent validity and lower ceiling, EQ-5D-5L may be preferable to EQ-5D-3L for the assessment of HRQoL among cancer patients."[463] A review of Bucholz et al.[464] compares the performance of both the original 3L with the 5L version. They indicate evidence on (improved) responsiveness is inconclusive and requires further research. Nevertheless, they also conclude that "overall, studies showed similar or better measurement properties of the 5L compared with the 3L, and evidence indicated moderately better distributional parameters and substantial improvement in informativity for the 5L compared with the 3L." Furthermore, they also indicate "there is evidence that patients prefer the 5L to the 3L, although the reason is not clear.[465-467] Fewer patients reported problems filling in the EQ-5D-5L questionnaire, and more patients deem the 5L to be easier to answer than the 3L and can find statements to describe their own health state on the 5L."[464]

7.3.3 *Improvement needed in measuring and reporting QoL, and using the results in economic evaluations*

Although QoL is a very important parameter in cancer treatment, and that advice is given in several guidelines to measure this in complement to disease-specific measures with a generic utility instrument, we note that this is often not the case in the studies that we have identified in this report. In Table 2 we have brought together the findings from the HTA reports for the 12 selected cancer indications. Based on these results, a number of findings emerge:

- In a large part of the included studies, there is no head-to-head comparison of the intervention with the relevant comparator.
- In studies where there are head-to-head comparisons, a generic utility instrument (such as the EQ-5D) is often not included as an outcome parameter.
- In trials where the EQ-5D is an end point, we note that:
    - This outcome is not measured for the full follow-up period of the study. The questionnaire was not administered anymore after disease progression while important differences in QoL might be expected specifically at this moment.
    - The results for this endpoint are usually not reported transparently (i.e. for both treatment arms at all time points and including the uncertainty about the results). In some cases, only a general statement is provided (e.g. QoL scores did or did not show a clinically meaningful change from baseline or in comparison to the other treatment arm).
    - In several reports, details of the results for QoL are considered to be confidential.
- The results of the EQ-5D are not always used directly in the underlying economic models.
- In almost all studies, researchers try to make a link to EQ-5D outcomes to include utilities in their economic evaluation. Utilities were often obtained from indirect sources. The link is made by making assumptions about the quality of life in relation to the disease state of the patient (e.g. progression-free survival, progressed disease and death).
- Information was in some cases even based on studies in which other drugs were administered. This does not always take into account (the disutilities associated with) the adverse effects that can be associated with specific treatments.

In general, both the lack of head-to-head comparisons and the lack of measuring QoL with a generic utility instrument makes the calculation of QALYs difficult and surrounded with major uncertainty. It is pointed out that not measuring quality of life can lead to both overestimation and underestimation of the impact on quality of life. It is important to have an idea of both negative (e.g. because of treatment-related adverse events) and positive (e.g. by delaying the worsening of QoL) impacts on QoL and support this by providing evidence instead of making strong assumptions.

Setting up new studies afterwards to gather this relevant QoL information requires extra time and money and is often accompanied by extra uncertainty because this information is then collected in e.g. a non-comparative observational study. The EUnetHTA guidance document mentions that “researchers should avoid situations where no relevant QoL information is gathered, given that this information may be required to perform reliable economic evaluations.”[430] Authors of one of the included reports state 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.”[197] Trial-based measurements of QoL, including a generic utility instrument, are usually to be preferred above making strong assumptions and trying to map results of the trial to utility estimates. A direct measurement of QoL with a validated instrument, immediately within the comparative trials, transparent reporting of the results, as well as using these results in the economic evaluations would lead to more reliable results.

Table 71 – Overview of QoL findings in the 12 included cancer indications

Cancer indication	QoL findings
Breast cancer	• In three out of ten evaluations, no generic utility instrument was used in the underlying trial. In seven out of 10 evaluations, QoL was measured with a generic utility instrument in the underlying trial. Unfortunately, four of these underlying trials were no head-to-head comparisons. Both the lack of head-to-head comparisons and the lack of measured utilities make the calculation of QALYs difficult and surrounded with major uncertainty. ○ In some trials where QoL is measured, the questionnaire was not administered anymore after disease progression. As a result, assumptions need to be made to assess the (long-term) impact on QoL and QALYs. ○ None of the studies fully transparently presents the utility measurements, i.e. utilities per treatment arm and for all moments in time it was measured. Only a general statement is made. For example, in one of the evaluations, the following is mentioned: "quality of life scores showed no clinically meaningful changes from baseline and no meaningful differences between treatment arms."
CML	• All studies referred to utilities measured with a generic utility instrument, being the EQ-5D questionnaire, or the time trade-off technique. The quality of life input data were usually transparently reported. Utilities were however mostly obtained from indirect sources because of a lack of head-to-head trial or, when such a trial existed, because quality of life was not collected with a generic utility instrument. None of the economic evaluations in the TAs modelled the utilities per treatment arm and at different points in time.
Colorectal cancer	• The five studies that were not discontinued all have shortcomings in measuring QoL with a generic utility instrument: either there is no head-to-head trial, or no HRQoL measurement with a generic utility instrument was performed in the relevant population.
Head and neck cancer	• Measuring QoL with a generic instrument was not present in the underlying RCT in both of the identified HTA reports. In TA473 (2017), the Evidence Review Group (ERG) considered that the data from the EXTREME trial did not allow for reliable utility estimates for the 2 treatment arms. In TA145, there were also several concerns with the followed approach to estimate utility values.
Melanoma	• Canadian experts 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."[197] ○ The Norwegian study identified 17 trials reporting HRQoL. Only three used the EQ-5D questionnaire. When available, the quality of evidence was often poor (e.g. no information on the uncertainty associated with the results). ○ In seven of the identified NICE evaluations, utility estimates were collected in the underlying trial with the EQ-5D questionnaire. However, transparent reporting of the outcomes is problematic. Examples show such data are not always reported by the company in the clinical section of the submission. In other examples, HRQoL data remain confidential or general descriptions are provided making it difficult to include these estimates and the surrounding uncertainty in economic evaluations. ○ Impact on QoL is usually modelled by assuming a utility for the different health states. None of the identified evaluations includes utilities per treatment arm as measured during the follow-up period in the trial.
Mesothelioma	• In the underlying trial comparing pemetrexed plus cisplatin with cisplatin alone, no generic utility instrument was applied. For the economic evaluation, utility scores were taken from an ongoing observational study in patients with non-small-cell lung cancer who completed the EQ-5D questionnaire. This is linked to high uncertainty and the economic analysis may have underestimated the overall QoL benefits.

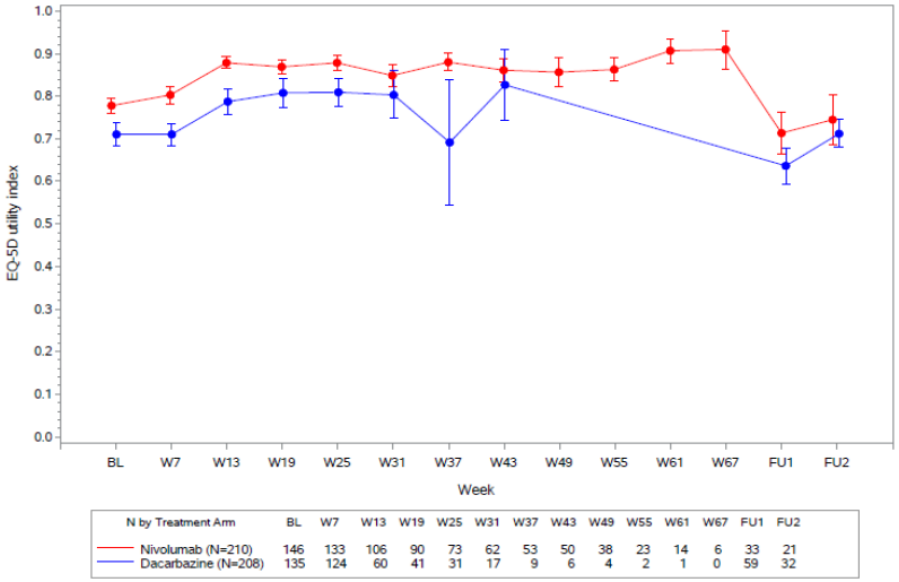
Multiple myeloma	• QoL was usually not measured with a generic utility instrument within the underlying head-to-head trial comparing the interventions of interest. Instead utilities were mostly obtained from indirect sources and were thus modelled per health state (instead of per treatment arm at different time points).
Non-Hodgkin lymphoma	CLL/SLL • QoL data were mostly obtained from indirect sources because of the absence of a head-to-head trial[288] or because of a lack of generic utility measures in the underlying trials.[289, 290] Further in two of those TAs,[289, 290] the utility estimates used in the model did not reflect the NICE reference case as they were obtained from indirect sources with a non-preference based instrument. One TA directly measured the utility estimates with the EQ-5D instrument within the underlying trial,[287] but the results indicated that this instrument may not be sensitive enough to fully captured the experience of CLL patients (e.g. whether fatigue is sufficiently covered in the EQ-5D). The impact on QoL was always modelled by assuming a mean utility value for each health state modelled (e.g. progression-free survival, progressed disease, death) irrespective of the treatments administered. QoL input data for the health states modelled were transparently reported in 2 out of the 4 TAs. Mantle cell lymphoma • EQ-5D QoL data was obtained from indirect sources because of the absence of a head-to-head trial comparing ibrutinib with rituximab plus chemotherapy in R/R MCL patients. The impact on QoL was modelled by assuming a mean utility value for each health state modelled (e.g. progression-free survival, progressed disease, death) irrespective of the treatments administered. QoL input data for the health states modelled was not reported.
NSCLC	• Measuring QoL with a generic utility instrument is not present in a large part of the underlying trials on which the economic evaluations rely. Studies referring to utilities measured with the EQ-5D do not always transparently publish results (i.e. provide results separately for all treatment arms at all points in time).
Ovarian cancer	• Measuring QoL with a generic utility instrument is not present in four out of five of the underlying trials on which the economic evaluations rely. In one of the evaluations, authors retrieve QoL information from another study with bevacizumab (the ICON7 trial), in which a lower dose of bevacizumab was administered. This approach would not capture AEs caused by the higher dose. In another study, QoL information from a study in ovarian cancer with another product (trabectedin) is included. It is preferable to measure QoL directly in the underlying RCTs with a generic utility instrument and include the results in the economic evaluation.
Prostate cancer	• QoL was measured with a generic utility instrument (EQ-5D) in the three underlying trials (PREVAIL, PROSPER and AFFIRM) on which the assessments are based. Unfortunately, several shortcomings appear: results for the EQ-5D measurement are not transparently presented (no results per treatment arm for the different points in time this outcome is measured), results are considered to be confidential, there is no measurement of QoL after disease progression, collecting EQ-5D data was not specified in the PREVAIL study protocol, and EQ-5D utility data were only collected at a selection of study sites and for a limited number of patients in the AFFIRM trial.
Renal cell carcinoma	• QoL input data were mostly obtained from indirect sources because of a lack of head-to-head trial. Only few TAs directly measured utility estimates with a generic instrument (in all cases the EQ-5D) administered alongside their underlying head-to-head trial. Unfortunately, the impact on QoL was always modelled by assuming a mean utility value for each health states modelled (e.g. progression-free survival, progressed disease, death) irrespective of the treatment administered, instead of directly using the utilities observed in the clinical trials (i.e. utilities per treatment arm and for all scheduled measurement times). QoL input data for the health states modelled were usually transparently reported.

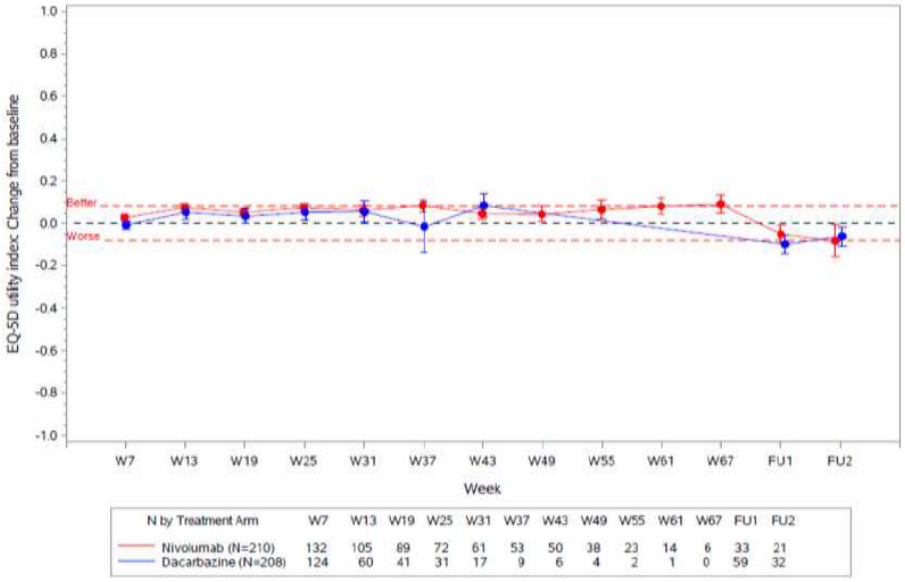
7.3.4 An example to show (the importance of) transparent reporting of QoL data

Just as an example we present how EQ-5D data was presented in one of the identified reports after request by the Evidence Review Group (ERG). In NICE TA384 (2016)[194], nivolumab is compared with dacarbazine, ipilimumab, dabrafenib and vemurafenib in patients with previously untreated advanced (unresectable, metastatic) melanoma. In the economic evaluation of BRAF mutation-negative disease, nivolumab is compared with dacarbazine and ipilimumab. 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.[194] "The CS [company submission] concludes that nivolumab does not impair HRQoL and in some cases HRQoL improved relative to baseline. However, the CS (p. 87-88) does not report individual scores for all analysis time points and it is therefore difficult to get a clear picture from the CS of whether there are any overall patterns in scores for the EORTC-QLQ-C30 and EQ-5D instruments."[468]

Additional HRQoL data were provided in the company's clarification response. The additional HRQoL data provided by the company for CheckMate 066 at the request of the ERG include graphs which clarify the time course of changes in the HRQoL measures. The graphs for 'EQ-5D' and 'change from baseline in the EQ-5D utility index' were reproduced and are presented in Table 72. According to the ERG, it appears unlikely that any of the differences between nivolumab and DTIC [dacarbazine] in the changes from baseline could be considered statistically significant. "In summary, based on the interim HRQoL evidence presented in the CS and in the company's clarification response, the ERG agrees with the company's conclusion that nivolumab does not impair HRQoL (relative to baseline), but the ERG notes that there is no current evidence that nivolumab leads to a consistent and sustained improvement in HRQoL."[468] Without a transparent presentation of these results, it is not possible to make an objective assessment of assumptions that are made in the economic evaluations or to validate the modelled results in comparison with the original outcomes of the trial.

Table 72 – Mean (±SE) EQ-5D utility index scores (left panel) and mean (±SE) changes from baseline in the EQ-5D utility index scores (right panel) for the nivolumab and DTIC arms of CheckMate 066





DTIC: dacarbazine. Source: Cooper et al., 2015[468]

In several other reports, such detailed information is not presented and QoL information is even considered being confidential.[ff] Quality of life reporting was often limited and considering the results from a patient-reported outcome in a clinical trial as being confidential should never be accepted. Such information should always be presented in full transparency.

Key points

- **EMA does not require marketing authorisation holders to evaluate quality of life, even when drugs are intended for late line palliative care.[451]**
- **In the study of Davis et al., "of the 68 study indications, 37 (54%) were supported by a pivotal trial in which quality of life was evaluated as a secondary endpoint, and for only seven (10%) was there a significant improvement in quality of life at time of market entry. Neither the EPARs nor the published studies were consistent in reporting whether significant improvements for specific quality of life outcomes were also clinically relevant. These are particularly troubling findings as many of the drugs in our sample were approved to treat advanced metastatic disease, when the purpose of treatment is palliative – that is, to improve quality of life – or to extend life while ensuring that any survival gains are not outweighed by a deterioration in quality of life from adverse events or other negative factors related to treatment.[452, 453"21]**
- **In line with the findings of Davis et al., we also note that QoL is often missing in systematic reviews on the efficacy of innovative oncology drugs.**
- **The EUnetHTA guidelines on health-related quality of life (HRQoL) generally recommend both the complementary use of a disease- or population-specific and a generic HRQoL measure to adequately capture the impact of a disease on daily life. Both context and purpose are important to determine how QoL should be measured.**
- **According to the EUnetHTA guideline, the EuroQoL-5 dimension (EQ-5D) questionnaire is the most commonly recommended [generic utility] instrument for the derivation of HRQoL weights. The EQ-5D is also explicitly recommended in the national guidelines for economic evaluations of UK, Belgium and the Netherlands.**
- **Both the lack of head-to-head comparisons and the lack of measuring QoL with a generic utility instrument are the main factors that make the calculation of QALYs in economic evaluations difficult and surrounded with major uncertainty.**
- **In trials where QoL is measured with the EQ-5D, we note that this outcome usually is not administered anymore after**

[ff] For example, just looking at the reports for the breast cancer indication, we are confronted with the following information related to QoL results:

- In TA495 (2017, palbociclib),[85, 92] the EQ-5D utility values and completion rates over time for the PALOMA-2 trial are presented as confidential.
- In TA563 (2019, abemaciclib),[86] "there was xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx in change from baseline in the EuroQol 5-Dimension 5-level (EQ-5D-5L) index score or visual analogue scale."[89]
- In TA593 (2019, ribociclib),[87] summary results of the patient reported outcomes (EQ-5D-5L) for the MONALEESA-3 trial were published confidentially in the underlying HTA report.[79]
- In TA496 (2017, ribociclib),[88] "quality of life scores showed no clinically meaningful changes from baseline and no meaningful differences between treatment arms."[93] However, results are not published transparently (i.e. per treatment arm for all points in time).

Similar findings occur in the identified HTA reports for the other included cancer indications. We refer to the appendix for further information.

disease progression while important differences in QoL might be expected specifically at this moment. The results for this endpoint are usually not reported transparently (i.e. for both treatment arms at all time points and including the uncertainty about the results). In some cases, only a general statement is provided. In several reports, details of the results for QoL are considered to be confidential.

- **A direct measurement of QoL with a validated instrument, immediately within the comparative trials, transparent reporting of the results, as well as using these results in the economic evaluations would lead to more reliable results.**

7.4 The use of progression-free survival as a surrogate endpoint

Surrogate endpoints are often used in clinical studies. Randomised clinical trials in oncology may need a long follow-up period to allow for the assessment of the effect of the studied intervention on overall survival (OS). Some even argue that treatment effects on OS are diluted by risks of death unrelated to the cancer or treatment toxicities or that effects on OS are potentially confounded by the further lines of treatment a patient will receive after failing on the new agent (see part 7.9 for further discussion).

However, its use is associated with a lot of controversy. The following quote from Davis's study (BMJ, 2017) clearly illustrates the problem: "Before new prescription medicines are allowed onto the market, they must be tested in studies and show, to the satisfaction of drug regulatory agencies, that their benefits outweigh the harms of drug toxicity. The most informative and valuable studies are those providing robust evidence from well designed randomized controlled trials that a new drug has a significant effect on outcomes that are important to patients and that the magnitude of those effects, compared with other treatment options, are clinically meaningful. Although the goal of cancer treatment is to improve the quantity and quality of life,[469-471] clinical trials designed to gain regulatory approval for new drugs often evaluate indirect or "surrogate" measures of drug efficacy. These endpoints show that an agent has biological activity, but they are not reliable surrogates for improved survival[65, 472-478] or quality of life[472, 474, 478-480] in all settings, and two recent systematic reviews suggest that the strength of association between surrogates in cancer clinical trials and life extension is generally low.[475, 481"21]

7.4.1 Is PFS a valid surrogate for OS?

PFS is a controversial endpoint because some new agents (e.g., the anti-angiogenic drug bevacizumab in breast cancer[482]) were shown to have a marked effect on PFS, which led to their regulatory approval, but no sizable benefit on OS. The two systematic reviews referred to in the above quote confirm the doubt around the use of this endpoint:

- In the objectives of the study of Ciani et al., the authors mention that "licensing of, and coverage decisions on, new therapies should rely on evidence from patient-relevant endpoints such as overall survival (OS). Nevertheless, evidence from surrogate endpoints may also be useful, as it may not only expedite the regulatory approval of new therapies but also inform coverage decisions. It is, therefore, essential that candidate surrogate endpoints be properly validated." Their results show that "a wide variety of statistical methods have been used to assess surrogacy. The strength of the association between the two surrogates and OS was generally low. The level of evidence (observation-level versus treatment-level) available varied considerably by cancer type, by evaluation tools and was not always consistent even within one specific cancer type."[481]
- In the study of Prasad et al., the objective was "to identify and evaluate trial-level meta-analyses of randomized clinical trials quantifying the association between a surrogate end point and overall survival in medical oncology. Trial-level correlations test whether treatments that improve the surrogate end point also improve the final end point and are widely considered the strongest evidence to validate a surrogate end point." Based on their study, the authors concluded that "most trial-level validation studies of surrogate end points in oncology find low correlations with survival." and that "the evidence supporting the use of surrogate end points in oncology is limited."[475]

In solid tumours, PFS is typically assessed using the RECIST criteria (Response Evaluation Criteria in Solid Tumors). These are based on the visual assessment of tumour size using computed tomography or magnetic resonance imaging. The RECIST criteria were developed mainly for cytotoxic chemotherapy. The response to other types of cancer treatment may not be optimally captured using the RECIST criteria. For example, after checkpoint inhibitor treatment, pseudo-progression may be observed with biopsy demonstrated inflammatory cell infiltrates, edema or necrosis. This has led to specific immune RECIST criteria, based essentially on defining true progressive disease after a confirmatory imaging.[483]

In case survival assessment is difficult, the European Medicines Agency has suggested to assess PFS on next-line therapy (PFS2) as an endpoint.(https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-evaluation-anticancer-medicinal-products-man-revision-5_en.pdf) For specific solid tumours and therapies PFS2 may be better correlated with OS compared with PFS.[484]

Whatever method is used to define PFS, it needs to be validated as a surrogate. Surrogate endpoints need to be validated for each indication and each intervention.[485] Each time a new drug is introduced having a substantially different mode of action, another prospective evaluation of surrogacy may be needed. As Buyse et al stated "The more we understand about surrogates, the more we realize how difficult it is to formally "validate" them."[486] An association between the potential surrogate and the clinical endpoint is desirable but is not sufficient. What is required to replace the clinical endpoint (OS) by the surrogate (PFS) is that the effect of the treatment on the surrogate endpoint reliably predicts the effect on the clinical endpoint(OS).[486] The surrogate should be biologically plausible and ideally lies on the causal pathway of the treatment effect on the true endpoint. The most adequate method to validate a surrogate is a meta-analysis of individual patient data from the clinical trials.[485] As recommended by Buyse et al, "When data are available from several trials, one can additionally assess the "trial level association" between the treatment effect on the surrogate and the treatment effect on the true endpoint. In the latter case, the "surrogate threshold effect" can be estimated as the minimum effect on the surrogate endpoint that predicts a statistically significant effect on the clinical endpoint."[486]

In general, the quality of studies evaluating the surrogacy of PFS and the reporting can be improved. In addition, the surrogate threshold effect is often poorly reported. A systematic review found 91 studies evaluating the validity of PFS as a surrogate for OS in 24 cancer localisations. Only half of studies concluded on the validity of PFS as a surrogate for OS. However, among these, for 15, this conclusion was not supported by the results, with no quantitative argument in favour of surrogacy given. Therefore, the interpretation of the results of surrogacy studies should be made with care.[485] The authors note also that *"a mapping of the localisations and treatments for which PFS has been validated as a surrogate for OS would help in planning future trials. Unfortunately, this mapping is currently not possible because of the heterogeneity of methods used."*

Making abstraction of the methodological challenges and as an example, Gyawali et al.[487] searched correlation studies of surrogate measures of OS for breast cancer, in particular the endpoints FDA considered appropriate for accelerated or regular approval: event-free survival (EFS), disease-free survival (DFS), objective response rates (ORR), and progression-free survival (PFS), and in addition, pathological complete response rates (pCR) which was listed as appropriate only for accelerated approval. (https://www.fda.gov/drugs/development-resources/table-surrogate-endpoints-were-basis-drug-approval-or-licensure) The results from correlation studies evaluating pCR, DFS, ORR, and PFS suggest that the treatment effects on none of these surrogate measures were strongly correlated with treatment effects on OS ($r<0.85$ or $R2 < 0.7$, except for DFS in HER2 positive early breast cancer ($R2 = 0.75$).

7.4.2 Can PFS be considered as a surrogate for quality of life?

In addition to OS, one may wonder if PFS could be considered a surrogate of quality of life. Hwang et al.[488] checked the association between PFS and quality of life for the phase III clinical trials of drugs for advanced or metastatic solid tumours published between 2010 and 2015. QoL was included as an endpoint in 190 out of the 352 trials (54%), but reported only for 147 of 190 trials (77%): 106 (56%) in the main paper, 36 (19%) in a subsequent publication or 5 (3%) in a conference abstract. These observations also confirm the problems identified in this report concerning

both measuring and reporting QoL in cancer drug trials (see part 7.3). For the trials with QoL reported, the overall trial-level correlation between positive PFS and positive quality of life was of low strength (r = 0.34). The hazard ratio for PFS was not a strong predictor of positive quality of life (AUC, 0.72; 95%CI 0.59–0.84). The association between PFS and improvement in any domain of quality of life was also weak.

Industry and HTA agencies in Germany tend to disagree on the exclusion of disease progression as a patient-relevant endpoint because radiologically assessed progression might not necessarily be associated with morbidity and because longer PFS is often not statistically significantly associated with longer survival. Industry has argued that the disease progression itself is associated with a decrease in QoL and found supportive data in cohorts of patients with breast, lung, pancreatic, and colorectal cancer in Germany.[489]

In one of the identified HTA reports on the impact of metastatic breast cancer (MBC) on quality of life, the researchers refer to part of the company submission, in which the company argues that "prolonging progression-free survival (PFS) also maintains a patient's HRQoL. Reasons for this include: - Symptoms associated with disease progression are avoided while patients remain progression-free[490-492] and disease progression has been found to have a negative impact on HRQoL[493]; - Remaining progression-free delays the onset of chemotherapy which may be associated with many toxicities and reduced HRQoL[493-498]; - There exists among patients a perceived fear of chemotherapy[499, 500] which can have a detrimental effect on HRQoL; in particular, high levels of anxiety have been reported[501, 502]; - Patients who are progression-free are alive[503] and able to work[504] and maintain 'normality', e.g. fulfilling one's caring duties as partners, friends and mothers.[505] In addition to the effect of MBC on a patient's HRQoL, diagnosis with MBC and subsequent treatment can negatively affect the caregivers of patients.[506] In particular, carers are at increased risk of depression and reduced quality of life compared to the general population.[507"92] The previous arguments are in fact not an argument to rely solely on PFS. They are rather an argument to include instruments that are able to measure the impact on these elements. For example, the EQ-5D includes a dimension related to daily activities and another dimension related to anxiety and depression. There are also ways to measure the impact on work absenteeism and presenteeism and carers' QoL.[gg] This is more reliable than making assumptions related to PFS which are susceptible to criticism.

7.4.3 The problem of PFS in economic evaluations

In the economic evaluations, impact on PFS is often translated into an OS and QoL benefit. Unfortunately, the underlying evidence to support the relationship is often lacking. It is exceptional that additional evidence is provided regarding the relationship between PFS and OS. For example, in the breast cancer indication, we have identified two comments from the Evidence Review Group (ERG) that illustrate the problem of using PFS in economic evaluations:

- TA593:[87] "… 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."[79] "The economic analyses still have some remaining uncertainty in the results, mainly because of the potentially implausible assumption of a full surrogacy between PFS and OS. Immature overall survival data in the first-line model make this difficult to assess fully."[79]

[gg] The Belgian guidelines for economic evaluations[458] recommend to perform the reference case fro a health care payer perspective (including both costs for government and patient co-payments). However, the guidelines also clearly state that "this does not mean that broader consequences of a treatment cannot or will not be taken into account in resource allocation decisions. Decisions are not necessarily made on the basis of cost-effectiveness information alone. Other considerations, such as substantial reductions in the absence from work, may be important factors in determining the value of a therapy. … Analyses from a broader perspective are allowed but should be clearly distinguished from the reference case." In case researchers include productivity costs, the guidelines also state that "the impact of the medical intervention on the level of productivity must be real and well documented" and the friction cost method should be applied. We refer to these guidelines for further details.

- TA496:[88] "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."[93]

The above examples also show that making the assumption that a gain in the PFS would lead to an equal gain in the OS, when not supported by evidence, can result in very optimistic results, underestimating the ICER.

7.4.4 Do we try hard enough? Searching for a solution that fits both goals

The evidence for using surrogate endpoints such as PFS to replace OS and QoL is unsatisfying. Nevertheless, researchers often support PFS as an important endpoint since designing studies with the final OS endpoint would require larger studies and longer follow-up, making the study even more expensive. So there is a dilemma. On the one hand you have the desire for fast market access and not making the underlying trials too expensive. On the other hand, you have the request to provide good evidence about the impact on patient relevant outcomes. In any case, we recommend to follow the EUnetHTA guideline: "If progression-free survival (PFS) is used as an endpoint there should be sufficient independent evidence to demonstrate that this is associated with overall survival. … Overall survival is the gold standard for demonstrating clinical benefit and as such should be used where possible. … In the metastatic setting, data on PFS alone is insufficient and should be coupled with quality of life assessment and survival data, the maturity of which will be considered on the case by case basis."[508]

The question is also whether there is no solution that can reconcile both goals (quick market access and providing evidence for OS and QoL). The central question is whether we try hard enough to conduct the randomised trials that could assess if there is an added benefit, measuring quality of life and OS. We may need another phased regulatory/marketing system to introduce innovative cancer drugs, making sure the comparative evidence is generated as soon as possible. This means starting the active control comparative trial in the pre-marketing phase and probably continuing the same trial under some type of (conditional) marketing when a surrogate effect is seen until OS can be evaluated.

Key points

- **Two recent systematic reviews suggest that the strength of association between surrogates in cancer clinical trials and life extension is generally low.[475, 481] In another study searching for correlation studies of surrogate measures of OS for breast cancer, none of the surrogate measures were strongly correlated with treatment effects on OS.**
- **In a study checking the association between PFS and quality of life for the phase III clinical trials of drugs for advanced or metastatic solid tumours published between 2010 and 2015, The association between PFS and improvement in any domain of quality of life was also weak.**
- **This evidence makes the use of PFS in clinical and economic evaluations to estimate the impact on OS & QoL problematic.**
- **The EUnetHTA guideline states that "if progression-free survival (PFS) is used as an endpoint there should be sufficient independent evidence to demonstrate that this is associated with overall survival. … Overall survival is the gold standard for demonstrating clinical benefit and as such should be used where possible. … In the metastatic setting, data on PFS alone is insufficient and should be coupled with quality of life assessment and survival data, the maturity of which will be considered on the case by case basis."[508]**

7.5 Substantial increase in gross expenditures, limited by refunds and taxes

We have previously observed in this study that for almost all included cancer indications there is a very large increase in gross cancer drug expenditures, while the improvement in overall survival remains limited. However, just like we have to nuance the results for OS based on observational data, we also need to nuance the observed increase in gross cancer drug expenditures. In Table 1 in the introduction, we presented the NIHDI net expenditures for medicines. However, these net expenditures differ from the net costs of medicines for NIHDI because refunds in the context of managed entry agreements (MEAs), taxes and 'clawback' provide a financial flow from the pharmaceutical industry to the NIHDI.

The MORSE report mentions that a detailed analysis is not possible due to the confidentiality of the compensation mechanisms. However, to obtain a global view of the budgetary compensations, data from the permanent audit are presented. To be complete, the MORSE report also mentions the revenues from the annual taxes payed by the pharmaceutical industry. The evolution of these revenues is shown in Table 73.

Table 73 – Evolution of gross expenditures for medicines and net costs for the NIHDI (2014 – 2019) (in € 000)

	2014	2015	2016	2017	2018	2019
Gross expenditures medicines (1)	4 033 476	4 277 705	4 378 171	4 594 786	4 891 838	5 263 274
Refunds MEAs (2)	41 346	54 516	123 556	273 351	359 310	605 043
(3) = (1) – (2)	3 992 130	4 223 189	4 254 615	4 321 435	4 532 528	4 658 231
Taxes and clawback (4)	223 896	281 085	321 517	344 371	399 283	431 510
Net costs (5) = (3) – (4)	3 768 234	3 942 104	3 933 098	3 977 064	4 133 245	4 226 721

MEA: managed entry agreement. Source: MORSE report (2020).[1]

7.5.1 Managed entry agreement refunds

In the MEAs, different (combinations of) compensation mechanisms are used. The MORSE report refers to the following possibilities:[1]

- Refund of a percentage of the turnover realized for the specialty concerned, with or without an expenditure ceiling at individual or group level (e.g. per therapeutic class, per indication), whereby the excess expenditures must be partially or fully refunded. Most of the contacts (71.6%) are of this type.
- Refund of a fixed amount per unit sold. This type is applied in 9.76% of cases.
- Refund of an amount corresponding to all or part of the difference between the anticipated expenditures and the actual expenditures for the specialty concerned. This type is applied in 6.66% of cases.
- Implementing a reduction in the reimbursement basis of another pharmaceutical specialty/ies marketed by the applicant, reducing the health insurance expenditure for a medicine other than the specialty concerned. This modality is only applied in 0.41% of cases.
- Any other modality at the expense of the applicant that allows to limit the expenditures. In the remaining 14.63% of contracts, a combination of two or more compensation mechanisms was combined.

The NIHDI notes that "these different forms of compensation might give the impression that purely financial agreements are being made, but behind each mechanism there is a rationale, and this is often scientific in

nature. For example, the mechanism of “refund of a percentage of sales” may be based on a system where health insurance only bears those costs of patients estimated to benefit from treatment with the specialty concerned ('outcomes -based agreement '), or only reimburses those costs when the specialty concerned is administered for a treatment for which there is sufficient scientific evidence on, for example, efficacy and safety.”[1] We come back to the issue of providing further evidence and the impact of (the possibility of entering into) such agreements on the initial price setting (see part 7.6).

The MORSE report refers to the increasing number of applications to conclude a contract and contracts being concluded under article 81/111 (i.e. MEAs). The gross turnover of products under contract is increasing sharply, from about €225 million in 2014, to €653 million in 2016, and more than €1.5 billion in 2019 (see Table 74). The amount of refunds related to these confidential contracts is also increasing sharply over time from about €41 million in 2014, to about €121 million in 2016, and more than €600 million in 2019. Expressed in percentages, the size of the refunds is also increasing with a peak of 38.5% in 2019.

Table 74 – Overview of turnover figures, compensations and net expenditures in the context of MEAs (2010-2019) (in € 000)

	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Gross turnover	2 349	8 680	53 411	131 470	225 160	466 079	652 716	1 070 151	1 316 037	1 570 255
Advanced refunds	/	/	/	/	/	/	/	100 491	195 504	387 036
Remaining refunds	/	1 249	1 249	23 729	41 428	56 629	121 316	172 656	162 078	218 136
Total refunds MEAs	**-**	**1 249**	**1 249**	**23 729**	**41 428**	**56 629**	**121 316**	**273 147**	**357 582**	**605 172**
Net expenditures	2 349	7 432	50 780	107 741	183 731	409 450	531 400	797 003	958 455	965 083
Compensation (%)	**0.0%**	**14.4%**	**4.9%**	**18.0%**	**18.4%**	**12.2%**	**18.6%**	**25.5%**	**27.2%**	**38.5%**

Source: MORSE report (2020).[1] Remark: differences with numbers in Table 1 is due to the moment calculations for these tables were made and the availability of data. For example, for 2018 and 2019, the actual refunds are somewhat different due to the non-inclusion of the tax modulation, linked to a difference of approximately €42 million due to this (personal communication with NIHDI and Pharma.be).

7.5.2 Taxes and clawback

Next to the refunds in the context of MEAs, there is also a substantial amount of other taxes and contributions paid by the pharmaceutical industry (seeTable 1). A document of Pharma.be summarizes this as follows:

A) A contribution of €1 487.36 for each reimbursable package entered on the list of reimbursable medicines with an annual turnover exceeding €61 973.38.

B) The pharma tax, being different taxes calculated on the turnover of reimbursable medicines:

- B.1. Various fixed charges:
  - “Basic” tax of 6.73% on turnover
  - Crisis tax of 1% on turnover
  - A specific tax on the turnover of orphan drugs which replaces both previous taxes:



        - 0% on turnover below €1.5 million
        - 3% on turnover between €1.5 million and €3 million
        - 5% on turnover above €3 million
    - Marketing taxes of 0.13% on turnover
- B.2. A compensatory tax (clawback) when the budget for the medicines has been exceeded. In 2018, this tax amounted to 3.22% of turnover."[509] This clawback tax is currently capped at 2.5% of the budget for medicines (personal communication NIHDI). So if there is a very large budget overrun, not everything can be recovered through this tax.

In this document, it is also stressed that the increase in net expenditures for medicines, taking into account the refunds through MEAs and taxes, grows at a slower pace than the increase in other NIHDI expenditures (+7.4% versus +16% over the period 2012-2018).[509] However, we would like to note that it is not the increase of expenditures only that is of importance. Whether the level of expenditures is appropriate depends in first instance on the added value generated towards the patient. And being confronted with limited budgets and opportunity costs, resources should be invested where most added value is created in relation to the extra expenses.

Key points

- **The gross turnover of products under contract is increasing sharply, from about €225 million in 2014, to €653 million in 2016, and almost €1.6 billion in 2019.**
- **The amount of refunds related to these confidential contracts is also increasing sharply over time from about €41 million in 2014, to about €121 million in 2016, and more than €600 million in 2019. In 2019, the size of the refunds was 38.5%.**
- **Taxes and a 'clawback' also provide a financial flow from the pharmaceutical industry to the NIHDI. In 2019, this was more than €400 million. As such, about €1 billion is paid by the industry in refunds, taxes and clawback, resulting in a net cost for the NIHDI of about €4.2 billion for medicines in 2019.**

7.6 Managed entry agreement

7.6.1 Managed entry agreement – when the exception becomes the rule

"Evidence on relative effectiveness and cost-effectiveness of innovative treatments is often limited at the time of licensing. Public health authorities and pharmaceutical companies have therefore looked for alternative funding mechanisms, like managed entry agreements (MEA), to share the risks and uncertainties arising from public coverage of pharmaceuticals, whose (cost-)effectiveness is still unknown or for which the budget impact is expected to be very high, but for which early access for the patient is wanted. Rather than waiting for more solid evidence before making a definite reimbursement decision, MEAs should allow granting early access to pharmaceutical products, while at the same time collecting the relevant data to assess (cost-)effectiveness, controlling the budget impact, monitoring the (rational) use in clinical practice, or generating real-life data on effectiveness and use. These data should then support a more informed reimbursement decision at the end of the MEA."[510, 511]

The initial idea was very nice, that is, to find a solution for situations where there are high unmet needs and meanwhile solve the uncertainties. As mentioned by De Ridder, "art.81 agreements were intended as an exception." But nowadays, MEA are rather the rule. "This way, solutions for a relatively small group of patients weighs on the healthcare expenditures."[512] "The share of expenditures on specialties that are temporarily registered in the list of the reimbursed pharmaceutical specialties, being the specialties for which an agreement 'art 81/111' has been concluded between the NIHDI and the company, increases year after year by an increasing number of agreements, bigger volumes and higher prices of medicines under agreement."[1] Most agreements (58%) were for ATC class L drugs (Antineoplastic and immunomodulating agents), i.e. cancer drugs.[1]

Based on a previous KCE report on MEAs in Belgium, published in 2017, it was stated that "with the unlimited possibility to be reimbursed under a MEA, the price setting and introduction of generics on the market might be complicated. The negotiated price is not public and, in Belgium, the price

setting of the generic is based on the facial price of the original. Some stakeholders stated the negotiated price should become public, once generics enter the market. However, from a legal point of view, this is not in agreement with the initial contract. Will generics also need a confidential price negotiation if the real price of the comparator is not made public? This does not reflect the initial idea behind MEAs. Furthermore, if generic companies have no idea in advance about the price that will be accepted in Belgium, this might delay the introduction of the product on the Belgian market. Such unwanted side effects need to be monitored and tackled in time."[510, 511] Since July 1, 2014, it is possible that companies submit an application for Article 81/111 procedure for class 2 dossiers (i.e. for medicines with no therapeutic added value) in case the reference specialty on the positive list is reimbursed under a confidential MEA. Furthermore, Since 2018, the possibility for the CTG exists (art.112) to formulate a proposal to start negotiations for each pharmaceutical specialty for which reimbursement is requested, if the reference specialty is reimbursed under a confidential MEA. So also for e.g. biosimilars.[1] The Morse report shows that after a negative opinion of the CRM in about half of the cases (48.4%, 31 out of 64 cases), an agreement was nevertheless concluded. Furthermore, it is also stated that if no added value is claimed, the specialty is temporarily registered in 86.2% (25 out of 29 cases) of applications for a negotiated procedure. The reference specialty is also under contract in these cases.[1] Confidential contracts are thus not only concluded for medicines where there is a high unmet need and a high potential for an added value.

7.6.2 Incentives to demonstrate survival or QoL benefits for the patients

In their retrospective analysis on the availability of evidence of benefits on overall survival and quality of life of cancer drugs approved by European Medicines Agency, Davis et al.[21] state the following: "Though surrogate endpoints are argued to have the advantage of allowing quicker drug development and patient access, it is questionable whether studies based on surrogate measures of efficacy provide optimal, or even meaningful, information for patients and clinicians.[445] Moreover, our analysis raises the possibility that regulatory and current research practices have created a situation in which critical information about the outcomes that matter most to patients might never be generated once oncology drugs are approved for widespread use. The limited availability of studies showing either benefits to overall survival or quality of life in the postmarketing period underscores the importance of requiring robust evidence of clinical benefit at the time of marketing authorisation.[513-515]" The widespread use of MEAs creates further incentives to submit reimbursement requests with immature data without providing incentives to generate reliable evidence during such a temporary contract. We explain this in the following two parts and also refer for further reading to two interesting papers published on generating comparative evidence on new drugs and devices before[11] and after[14] approval.

7.6.2.1 *Before marketing approval*

Naci et al. summarize clearly the main problem with regulatory approvals: "Fewer than half of new drugs have data on their comparative benefits and harms against existing treatment options at the time of regulatory approval in Europe and the USA. Even when active-comparator trials exist, they might not produce meaningful data to inform decisions in clinical practice and health policy. The uncertainty associated with the paucity of well designed active-comparator trials has been compounded by legal and regulatory changes in Europe and the USA that have created a complex mix of expedited programmes aimed at facilitating faster access to new drugs."[11] The authors also propose a set of five key principles relevant to EMA/FDA, European medical device regulatory agencies, and payers (we refer to the original paper for further details):

- "First, labelling should routinely inform patients and clinicians whether comparative data exist on new products.
- Second, regulators should be more selective in their use of programmes that facilitate drug and device approvals on the basis of incomplete benefit and harm data.
- Third, regulators should encourage the conduct of randomised trials with active comparators.
- Fourth, regulators should use prospectively designed network meta-analyses based on existing and future randomised trials.

- Last, payers should use their policy levers and negotiating power to incentivise the generation of comparative evidence on new and existing drugs and devices, for example, by explicitly considering proven added benefit in pricing and payment decisions."[11]

The first four principles are recommendations towards regulators. The current regulatory context with a benefit-risk approach instead of a comparative effectiveness assessment approach is not ideal for HTA and policy makers deciding on reimbursement. As Naci et al. mentions, "comparative evidence on newly approved drugs is limited for several reasons. One primary reason is that pharmaceutical manufacturers do not routinely collect such data in the studies leading to drug approval. In both the USA and Europe, the regulatory agencies' statutory mandate is to evaluate a drug's benefit–risk balance and intended effects, not its comparative benefits and harms against existing alternatives."[11] However, as mentioned before, current programmes are rather focused on faster access and not on producing evidence that is more suited to decide on which is the most appropriate therapy for patients, nor on providing reliable input in the HTA process supporting policy makers when deciding on reimbursement.

The last principle is addressed to the national policymakers. The system of MEAs could fit this principle if properly applied. However, the current application of MEAs provides the wrong incentives since also with immature and uncertain data, there is a high probability of achieving reimbursement through MEAs. As mentioned in the MORSE report: "The uncertainties are probably one of the reasons for the increase in the number of agreements that has been noticeable in recent years. There is often a large therapeutic uncertainty reported by the CRM (often the reimbursement requests contain immature data due to early submission to EMA, e.g. with phase II study results); and/or large budgetary uncertainties (high treatment costs per patient; high budget impact due to often broad target population). While the CRM strives to propose definitive inclusion in the list of reimbursable pharmaceutical specialties, following a negotiation process is often the only way to make medicines accessible to the patient."[1] Companies are also aware of this possibility. So with the current focus at EMA for fast market access and the more widespread use of MEAs, there is neither at regulatory nor at national level an increased incentive to generate better evidence. For a better use of MEAs, providing the correct research incentives, we refer to the following part.

This is also reflected in the HTA reports identified in the 12 selected cancer indications. As mentioned in the general findings, in the economic evaluations, the greatest uncertainty relates to the estimation of the treatment effect on overall survival, mainly due to the absence of a head-to-head trial comparing the intervention with the appropriate comparator(s). Other approaches to handle the lack of direct treatment comparisons are always accompanied by the necessary uncertainty. For example, in TA417, "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 ."[411]

If such a trial was available, presented data was often immature. As a consequence, in the absence of long-term trial data to appropriately inform the OS curve in the economic model, there was often the difficulty to model and extrapolate OS. A large part of the calculated (gains in) QALYs is therefore often based on extrapolations. For example, in an evaluation of crizotinib in advanced non-small-cell lung cancer, "the company's first-line base case model yields a substantial post-progression survival (PPS) benefit for treatment with crizotinib versus pemetrexed+platinum, which means that the extra survival gained beyond progression constitutes 74% of total OS gain for treatment with crizotinib. This suggests that the treatment effect is better after progression than before progression and, therefore, that the OS treatment effect is better than the PFS treatment effect. The ERG acknowledges that there may be some PPS benefit attributable to treatment with crizotinib, especially since many patients are treated beyond progression. However, the ERG considers it questionable to model an OS treatment effect that is substantially better than the PFS treatment effect without robust evidence to support that assumption."[516] In TA321, the ERG noted that "the majority of the estimated QALY gain in the company's model

arises from the estimated life-years after disease progression (… 93% for the comparison with vemurafenib). It also noted that the estimated mean survival in the company's model is much larger than is normally observed in clinical trials or in registry data."[204] Or another example, in TA357, where the company reported that "because overall survival data from KEYNOTE-002 were immature and standard parametric curve fitting resulted in survival estimates that were not clinically plausible, alternative methods were needed to extrapolate survival beyond the trial period."[199] In an extreme case, the Evidence Review Group even noted that only 1% of the total discounted QALYs came from the actual trial data.[198] As a consequence of accepting immature data, a large proportion of the estimated survival benefit is often based on the extrapolated period rather than the trial data.

In a number of cases, explicit reference is also made to the problems surrounding cross-over that biased the intention-to-treat analyses. For example, in TA432 comparing everolimus with BSC in advanced renal cell carcinoma,[409] "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." Early crossing over of patients to the innovation should be avoided as long as there is a reasonable doubt about any patient benefit of switching to the innovative drug.

It would be an improvement if from the beginning (i.e. in trials set up for regulatory approval), more attention is paid towards including the appropriate (active) comparator(s), relevant endpoints (including OS and QoL), and sufficient follow-up without cross-over of patients in order not only to get marketing authorization, but also to gather the necessary evidence to support reimbursement decisions. Achieving this goal is an international affair that requires cooperation between HTA agencies, EMA and companies through e.g. early dialogues.

7.6.2.2 After marketing approval

Another moment in a product's life cycle when national policymakers can have a major influence on the gathering of the necessary evidence is the moment when reimbursement decisions are made. However, the current use of MEAs in Belgium does not respond optimally to this opportunity. In a previous KCE report, various elements were already mentioned that do not optimally support (incentives for) evidence generation:[510, 511]

- "Evidence generation

  The possibility of a MEA entails a danger that manufacturers already submit their reimbursement request when no sufficient reliable evidence is available yet, while without that possibility, such requests would probably have resulted in a negative reimbursement decision. On the one hand, MEAs make it possible to give earlier access to promising medicines for severe diseases, for which the level of uncertainty does not outweigh the possible benefits. On the other hand, this should only be a temporary solution in attendance of more evidence and less uncertainty. If further evidence collection is required, this should be part of the contract, because otherwise, manufacturers might have no incentives to gather more reliable evidence. On the contrary, gathering such evidence entails costs for the company and runs the risk of providing evidence that their product might not be as good as expected and should not be reimbursed anymore. In Belgium, the analysis of the first sixteen expired MEAs showed no extra evidence was generated within the framework of the MEA providing an answer to the research questions identified in the initial evaluation, before the start of the MEA."[510, 511]

- "Delisting from reimbursement

  During the Belgian stakeholder meetings it was revealed that once a product is reimbursed under a MEA, it might be difficult to delist it from reimbursement, regardless of the (lack of) evidence. If delisting or price reductions do not follow when medicines are found not to be (cost-)effective, the ability for these schemes to control costs should be put into question. Stakeholders also indicated that difficulties to delist products also have an impact on the incentives to gather further



evidence (see previous point)."[510, 511] The consequences of not performing the necessary study and providing the requested evidence should be stipulated from the beginning in order to provide incentives to perform this research in time.

- Choosing the wrong type of MEA

  In an ideal situation, the type of MEA should be tuned with the uncertainty it is expected to resolve. If uncertainty can only be tackled by e.g. an RCT, such evidence should be strived for. The danger exists that less complex and less expensive financial-based agreements are made. Stakeholders confirmed this statement and indicated that the follow-up of financial-based MEAs is less resource intensive and more straightforward when compared to coverage with evidence generation MEAs. Indeed, stakeholders indicated they do not always feel they have the correct expertise to appropriately design a valid evidence generation agreements including, e.g. the proper research design, which endpoints should be chosen, etc.. In fact, in Belgium, pharmaceutical companies are free to choose how they collect data in a MEA."[510, 511]

Indeed, the MORSE report mentions that in MEAs in Belgium, "It is up to the pharmaceutical companies to determine what's the best way to provide an answer to the existing uncertainties. A company can report new study results (e.g., from a post-marketing study), or interim analyzes (e.g., from an ongoing phase III study) that reveal new data concerning the initial uncertainties. A company can also rely on registers or request data from the Intermutualistic Agency (IMA) for 'real life data'. Information can be obtained through IMA from the data invoiced to the sickness funds regarding, among other things, the number of patients or packages per indication for the same molecule, the duration of treatment, any co-medication, etc."[1] We note that real-world evidence is often referred to for the collection of further evidence. However, the lack of a comparative group makes it extremely difficult to make firm statements about efficacy on the basis of this data (as is the case in this report).

The previous report on MEAs in Belgium also found that, based on the experience with the first MEAs, not much evidence is indeed generated. The main uncertainties initially identified, e.g. about the added value of interventions versus the relevant comparator, still existed at the end of the MEA. The results of the first evaluated MEAs show the current approach falls short in resolving uncertainties related to the clinical benefit of interventions.[510, 511] Many of the expired agreements are also being renewed again. The latest MORSE report stated that for 56.48% (61/108) of the expired agreements, a new CRM procedure was started and the specialty/indication was again temporarily included in the list of reimbursable specialties through a new MEA.

The combination of being able to conclude MEAs when there is high uncertainty on the treatment effect, no contractual agreement is made on the type of study design, comparator(s), endpoints, etc,, the difficulty of delisting, the possibility of extending MEAs, etc. does not provide a lot of incentives to generate the necessary evidence patients, physicians and policy makers need to make proper decisions. Decision makers should be aware of these problems and try to find ways to improve this situation.

In their article 'Generating comparative evidence on new drugs and devices after approval', Cipriani and colleagues discuss the problem of providing evidence in the post-marketing period and formulate seven key guiding principles that could provide the necessary incentives for pharmaceutical (and device) manufacturers to generate comparative data in the post-marketing period. We would like to quote these well-considered guiding principles:[14]

- "First, regulators (for drugs and devices), notified bodies (for devices in Europe), health technology assessment organisations, and payers should develop customised evidence generation plans, ensuring that future post-approval studies address any limitations of the data available at the time of market entry impacting the benefit–risk profiles of drugs and devices.
- Second, post-marketing studies should be designed hierarchically: priority should be given to efforts aimed at evaluating a product's net clinical benefit in randomised trials compared with current known effective therapy, whenever possible, to address common decisional dilemmas.

- Third, post-marketing studies should incorporate active comparators as appropriate.
- Fourth, use of non-randomised studies for the evaluation of clinical benefit in the post-marketing period should be limited to instances when the magnitude of effect is deemed to be large or when it is possible to reasonably infer the comparative benefits or risks in settings, in which doing a randomised trial is not feasible.
- Fifth, efficiency of randomised trials should be improved by streamlining patient recruitment and data collection through innovative design elements.[hh]
- Sixth, governments should directly support and facilitate the production of comparative post-marketing data by investing in the development of collaborative research networks and data systems that reduce the complexity, cost, and waste of rigorous post-marketing research efforts.
- Last, financial incentives and penalties should be developed or more actively reinforced."[14]

Several of the above recommendations could be incorporated in MEAs in Belgium and improve its ability to generate the necessary evidence: having a clear description of the open research question and linking this to the correct research design – if only an RCT can provide an answer, then no observational study design should be accepted since it will still leave the decision makers with the same uncertainty. As mentioned before, "it might be better to go for fewer MEAs with the appropriate research design that can provide an answer to important research questions, than going for a higher number of less stringent agreements where it can already be predicted from the beginning of the MEA that the same important uncertainties will remain present."[510, 511] Coverage with evidence development, making use of reimbursement 'only with research' or 'only in research' settings, should be used more often to ensure the necessary trials with the appropriate active comparator and patient-relevant endpoints are performed. Government could consider only providing initial reimbursement in the context of an RCT to avoid the problem of delay due to patient recruitment problems. Only when e.g. sufficient patients are included, and the study is continued, the intervention can be reimbursed outside of the trial. Once the results are provided, a reassessment of the intervention can be performed (e.g. refitting survival curves to more mature data). This approach is already possible, but not often used. Also in the UK, this has been suggested before: "It would have been much better if money spent by the Cancer Drugs Fund had been used to implement a little used tool available to NICE that can, if it wishes, approve new drugs for use "only in research." If greater use were made of this power, proper randomized controlled trials of new drugs could be done, which would provide real evidence of whether they were effective."[524] Also some of the external experts reviewing the individual chapters note that uncertainty about the added value of an intervention versus comparator(s) "should immediately be a reason for prospective research supported by

[hh] Cipriani et al. mention "RCTs could benefit from innovative methodological designs (i.e., adaptive design trials, basket trials, registry trials, umbrella protocols), which have their own strengths and weaknesses"[14] We refer to table 2 in the original article for an overview of base characteristics, advantages and disadvantages. We like to quote from this article[14] the brief description of these innovative study designs for randomised trials:[517]
"**Adaptive trials** are designed to maximise flexibility, without compromising the validity and integrity of the trial.[518] Modifications (so called adaptations) to aspects of the ongoing trial can be pre-specified and prospectively planned, including adding or dropping treatment arms, changing dosages, and sample size re-estimations and alterations.[519]
Basket trials are used to test the effect of a single drug, or a combination of drugs on single mutation (a single target) in multiple diseases (baskets).[520]
Platform trials, also called **adaptive platform trials**, can study multiple interventions in a disease or condition in a perpetual manner, with interventions entering and leaving the platform on the basis of a predefined decision algorithm.[521, 522]
Registry-based trials are pragmatic trials that use registries as platforms for health records, data collections, randomisation, and follow-up.[523] The advancement of electronic data collection systems has led to the increasing number of developed registries used for research, policy, and administrative purposes. A clinical registry can be used for collection of baseline variables and to identify eligible patients for a study.
Umbrella trials are designed to evaluate the impact of different drugs on different mutations in a single type of cancer.[520]"

NIHDI to only reimburse the first x patients and see whether it is not sufficient to start treatment y … .” Applying such coverage with evidence development could have a big impact on setting the research agenda.

A major problem is the negotiation position of Belgium. Since the above is not only a problem for Belgium and the position of individual (small) countries is not very strong, international collaborations might be the way forward. The further expansion of international collaboration, e.g. in the context of BeNeLuxA, could mean great progress. As mentioned in the KCE report on MEAs, this would be very helpful both for requesting further evidence as well as in price negotiations.

7.6.3 Confidential prices

7.6.3.1 A short-term advantage creating long-term problems and making the system intransparent

As mentioned in a previous KCE report on MEAs, “in the short-term, stakeholders indicated that confidential price reductions might tackle the problem of too high prices and provide access for patients. Several stakeholders also referred to the cost savings due to the introduction of MEAs. … These MEA-related cost savings should nevertheless be regarded with caution. Calculating e.g. an average percentage of all discounts does not say much about the success of MEAs. What is a discount of 10%, 20% or 50% if this still results in a much higher price versus alternatives and if the product does not offer much added value?[510, 511] Of course, in the first place, evidence on the added value is of utmost importance to assess this added value. Furthermore, an “identified long-term risk is that confidential price discounts do not provide incentives to set acceptable list prices. On the contrary, if manufacturers know confidential discounts can be negotiated in MEAs, they might already take this into account in their initial (higher) price setting.”[510, 511] The asymmetric information about negotiated prices in other countries also improves the negotiation position of the company and makes the reference pricing system based on public prices irrelevant.

As mentioned by Dr. De Ridder, former head of the NIHDI, “The problem is that the negotiations on the price being paid between the competent minister and the companies are done in complete secrecy and that no one has any insight into the amounts the company is negotiating. There is a total lack of transparency, no one knows the effective cost of developing the drug, and there are no independent audits evaluating these types of contracts.”[512] We note that regarding the latter, in 2020, “the Chamber’s commission public health has approved a bill that the Belgian Court of Audit, the parliament’s watchdog, can inspect new confidential agreements. This is possible if the Chamber has, for example, questions on the budgetary arrangements. The law was signed on 4 May 2020 [and published on 17 June 2020] and improves the transparency and accountability … . However, a first limitation is that access only applies to future contracts. Furthermore, the Court of Audit does not have the medical or methodological competence, which is, for example, necessary to assess requests for further research.”[510] Based on information from Pharma.be, received after the stakeholder meeting in May 2021, further background information was received related to this so-called increased transparency. Reference is made to a 36-eye principle, stating that at least 18 persons from government and stakeholders can be involved in the negotiations and know the details of the MEA. Furthermore, it is refers to the possibility to give a specific research assignment to the Belgian Court of Audit. However, in the information received, it was also explicitly stated that “the law does not call into question the general principle of confidentiality of certain parts of an MEA”. The Court of Audit “must respect the confidential nature of contracts, is bound by confidentiality in reporting of its findings back to the House, and can only report back in general terms to the House”. In other words, this possibility does not change the non-transparency of the whole system of MEAs and still does not allow independent researchers to make policy relevant cost-effectiveness calculations. While decision makers within the system might have access to the confidential data, the public cannot judge these decisions because of the confidentiality of important information.

Dr. De Ridder mentions “the Article 81 agreements [i.e. MEAs] were intended as an exception, but in 2018 almost 1 billion euros went to such secret contracts. … In this way, solutions for a relatively small group of patients put a lot of pressure on the health insurance expenditures.”[512] It is up to the policymakers to think about the direction they want to take with the MEAs. In this discussion we formulate several constructive proposals to go back to a system that not only seeks to address budgetary uncertainties but

also becomes an evidence-generating system that also helps resolve clinical uncertainties.

7.6.3.2 *Confidential prices making economic evaluations and policy decisions intransparent*

Already in the previous KCE report on MEAs, it was noted that "with the confidentiality of prices, stakeholders confirmed that all economic evaluations on interventions or comparators reimbursed under confidential conditions become more complicated. The calculations and results may become less transparent for the public since these depend on the confidential agreements (e.g. which price discounts, which possibly depend on the turnover, were obtained for the intervention and/or comparator)."[510, 511] "The confidential character of price and reimbursement agreements have a negative impact on the external public accountability of policymakers towards patients and citizens. In Belgium, products with no added value versus relevant comparators should not be reimbursed at a higher price versus these alternatives. However, with MEAs, it is not clear whether for such interventions the price was lowered up to the level of the equivalent alternative or whether relevant research questions were posed."[510, 511] "We also observed that more and more pharmaceuticals become reimbursed under MEAs in situations for which MEAs were initially not intended, e.g. for pharmaceuticals without any added value versus the comparator. However, when the comparator is under a MEA, transparent price negotiations are hampered and therefore, also the new intervention is put in a MEA."[510, 511] This snowball effect gradually increases the non-transparency of the system which is also confirmed by the increasing percentage of pharmaceutical expenditures that is reimbursed within a MEA (see part 7.5).

Also in the largest part of the identified economic evaluations in this report, the following notification is included: "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."

This problem can partly be solved by applying sensitivity analyzes to the price. However, in the end, it is only a limited group of people who are aware of the confidential price who have an idea of the cost-effectiveness of the intervention. Furthermore, due to the increasing use of MEAs, a confidential prices does not only apply for the intervention, but possibly also for the comparator and possible subsequent treatments. Also for researchers who carry out the evaluation for the company it is not possible to make correct calculations if the discount of the comparator is not known. For example, in one of the reports, the authors mention the results "include the agreed and tentative commercial access agreements (CAAs) for pembrolizumab. They do not include existing agreements for comparators."[525] Or in another example, "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."[370] So it also becomes impossible for the manufacturer to make appropriate calculations. Also the costs of follow-up treatments can be over- or underestimated. Without taking into account the confidential discounts, incorrect cost offsets can be modelled resulting in incorrect ICER calculations and in economic evaluations, the ICER can change substantially depending on the cost of subsequent treatment. So in general, calculating and presenting an interventions cost-effectiveness becomes completely intransparent, both for independent researchers, as well as for the company when confidential discounts apply on comparator(s) and/or subsequent treatments.

In an HTA report of Edwards et al.,[406] ICERs were derived based on list prices, while confidential PAS existed for the drugs considered. This illustrates the difficulty for external researchers to derive exact ICERs when they do not have access to the confidential discounts for the NHS, as stated in the conclusion by Edwards et al.:[406] "*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.*" In conclusion, the whole system with confidential pricing makes evaluations clearly more complex and is problematic for any form of transparency. Again, policy makers should question whether this was the initial purpose of

the MEA system and whether they want to pursuit the system as it is currently running.

Key points

- **As stated by Davis et al., "regulatory and current research practices have created a situation in which critical information about the outcomes that matter most to patients might never be generated once oncology drugs are approved for widespread use. The limited availability of studies showing either benefits to overall survival or quality of life in the postmarketing period underscores the importance of requiring robust evidence of clinical benefit at the time of marketing authorisation.[513-515]"**
- **Managed entry agreements (MEAs) are not only concluded for medicines where there is a high unmet need and a high potential for an added value. Such confidential contracts can also be used for class II drugs, biosimilars and generics.**
- **The widespread use of MEAs creates further incentives to submit reimbursement requests with immature data without providing incentives to generate reliable evidence during such a temporary contract.**
- **As a consequence of accepting immature data, a large proportion of the estimated survival benefit is often based on the extrapolated period rather than the trial data.**
- **With the current focus at EMA for fast market access and the more widespread use of MEAs, there is neither at regulatory nor at national level an increased incentive to generate better evidence.**
- **The moment of providing a drug market authorization (EMA) or reimbursment (national level) are two key moments in the life cycle of a drug. Both moments can be used as a leverage to receive the required evidence.**
- **It would be an improvement if from the beginning (i.e. in trials set up for regulatory approval), more attention is paid towards including the appropriate (active) comparator(s), relevant endpoints (including OS and QoL), and sufficient follow-up without cross-over of patients in order not only to get marketing authorization, but also to gather the necessary evidence to support reimbursement decisions. Achieving this goal is an international affair that requires cooperation between HTA agencies, EMA and companies through e.g. early dialogues.**
- **MEAs provide the short-term advantages of receiving a confidential price reductions and providing access for patients. However, the current widespread use of MEAs does not provide incentives to set acceptable list prices (on the contrary) and makes the whole system non-transparent. The current use of the system is also not optimal for evidence generation. MEAs that were meant a solution for a relatively small group of patients now puts a lot of pressure on the health insurance expenditures.**

7.7 Why we mainly relied on UK dossiers for information on economic evaluations in this report

At the beginning of the project, we planned to go through all NIHDI dossiers for the selected cancer drugs in the 12 cancer indications. We started looking at a limited number of NIHDI files in breast and ovarium cancer and observed many similar findings with the comments as in the identified files in this report. For example, in the motivated final proposal for palbociclib for the first-line treatment of patients with HR+/HER2- advanced breast cancer, the following issues were noticed by the reviewer: the use of surrogates like PFS, the remark that correlation between PFS and OS does not equal to 1, referring to the existence of EQ-5D data making it not necessary to use a surrogate for QoL, the company not making QALY calculations and expressing ICERs in extra costs per progression-free life year (PF-LY) and noting these QALY calculations will be provided after a temporary reimbursement through art.81, etc. The reviewer stated that "modeling has a major impact on ICERs. This should not be interpreted as "useful to lower the ICER" but as "an indication that there is great uncertainty" in the analysis "[526]and that more mature results are needed.

On the basis of the first NIHDI files, we noticed that the same issues appear. This is not surprising since the underlying evidence used in these dossiers comes from the same international trials. Due to practical considerations (given the large amount of reports) and given the publication bias in published economic evaluations,[430] we focused on independent HTA reports that made cost-effectiveness calculations based on a critical assessment of clinical evidence. Of course, this does not alter the fact that there are price differences between different countries. We refer to appendix 14 for information about list prices in Belgium[ii] and UK and the presence of confidential contracts. We note that confidential prices are frequently used in both countries. As a result, in these cases, we do not have any insight into the ICERs used by policymakers. Some external experts suggested to make calculating taking into account the average refund percentage, as published in the MORSE report. However, the average is not a good representation of the refund percentage in individual cases. Furthermore, as mentioned before, the goal of this report was not to make an individual HTA report for all selected cancer drugs since this would require a more detailed approach in searching for and assessing the underlying evidence.

Another reason for using published HTA reports, mainly from the UK, is because they are easy to retrieve from NICE's and the NIHR websites. In Belgium, information is also available through a web application on NIHDI's website: https://ondpanon.riziv.fgov.be/SSPWebApplicationPublic/nl/Public/Publication. In this web application, visitors can find the ministerial decisions and the syntheses of the final assessment reports approved by the CRM. However, as mentioned in NIHDI's web application, "full reports and reports completed before January 1, 2019 are available upon request at Specpharma@inami.fgov.be." We would recommend the NIHDI to also make full reports and previous decisions from the minister publicly available through their web application. Previous ministerial decisions could be retrieved in the past, which is not possible in the current system. This requires an investment from the NIHDI that should not be underestimated, but this could outweigh the time and effort needed to deliver the information requested from external stakeholders and would increase transparency.

The advantage of the UK dossiers is that "the STA process does not involve the independent academic group (ERG) in developing their own decision model. However, it does require the ERG to comment on the robustness and accuracy of the submitted model and the data used to populate the model, and where possible to carry out sensitivity analyses using the manufacturer's submitted model to indicate what they consider to be the most reliable estimate of cost-effectiveness."[94] So it contains information submitted by the company, as well as remarks and/or corrections from the independent researchers. Furthermore, the focus is also on the (cost-)effectiveness of interventions: "The committee reminded itself that its role was limited to making recommendations to NICE about the clinical and cost effectiveness of treatments for use within the NHS, in line with the guide to the methods of technology appraisal (2013). This states that the committee should not recommend treatments that are not cost effective. It also recalled paragraph 6.2.14 of the guide, which states that: 'The potential budget impact of the adoption of a new technology does not determine the appraisal committee's decision'."[82] Also in HTA, the primary focus should be on the safety, efficacy/effectiveness and cost-effectiveness of an intervention and not on the budget impact in first instance. The budget impact is of course also a very important element, but it is not efficient to spend resources on an intervention if it's evaluations of the previous mentioned elements is not positive. Of course, also other considerations outside these elements might influence policy makers' decisions. But this is not the focus of this report. For identifying issues regarding intervention's cost-effectiveness, the international published HTA reports where thus considered to be an independent and transparent source providing interesting information also relevant for the Belgian situation.

[ii] The maximum list price is authorised by the Minister of Economic Affairs.

Key points

- **For identifying issues regarding intervention's cost-effectiveness, the international published HTA reports were considered to be an independent and transparent source providing interesting information also relevant for the Belgian situation.**

7.8 The importance of the (discount for the) comparator

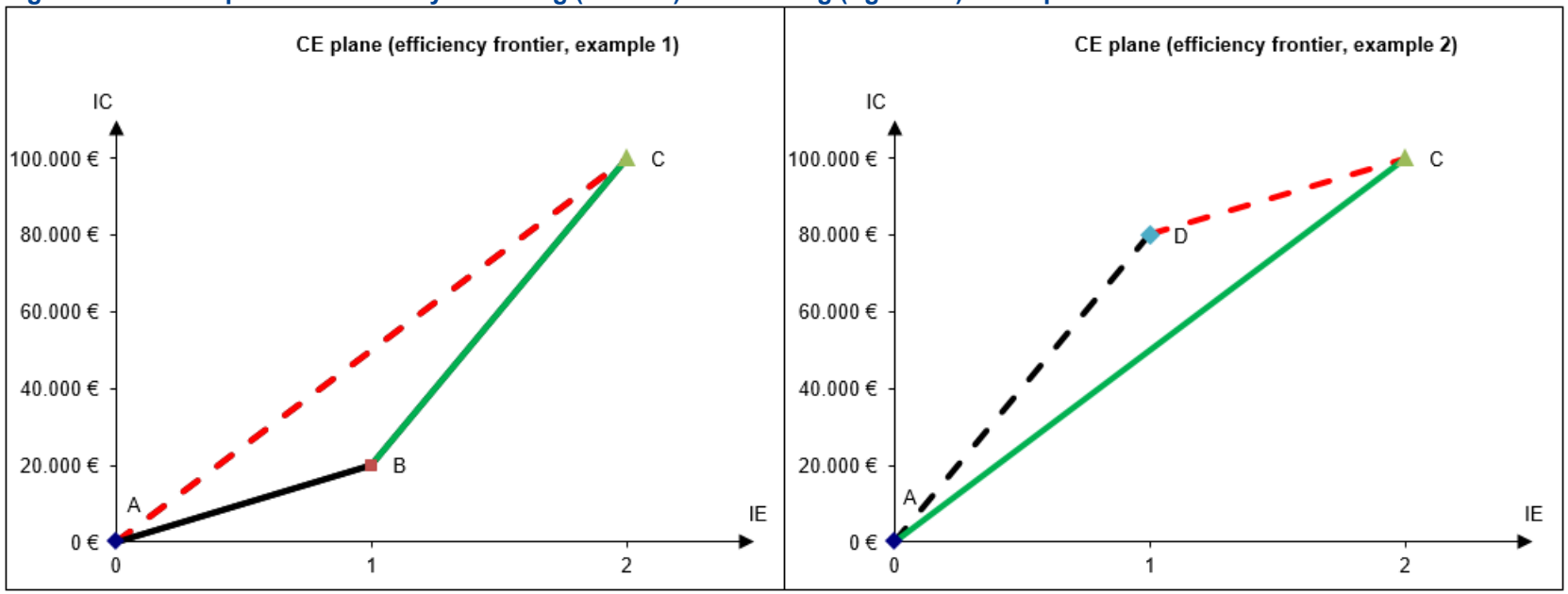
The first recommendation of the EUnetHTA guideline on criteria for the choice of the most appropriate comparator(s) states that:

- "Under ideal circumstances the comparator for a REA [Relative effectiveness assessment] applicable across European countries should be the reference treatment according to up to date high-quality clinical practice guidelines at European or international level with good quality evidence on the efficacy and safety profile from published scientific literature, and with an EU marketing authorisation or another form of recognised regulatory approval for the respective indication and line of treatment."[527]

The choice of the comparator is very important. For the clinical assessment, comparing with the appropriate comparator shows the real added value of an intervention in a specific indication. "Data derived from studies with a comparator (control) arm inferior to the standard of care (SOC), may bias the outcome by generating a larger benefit than if SOC had been used.[528-531]"[532] This can also strongly influence the cost-effectiveness calculations. As indicated in the EUnetHTA guidance document giving practical considerations for critically assessing economic evaluations, there is a problem in both incorrectly excluding a comparator with better cost-effectiveness, as well as incorrectly comparing an intervention with an alternative with an unfavourable cost-effectiveness. We explain both issues with a hypothetical example presented in Figure 14.

- Example 1 (left box): Suppose intervention C is only compared with intervention A. Then the researchers calculate a cost-effectiveness for intervention C of €50 000 per QALY gained (i.e. IC = €100 000 and IE = 2 QALYs, and ICER = IC / IE). If intervention B is an alternative with a better cost-effectiveness (i.e. €20 000 per QALY gained), then intervention C should have been compared with intervention B. The correct ICER is therefore not €50 000 per QALY gained, but €80 000 per QALY gained. The incorrect exclusion of an alternative with a better cost-effectiveness (i.e. intervention B) therefore results in an over-optimistic ICER for intervention C.
- Example 2 (right box): Suppose intervention C is compared with intervention D. Then the researchers calculate a cost-effectiveness for intervention C of €20 000 per QALY gained. But if intervention D had a worse cost-effectiveness then intervention C, then intervention C should actually be compared with intervention A. The ICER would then be €50 000 per QALY gained. Incorrectly including an alternative with poorer cost-effectiveness (i.e. intervention D) therefore results in an over-optimistic ICER for intervention C.
- Extension to example 2 (right box): If the policymaker negotiated a price for intervention D so that the incremental cost would be €20 000, point D would be in place of point B (exactly the same as in the left box) and the ICER for intervention C would also become €80 000 per QALY gained as in the first example. Not taking into account the confidential discount for the comparator obviously also has an important impact on the ICER.

Figure 14 – The impact of incorrectly excluding (left box) or including (right box) a comparator on cost-effectiveness of an intervention



IC: incremental cost, IE: incremental effect (expressed in QALYs gained).
Remark: The ICER (= IC / IE) is reflected by the slope of the line that can be drawn between the two interventions on the so-called cost-effectiveness plane. In reality, there is uncertainty about the input variables in an economic model. According to the Belgian guidelines for economic evaluations,[458] this should be taken into account with probabilistic modelling. In this figure, we opted for a simplified representation with only hypothetical point estimates. The red dotted line represents an incorrect calculation of the ICER, while the green line represents the appropriate calculation.

In the identified HTA reports with an economic evaluation, several examples stress the importance of the comparator. For example, in TA563, the researchers remark that "intervention's ICERs are very dependent on the comparator being used. For example, in an evaluation of abemaciclib, the intervention is considered a cost-effective use of NHS resources by comparing the intervention with palbociclib or ribociclib. In contrast, the resulting ICERs of these interventions (with list prices) in comparison with a non-steroidal aromatase inhibitor (NSAI) was just under £200,000 per QALY gained for abemaciclib + NSAI compared with NSAI alone."[86]

Key points

- **Inappropriate exclusion of a comparator with a better cost-effectiveness, as well as incorrectly comparing an intervention with an alternative with an unfavourable cost-effectiveness might strongly influence an intervention's cost-effectiveness and provide biased calculations.**

7.9 Different arguments used from different perspectives

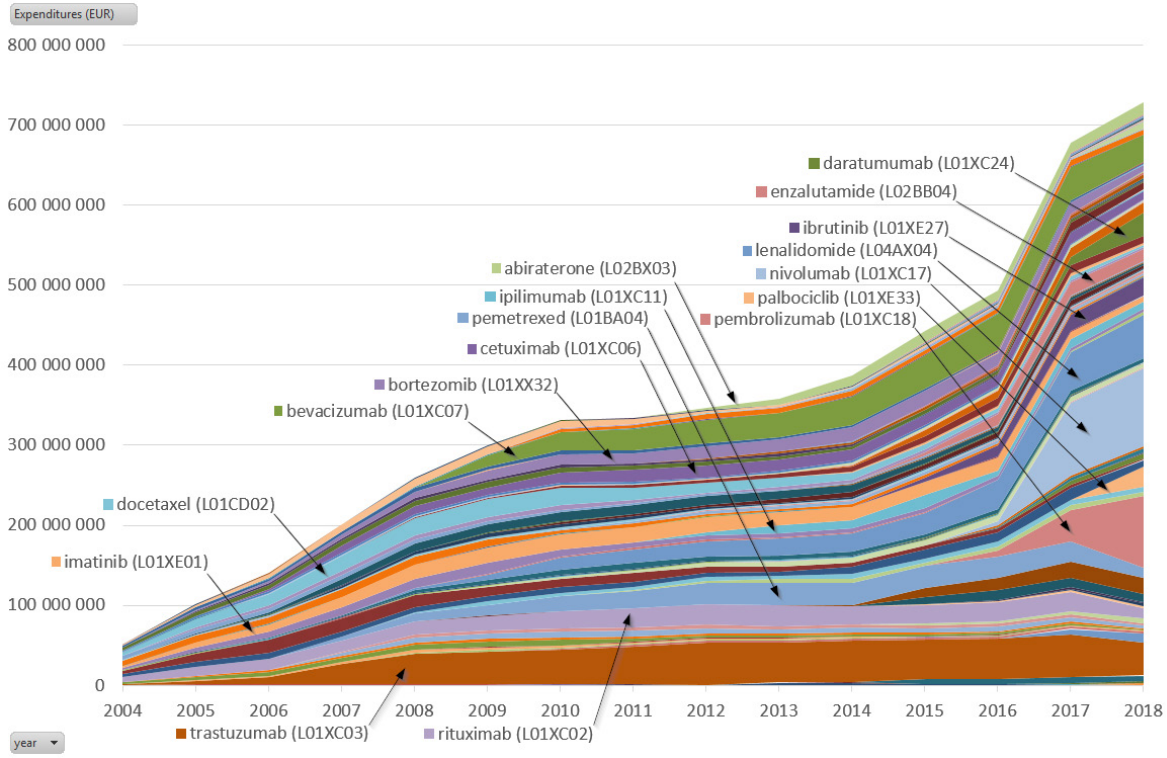
Different stakeholders will look differently at the information presented in this report. Many arguments in support of or against the (accelerated) use of cancer drugs and (high) prices of these drugs are often thrown into the fray. In this part, we list some of these arguments. It is not our intention to provide a complete overview. Neither do we want to confirm or disprove all of these arguments. Our main intent is to indicate that a critical look at the often repeated arguments of different stakeholders is absolutely necessary.

One of the arguments is that progress in cancer research is done in small steps. If we would not allow these small steps to be made, we would also miss the greater progress that can be made in the longer term. Important advances for specific subgroups might also be snowed in when looking at survival and expenditures of larger populations as was done in this report. Nevertheless, there is a "growing recognition that many cancer medicines provided modest benefits disproportionate to their high costs,"[532] and that reimbursement decisions should better be based on reliable evidence and not only on (unfulfilled) expectations.

A possible explanation that is cited for the modest benefits is the crossover of patients and the impact of the post-progression treatments. With regard to the crossover, a distinction must be made between desirable and undesirable crossover: "When a medicine has already been approved, is the SOC for later lines, and is being evaluated for an earlier line, the trial design should incorporate crossover. This is called appropriate or desirable crossover.[533, 534] … Failure to incorporate crossover in this setting harms participants on the control arm by not ensuring that they receive optimal post-progression therapy and may exaggerate the observed OS benefits. … If a medicine, never approved for a condition, is being tested in a trial, then crossover design is generally undesirable.[533-535] Since the new medicine's efficacy is unknown, there is no ethical mandate for the control arm patients to receive the medicine upon relapse.[535] Furthermore, crossover in this setting undermines the ability to determine the impact of the intervention on OS, and if crossover delays initiation of proven subsequent therapies, it may adversely impact patient well-being. For these reasons, crossover in this setting is discouraged by the EMA and FDA.[529, 530]"[532] Inappropriate crossover thus prevent proper evaluation of the effect of a new drug on OS and concluding that an OS benefit is present but has been attenuated by crossover is not self-evident. Next to avoiding inappropriate crossover, Gyawali et al. also refer to early stopping of clinical trials which might overestimate the magnitude of benefit. Regarding the impact of post-progression therapy, Gyawali et al. note that "failure to provide optimal post-progression treatment can exaggerate the impact of a PFS gain on OS even when both arms receive the same suboptimal therapies.[533, 536, 537] This underscores the importance of documenting post-progression subsequent treatments until death as part of routine follow-up data.[537]"[532] Both the comparator arm and the subsequent treatments should thus provide optimal treatment.

On the expenditure side, it is argued that in recent years the relative increase in expenditure has been lower than the increase in other expenditures in the healthcare sector. Such comparisons of course depend on which costs are included and which reference year is used. For example, Figure 15 shows the drug expenditures per calendar year for the drugs included in our report (see methodology). We note this does not provide a complete picture since we only have expenditures within 5 years after diagnosis at our disposal. The figure shows a relative strong increase in gross expenditures between 2004-2010 and the last two years (which are not yet complete). Refunds and levies must also be deducted from these expenses (see part 7.5). Furthermore, it is possible that a specific area in health care (e.g. mental health care) was underfinanced and there might be good arguments to increase the budget faster in this specific area and vice versa. Also for this argument, it is thus key to look at the added value that is created for the population.

Figure 15 – Oncological drug expenditures per calendar year (2004-2018)



Another cited argument is that the reimbursement of medicines provides a financial flow to companies, which in turn generates investment in research and thus keeps the engine for innovation running. It is also mentioned that the sector provides a large employment in Belgium. A counter-argument that is raised is that research is partly also paid by the public sector and that e.g. spin-off companies created from the public sector are taken over by for-profit players in the latest stage of developing new drugs. When the intervention is patented and high prices are requested, it is argued that society pays twice. “The relative contributions of publicly supported research and the pharmaceutical industry can be difficult to separate for a particular product. However, the upstream, pre-competitive, basic science research that so many new drugs depend on is generally thought to be predominantly funded by public support, while clinical trials are generally thought to be predominantly funded by the pharmaceutical industry.”[538] In a US-based study, researchers tried to determine the extent to which late stage development of new drugs relied on support from public funding. “Important and costly contributions come from both the public and the private sectors, in varying proportions. … However, an entity (usually a pharmaceutical company) that performs these final steps [to win intellectual property rights] is usually granted ownership over the product, and thus the chance to establish its price (in the US) and own the revenue it generates.”[538] Based on their review of the patents associated with new drugs approved over the past decade (2008-2017) by FDA, they conclude that “publicly supported research had a major role in the late stage development of at least one in four new drugs, either through direct funding of late stage research or through spin-off companies created from public sector research institutions. These findings could have implications for policy makers in determining fair prices and revenue flows for these products.”[538]

A classic argument that is also made to defend the high prices is the expensive and complex development process for bringing new drugs to the market, where the cost of failures must also be taken into account. Costs that usually are not made transparent. A counterargument is made by referring to the large budgets spend for acquisitions and the high profit margins that are applied for the patented products. The returns from cancer drugs have been so high that they might have over-incentivized the pharmaceutical industry to dedicate a substantial and perhaps disproportionate level of investment toward the development of cancer drugs, possibly at the expense of research in other disease areas.[539] Sales by the end of 2017 of 99 cancer drugs approved by the FDA from 1989 to 2017, was 14.5 times the investment in research and development.[539] Whereas patents are a stimulus to perform research, they are also responsible for the strong negotiating power of companies at the reimbursement request.

Arguments that are used also differ between a healthcare payer perspective versus the perspective of patients and physicians. The latter group obviously wants the best possible treatment. Even a small or uncertain added value might be sufficient to make them choose for a specific treatment. Whether society is able to pay for specific treatments is often a difficult choice to be made by the policy makers. Making a decision for a population is different from making a decision for individual patients. And for policy makers, especially the Minister, it is not obvious to defend a healthcare payer perspective, in which they try to do as good as possible with the available resources, when it comes to very sensitive topics where patients’ (quality of) lives are involved. The role of the media and the public pressure might also undermine rationale decision making. In addition, expectations of patients might not always reflect actual gains offered by interventions. As mentioned in the study of Davis on end-of-life care, “widespread overestimation of the benefits of chemotherapy appears to influence some patients' choice to undergo treatment. For example, in a study of 134 patients with metastatic disease who had already received a median of 6-months of chemotherapy, Mende et al. (2013)[540] found that 88% stated they would undergo treatment again. However, when asked to specify the minimum survival gain necessary for them to repeat therapy, study participants' median thresholds for survival were 18 months for non-colorectal cancer patients and 36 months for colorectal cancer patients. So while the majority of patients in this study would repeat chemotherapy, this was based on expected benefits that far exceed the actual survival gains offered by anticancer agents in the metastatic disease setting.”[418] Reliable evidence on the added value of interventions/breakthroughs on both survival and QoL is not only necessary to support governments in making reimbursement decisions, but also for physicians and patients to support their treatment choices.

That the market for cancer drugs is a market with specific features is a fact: the presence of patents and monopolies, the asymmetric price information

due to confidential prices (where it is noted that Belgian pays a good price, but no one can actually verify this), a third-party payer system in which the patient and health care provider do not pay for the intervention and government has to make difficult reimbursement decisions, a system in which international collaboration is often recommended but not easily established, etc. All of the above and much more issues show that the discussion is complex and sensitive and always needs sufficient nuance.

Nevertheless, one of the most important messages based on this report, hopefully supported by all stakeholders, is that there is a need for better evidence about the added value of cancer drugs on overall survival and quality of life. Preferably this information is already provided when these drugs enter the market. However, if reliable evidence is missing, national policy makers can still take different steps (to provide incentives) to gather such information in due time. The Belgian observational data and the evidence from the identified systematic reviews and HTA reports presented in this report do not always provide a positive image and support the need for obtaining reliable evidence. We would therefore like to refer to the synthesis of this report where we formulate a number of recommendations for our policy makers.

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