Trastuzumab pour les stades précoces du cancer du sein

KCE reports vol. 34B

Federaal Kenniscentrum voor de gezondheidszorg
Centre fédéral d'expertise des soins de santé
2006

Le Centre fédéral d'expertise des soins de santé

Présentation : Le Centre fédéral d'expertise des soins de santé est un parastatal, créé le 24 décembre 2002 par la loi-programme (articles 262 à 266), sous tutelle du Ministre de la Santé publique et des Affaires sociales, qui est chargé de réaliser des études éclairant la décision politique dans le domaine des soins de santé et de l'assurance maladie.

Conseil d'administration

Membres effectifs : Gillet Pierre (Président), Cuypers Dirk (Vice-Président), Avontroodt Yolande, De Cock Jo (Vice-Président), De Meyere Frank, De Ridder Henri, Gillet Jean-Bernard, Godin Jean-Noël, Goyens Floris, Kesteloot Katrien, Maes Jef, Mertens Pascal, Mertens Raf, Moens Marc, Perl François Smiets Pierre, Van Massenhove Frank, Vandermeeren Philippe, Verertbruggen Patrick, Vermeyen Karel

Membres suppléants : Annemans Lieven, Boonen Carine, Collin Benoît, Cuypers Rita, Dercq Jean-Paul, Désir Daniel, Lemye Roland, Palsterman Paul, Ponce Annick, Pirlot Viviane, Praet Jean-Claude, Remacle Anne, Schoonjans Chris, Schrooten Renaat, Vanderstappen Anne,

Commissaire du gouvernement : Roger Yves

Direction

Directeur général : Dirk Ramaekers

Directeur général adjoint : Jean-Pierre Closon

Contact

Centre fédéral d'expertise des soins de santé (KCE).
Résidence Palace (10ème étage)
155 Rue de la Loi
B-1040 Bruxelles
Belgium

Tel: +32 [0]2 287 33 88
Fax: +32 [0]2 287 33 85

Email : info@centredexpertise.fgov.be
Web : http://www.centredexpertise.fgov.be

Trastuzumab pour les stades précoces du cancer du sein

KCE reports vol. 34B

MICHEL HUYBRECHTS, FRANK HULSTAERT, MATTIAS NEYT, FRANCE VRIJENS, DIRK RAMAEKERS

Federaal Kenniscentrum voor de gezondheidszorg
Centre fédéral d'expertise des soins de santé
2006

KCE reports vol. 34B

Titre:	Trastuzumab pour les stades précoces du cancer du sein
Auteurs:	Michel Huybrechts, Frank Hulstaert, Mattias Neyt, France Vrijens, Dirk Ramaekers
Experts externes:	Marc Buyse, Véronique Cocquyt, Luc Dirix, Jacques Longueville, Martine Piccart, Hugo Robays, Steven Simoens, Philippe Van Wilder
Validateurs:	Minne Casteels, Maarten Postma, André Trouet
Conflit d' intérêt:	Dr Piccart a fait part d'un "unrestricted educational grant" obtenu de Roche par l'intermédiaire du "Breast International Group (BIG)".
Avertissement:	Les experts externes et validateurs ont collaboré à la rédaction du rapport scientifique mais ne sont pas responsables des recommandations aux Autorités. Les recommandations aux Autorités ont été rédigées par le Centre d'Expertise (KCE).
Mise en Page:	Dimitri Bogaerts, Nadia Bonnouh

Bruxelles, 30 juin 2006 (2nd edition ; 22 juin 2006, 1st edition)

Etude nr 2005-25-4
Domaine : Health Technology Assessment (HTA)

MeSH : trastuzumab ; Breast Neoplasms ; Receptor, erbB-2 ; Antibodies, Monoclonal ; Antineoplastic Agents
NLM classification : WP 870

Langage : français, anglais
Format : Adobe® PDF™ (A4)

Dépôt légal : D/2006/10.273/24

La reproduction partielle de ce document est autorisée à condition que la source soit mentionnée. Ce document est disponible en téléchargement sur le site Web du Centre fédéral d'expertise des soins de santé.

Comment citer ce rapport ?
Huybrechts M, Hulstaert F, Neyt M, Vrijens F, Ramaekers D. Trastuzumab pour les stades précoces du cancer du sein. Health Technology Assessment (HTA). Bruxelles: Centre fédéral d'expertise des soins de santé (KCE); 2006. KCE reports 34B (D/2006/10.273/24)

Préface

L'Herceptin était utilisée jusqu'il y a peu pour le traitement du cancer du sein disséminé. L'Herceptin est un cas d'école qui illustre comment une recherche avancée en biologie moléculaire peut déboucher sur des applications cliniques innovantes.

Fin 2005, différentes publications ont rapporté les effets prometteurs de l'adjonction de l'Herceptin à la chimiothérapie classique dans le traitement des cancers du sein aux stades précoces sans qu'un dossier d'élargissement de l'indication ne soit déposé simultanément. Ces résultats ont immédiatement suscité un énorme intérêt de la part des média. Sous la pression d'associations de patients et une intense couverture médiatique, certains pays ont accepté un remboursement du produit avant que l'examen obligatoire par l'autorité compétente ne puisse avoir lieu. De telles pratiques ne sont pas dénuées de risques ! C'est dans ce contexte que le Ministre des Affaires Sociales et de la Santé Publique a demandé une étude pharmaco-économique au KCE.

Une année de traitement à l'Herceptin, comme testé dans l'étude HERA mondialement reconnue où des chercheurs belges jouent un rôle de tout premier plan, coûte à l'Assurance Maladie environ 40 000 euro. Chaque année, au moins 500 malades avec cancer du sein pourraient bénéficier de ce traitement. Si ce dernier est dès à présent coût-efficace, vous le saurez à la lecture de ce rapport.

Un effet indésirable majeur de l'Herceptin est la décompensation cardiaque qui exclut de facto une partie des femmes avec maladies cardio-vasculaires. Mais la science ne s'arrête pas, et d'autres perspectives intéressantes se présentent. Récemment, le prestigieux *New England Journal of Medicine* a également publié l'étude FinHer. Dans cette étude, l'Herceptin était donnée avant plutôt qu'après la chimiothérapie et pendant une période plus courte, 9 semaines. Même après 3 années de suivi, on n'a pas constaté d'effets cardiaques indésirables alors que la survie sans rechute s'améliorait significativement.

Nous ne nous prononcerons pas dans le chapitre pharmaco-économique pour ou contre l'un ou l'autre mode d'administration ni sur leur durée respective. Par ailleurs, nous ne disposions pas d'arguments rationnels suffisants pour nous limiter (comme l'EMEA) aux seules données de l'étude HERA.

En tant que lecteur attentif, vous vous attendez à trouver une étude clinique comparative pour connaître la séquence idéale d'administration ainsi que leur durée optimale respective. L'histoire nous dira si cette étude comparative verra le jour.

Jean-Pierre CLOSON
Directeur Général Adjoint

Dirk RAMAEKERS
Directeur Général

Résumé

Une liste des abréviations utilisées suit ce résumé.

INTRODUCTION

Le trastuzumab (Herceptin, Roche) est un anticorps monoclonal génétiquement recombiné qui neutralise la protéine neu-HER2. La présence du récepteur de type 2 pour le facteur de croissance épidermoïde humain, HER2, peut se manifester à la surface des cellules mammaires cancéreuses et sensibilise ces cellules aux facteurs de croissance. Les tumeurs HER2 positives (HER2+) peuvent dès lors se multiplier plus rapidement. La proportion de tumeurs mammaires HER2+ diminue avec l'âge. Cependant, une tumeur initialement HER2 négative peut donner des métastases HER2 positives. La mise en évidence rapide de l'expression HER2 s'effectue par coloration immuno-histochimique (IHC). La confirmation de l'expression HER2 est basée sur l'amplification du gène codant pour l'HER2, qui est localisé sur le chromosome 17, suivie d'une hybridisation fluorescente in situ (FISH) ou d'une coloration enzymatique (CISH). Ces 2 dernières techniques bien que plus coûteuses ont une bien meilleure reproductibilité que la technique d'IHC.

Le trastuzumab est déjà employé dans le traitement du cancer du sein HER2+ disséminé. Quatre études avec allocation du traitement par tirage aléatoire testent l'efficacité et la sécurité du trastuzumab dans le traitement des cancers du sein HER2+ aux stades précoces. Les résultats des études en cours sont prometteurs et ont été rendu publics dès mai 2005 soit sous la forme de présentations lors de congrès médicaux, soit sous la forme de publications détaillées. Ces études constituent le cœur d'un dossier pour l'élargissement possible de l'indication officiellement reconnue du trastuzumab. La société pharmaceutique ROCHE n'a soumis ce dossier auprès de l'Agence Européenne des médicaments (EMEA) que le 16 février 2006. Pendant ce relativement long intervalle, des associations de patients de certains pays, ont exigé parfois avec succès l'accès immédiat et le remboursement du trastuzumab dans le traitement du cancer du sein HER2+ aux stades précoces. Tout ceci s'est produit avant l'évaluation critique impérative de l'efficacité et de la sécurité par les autorités compétentes. Cette approche n'est pas dénuée de risques. Au cours d'une procédure d'évaluation raccourcie, la commission pour les produits à usage médicaux de l'EMEA a approuvé en mai 2006 l'extension de l'indication du trastuzumab pour les stades précoces de cancers du sein HER2+.

C'est dans ce contexte et à la demande du Ministre belge des Affaires Sociales et de la Santé Publique qu'une étude a débuté au KCE. Le but de cette étude est d'estimer l'incidence du cancer du sein, le nombre de patientes à traiter, le rapport coût-efficacité et l'impact budgétaire pour l'Assurance-Maladie d'un remboursement du trastuzumab dans cette nouvelle indication. Les dossiers d'enregistrement des produits pharmaceutiques ne sont accessibles, ni publiquement ni même pour la plupart des agences impliquées dans les évaluations technologiques de santé comme par exemple le KCE. Ce rapport ne peut donc prétendre à une évaluation exhaustive de l'efficacité et des effets indésirables. Roche Belgique a été contacté pour l'obtention des données publiques. Les résultats présentés dans ce rapport sont donc basés sur les informations publiques qui couvrent l'efficacité et la sécurité, ainsi que sur des données épidémiologiques et de coûts dont certaines sont spécifiques pour la Belgique.

LE CANCER DU SEIN EN BELGIQUE

Le nombre absolu par classe d'âge de cancers mammaires diagnostiqués chaque année en Belgique a été calculé à partir des 5337 nouveaux cancers recensés en région flamande pour l'année 2001 par le réseau flamand du Registre du Cancer, qui couvre 60% de la population belge. L'incidence annuelle par tranche de 5 ans a été transposée à la population belge féminine au 1er janvier 2005 et représente un total de 9564 nouveaux cancers mammaires.

Le KCE a initié une enquête nationale en février 2006 auprès de 80 centres de traitement. Trente-deux hôpitaux ont accepté d'envoyer les données recouvrant la dernière année complète disponible et portant sur 4528 cancers invasifs stadifiés. La proportion de tumeurs qui exprimait neu-HER2 était la plus élevée chez les femmes jeunes. Cette proportion était aussi deux fois plus élevée pour les tumeurs disséminées que pour les tumeurs localisées sans envahissement

ganglionnaire et en particulier pour les tumeurs de moins de 2 cm de diamètre. En Belgique, la proportion estimée de tumeurs mammaires trouvées HER2 positives lors d'une hybridisation en fluorescence in situ s'élevait à 13.55% des cancers invasifs.

Pour les tumeurs mammaires non disséminées des stades I, II ou III, la chirurgie et la radiothérapie étaient les traitements principaux chez 99% et 88% des patientes de moins de 70 ans. La grande majorité des tumeurs avec récepteurs oestrogéniques (79%) recevait un traitement anti-hormonal, surtout le tamoxifène. La chimiothérapie était le 4ème pilier du traitement jusqu'à l'âge de 70 ans pour les tumeurs importantes ou avec envahissement ganglionnaire, c'est-à-dire aux stades II (71%) et III (86%). Le médicament principal était une anthracycline associée dans 97% des cas soit à un taxane, soit à d'autres agents cytotoxiques. La combinaison la plus fréquente était une série de cures comprenant 5-fluorouracil, épirubicine et cyclophosphamide (FEC) complétée le cas échéant par plusieurs cures de docetaxel. Les patientes neu-HER2 positives recevaient plus fréquemment une chimiothérapie que les patientes neu-HER2 négatives.

RÉSULTATS CLINIQUES

EFFICACITÉ

Le trastuzumab est actuellement distribué en Europe sous la forme unique de flacons de 150 mg de trastuzumab. Aux Etats-Unis, il existe des emballages multidoses de 440 mg. La dose recommandée pour le traitement du cancer mammaire disséminé est de 2 mg par kg de poids, administrée en perfusion intraveineuse chaque semaine. La première semaine, la patiente reçoit une dose initiale de charge de 4 mg par kg. Le mécanisme d'action du trastuzumab est peu connu. En particulier, on ignore si l'effet est cytotoxique (le trastuzumab tue les cellules) ou cytostatique (le trastuzumab bloque la croissance des cellules). L'effet cytostatique, basé uniquement sur des études chez l'animal, a justifié l'administration continue du trastuzumab dans les cancers disséminés et ce jusqu'à l'échappement de la tumeur.

Quatre grandes et 2 plus petites études avec tirage aléatoire sont en cours pour étudier le trastuzumab dans le cancer du sein HER2+ aux stades précoces (tableau I). La positivité HER2 était définie comme une IHC 3+ ou un FISH +. La plupart des malades inclus dans ces études avaient une atteinte ganglionnaire (N+). Une minorité de malades n'avait pas d'atteinte ganglionnaire mais courait un risque élevé. Tous les patients recevaient une perfusion intraveineuse standard de 2 mg/kg/semaine pendant 12 mois (après une dose de charge de 4 mg/kg la 1ère semaine) sauf dans l'étude HERA où une dose de 6 mg/kg était donnée toutes les 3 semaines (après une dose de charge de 8 mg/kg la 1ère semaine). Ce schéma d'administration assure une concentration minimale efficace de trastuzumab. Trois des 4 grandes études avaient 3 bras. Tous les participants des 4 études recevaient une anthracycline avant le trastuzumab à l'exception de 6% des patients de l'étude HERA et les patients d'un des 3 bras de l'étude BCIRG006. Dans l'étude FinHer, les malades HER2 CISH+ étaient assignés par tirage aléatoire à un traitement de 9 semaines soit par placebo soit par trastuzumab, associé au docetaxel ou à la vinorelbine, suivi d'une chimiothérapie comprenant 5-fluorouracil, épirubicine et cyclophosphamide. Ce schéma inversé a également été choisi dans l'essai E2198 où l'on a de plus étudié l'effet d'un traitement complémentaire de trastuzumab pendant 12 mois. Une cinquième grande étude, PACS04, est toujours en cours et suit l'effet de 52 semaines de trastuzumab après chimiothérapie par anthracyclines. Il n'y a pas encore eu d'analyse d'efficacité publiée.

Tableau I. Le trastuzumab dans le cancer mammaire non disséminé – schéma des études

Etude, région, patients, critères d'inclusion	anthracycline avant trastuzumab (ou après dans FinHer/E2198)	trastuzumab associé au départ à	trastuzumab précédé de	Trastuzumab
B31, US, 2 bras 1960 patients N^+ ou N0 à risque	doxorubicine et cyclophosphamide (AC)	paclitaxel		2 mg/kg/sem 12 mois
N9831, US, 3 bras 3046 patients N^+ ou T1cN0	doxorubicine et cyclophosphamide	paclitaxel (bras C)	paclitaxel (bras B)	2 mg/kg/sem 12 mois
HERA, ex-US, 3 bras 5090 patients N^+ ou N0 à risque	Anthracycline sans taxane (68%) anthracycline avec taxane (26%) pas d'anthracycline (6%)		chimiothérapie complète	6 mg/kg/3 sem 12 mois 6 mg/kg/3 sem 24mois
BCIRG006, monde, 3 bras 3222 patients N^+ ou N0 à risque	doxorubicine + cyclophosphamide	docetaxel		2 mg/kg/sem 12 mois
	pas d'anthracycline	docetaxel + carboplatine		
FinHer, Finlande, 2 bras 232 patients N^+ou stades II & III	5-FU + épirubicine + cyclophosphamide après trastuzumab	docetaxel ou vinorelbine		2 mg/kg/sem 9 sem
E2198, US, 2 bras 200 patients N^+, stades II & IIIa	doxorubicine + cyclophosphamide après trastuzumab	paclitaxel		2 mg/kg/sem 10 sem
			poursuite après chimiothérapie	2 mg/kg/sem 10 sem + 12 mois après AC

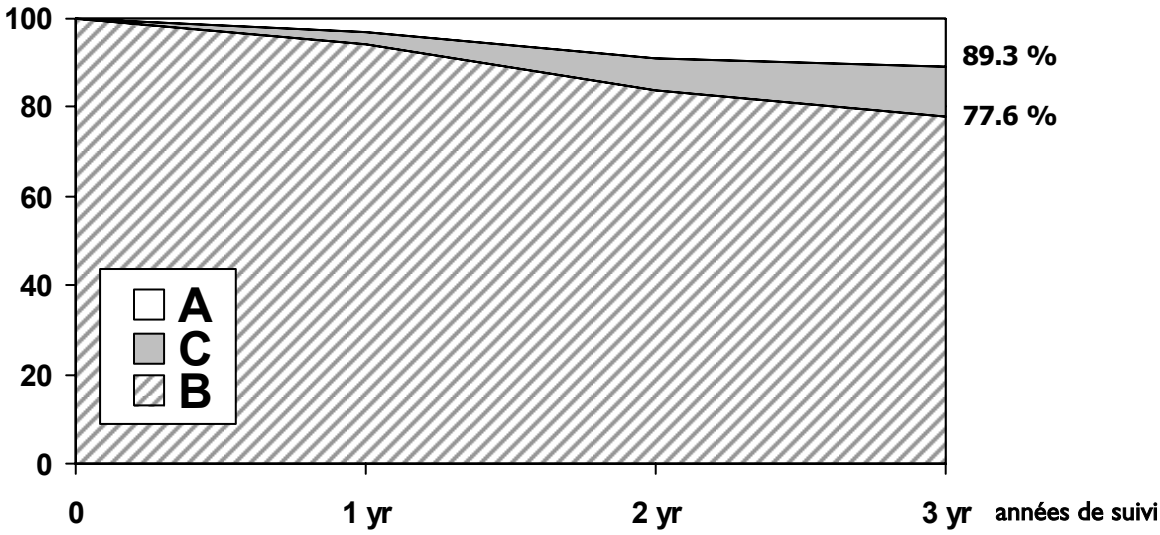
Le critère principal des études était le nombre de patientes survivantes en rémission (disease-free survival, DFS). Les résultats sont présentés sous forme de pourcentage de malades en rémission par bras d'étude. Si l'on dispose côte à côte les courbes de survie et du bras contrôle et du bras expérimental (figure I), on reconnaîtra 3 zones: La zone supérieure (A) qui comprend les patients en rechute ou décédés pendant la période de suivi parce qu'ils ne répondent pas au nouveau médicament; La zone inférieure (B), de loin la plus importante, qui comprend les patients qui auraient survécu ou seraient restés en rémission même s'ils n'avaient pas reçu le nouveau médicament. Cette zone correspond au bras contrôle qui a reçu le traitement habituel recommandé pour le même stade de gravité de la maladie ou dans certaines études l'absence de traitement parce que le risque de rechute est faible. La zone intermédiaire (C) comprend les malades qui auraient normalement dû rechuter ou décéder s'ils n'avaient pas bénéficié du nouveau médicament.

Les patients des zones A et B ne tirent aucun profit du nouveau médicament mais subissent la toxicité, les effets secondaires et le poids psychologique du nouveau traitement. La figure I traduit les pourcentages de malades en rémission 3 ans après le début du traitement dans l'étude FinHer. La zone C correspond à 11.7% (89.3% - 77.6%) des malades qui grâce au trastuzumab n'a pas rechuté. La somme des zones A (100%-89.3% ou 10.7%) et B (77.6%-0 ou 77.6%), donne 89.3% de patients qui n'ont tiré aucun bénéfice du nouveau traitement parce qu'ils étaient résistant au traitement (zone A) ou parce qu'ils n'auraient de toute façon pas rechuté même s'ils avaient reçu le trastuzumab (zone B).

Les résultats de survie en rémission peuvent également être présentés sous la forme simplifiée d'un rapport, dit risque relatif (Hazard Ratio, HR), entre le nombre de rechutes ou de décès cumulés au cours des 3 années après trastuzumab et le nombre de rechutes ou de décès pendant la même période dans le bras contrôle sans trastuzumab (survie sans rechute au tableau II).

Comme ce rapport prend en compte le moment où survient la rechute ou le décès, il diffère quelque peu d'un simple rapport des pourcentages de survie. Les patientes sous trastuzumab avaient un risque relatif de 42% par rapport au risque de rechute, néanmoins faible, encouru par les malades sans trastuzumab.

Figure I. Schématisation de la survie sans rechute dans un essai avec groupe contrôle



Les résultats du traitement par trastuzumab associé à un taxane après chimiothérapie par doxorubicine et cyclophosphamide (AC) ont été analysés conjointement pour l'étude B31 et le bras C de l'étude N9831. Les résultats du traitement par trastuzumab donnée après la fin de la chimiothérapie ont fait l'objet de 2 présentations distinctes : Une publication pour le bras à 12 mois de l'étude HERA et une présentation orale pour le bras B de l'étude N9831. Il est encore trop tôt pour observer l'effet du bras de 24 mois de trastuzumab. Le 4ème essai, BCIRG006, n'a mentionné que la survie sans rechute lors d'un congrès scientifique. Il est important de savoir que la survie globale (overall survival, OS) chez les malades du bras contrôle est influencée par le trastuzumab administré à partir du moment où la tumeur progresse.

Le trastuzumab administré avec un taxane après AC améliore significativement la survie sans rechute avec un risque relatif de 0,49 [0,41-0,57]), basé sur une analyse groupée des données publiées pour les études B31/N9138 (HR=0,48 [0,39-0,59]) et des données préliminaires du bras AC de l'étude BCIRG006 (HR=0,49 [0,37-0,65] ; figure II). L'analyse groupée B31/N9138 indique aussi une amélioration significative de la survie globale après trastuzumab (HR=0,67 [0,48-0,93]) après un suivi médian de 2 années (tableau II).

L'amélioration de la DFS lorsque le trastuzumab est administré à la fin de la chimiothérapie varie plus d'une étude à l'autre que dans les études précédentes où le trastuzumab était associé à un taxane : La DFS dans le bras B (séquentiel) de l'étude N9831 n'était pas significativement différente de la DFS dans le bras contrôle (HR=0,87 [0,67-1,13]) mais bien dans le bras à 1 an de l'étude HERA (HR=0,54 [0,43-0,67]). L'analyse groupée de la DFS pour ces 2 études donne un HR de 0,66 [0,56-0,78]. Pour chacune de ces 2 études, après seulement 1,5 et 1 an de suivi médian, la survie globale ne diffère pas de celle du bras contrôle. L'analyse groupée de la survie globale donnait un HR non significatif de 0,81 [0,58-1,12].

L'amélioration de la DFS dans l'étude FinHer est significative avec un HR de 0,42 [0,21-0,83] après un suivi médian de 3 années. L'administration d'anthracycline (épirubicine dans la combinaison FEC) complétait ici une cure de 9 semaines seulement de trastuzumab associé au docetaxel ou à la vinorelbine. Les résultats de l'efficacité du trastuzumab dans l'étude E2198 n'ont jamais été publiés.

Table II. Survie sans rechute après trastuzumab dans le traitement adjuvant du cancer du sein.

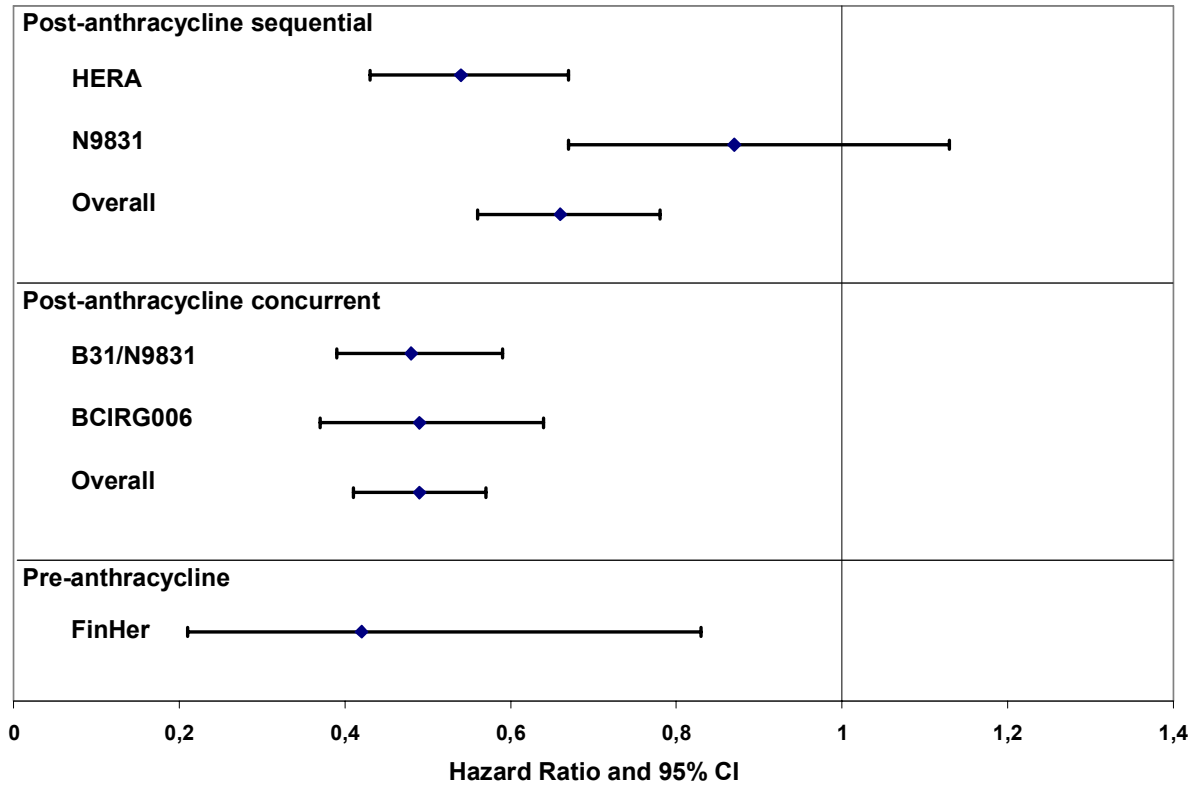
Etude (suivi médian)	**DFS dans le bras contrôle**	**DFS et risque relatif 1 an séquentiel après fin de chimiothérapie**	**DFS et risque relatif 1 an, combiné pdt 12 sem. au paclitaxel (après AC)**	**DFS (% et HR) 9 sem. comb. (avant FEC)**
HERA (1 an)	**77,4%*** (2 ans)	**85,8%** *HR 0,54 (0,43-0,67)*	pas étudié	
B31 (2.4 ans)	**74%** (3 ans)	pas étudié	**87%** *HR 0,45*	
N9831 (1.5 ans)	**78%**	*HR 0,87 (0,67-1,13)*	**87%** *HR 0,55*	
B31/N9831	**75,4%** (3 ans)		**87,1%** *HR 0,48 (0,39-0,59)*	
BCIRG006 (2 ans) AC ⟶ TH	**77,0%** (3 ans)	pas étudié	**86,0%** *HR 0,49 (0,37-0,65)*	
BCIRG006 (2 ans) TCH		pas étudié	**80,0%**** *HR 0,61 (0,47-0,79)***	
Groupé HERA/N9831		*HR 0,66 (0,56-0,78)*		
Groupé B31/N9831/BCIRG006			*HR 0,49 (0,41-0,57)*	
FinHer (3 ans)	**77,6%** (3ans)			**89,3%** *HR 0,42 (0,21-0,83)*

* La survie sans rechute (DFS) est de 78,2% dans les caractéristiques spécifiques du produit (SPC) publiées par l'EMEA

**Chimiothérapie sans anthracycline, exclue de l'analyse groupée

HR : risque relatif

Figure II. Survie sans rechute après trastuzumab selon la séquence et l'étude



L'incidence de métastases cérébrales comme premier événement était, dans les analyses rapportées, plus fréquente dans les bras trastuzumab que dans les bras contrôles avec 21 cas contre 15 dans l'étude HERA, 21 contre 11 dans l'étude B31 et 12 contre 4 dans l'étude N9831. Ceci pourrait s'expliquer par l'apparition plus précoce de métastases en d'autres endroits dans les bras contrôles. L'inefficacité relative du trastuzumab d'empêcher le développement de métastases cérébrales pourrait partiellement résulter du faible passage de la barrière hémato-encéphalique par l'anticorps. On ne connaît pas encore l'importance à long terme de la pénétration du trastuzumab sur la progression de la maladie et la survie.

EFFETS INDESIRABLES

Le trastuzumab se lie spécifiquement à la protéine HER2. HER2 se rencontre à la surface des cellules cancéreuses mais aussi en petites quantités sur les cellules musculaires cardiaques. La cardiotoxicité cardiaque pourrait être plus importante chez les patients qui expriment une variante génétique spécifique d'HER2. La décompensation cardiaque se rencontre surtout après un traitement antérieur ou simultané avec une anthracycline (doxorubicine et épirubicine). Les anthracyclines sont en elles-mêmes déjà cardiotoxiques, l'épirubicine moins que la doxorubicine. Au cours des quatre grandes études trastuzumab dans les stades précoces du cancer du sein, les anthracyclines étaient utilisées avant l'emploi du trastuzumab (sauf dans le bras sans anthracycline de l'étude BCIRG006). Après que l'on se fût rendu compte que la demi-vie plasmatique du trastuzumab était plus longue que décrite initialement, l'EMEA a mis en garde les médecins qui utilisent des anthracyclines après le trastuzumab. Cependant, dans l'étude FinHer, l'anthracycline (épirubicine) était donnée après 9 semaines de trastuzumab sans entraîner de cardiotoxicité. Dans l'étude E2198, un seul cas de décompensation cardiaque a été rapporté après trastuzumab et 4 cas après l'administration ultérieure d'AC. A côté de la toxicité cardiaque, il faut mentionner dans l'analyse B31/N9831 l'apparition de 9 cas de pneumonie interstitielle après trastuzumab (0,6% des malades traités) avec décès pour 2 d'entr'eux.

Au contraire des premières études cliniques conduites dans le cadre de cancers du sein disséminés, la fonction cardiaque était suivie prospectivement dans les études du trastuzumab

pour les cancers du sein aux stades précoces. La fraction d'éjection ventriculaire gauche (LVEF) était mesurée tous les 3 mois soit par échocardiographie soit par scintigraphie (MUGA). L'étude B31 n'a utilisé que le MUGA. La technique MUGA, qui utilise un isotope radioactif, est beaucoup plus reproductible mais est aussi plus coûteuse que l'échocardiographie. La limite inférieure d'un LVEF mesuré par MUGA est fixée à 50% de la valeur normale. A l'échographie, des méthodes de calcul différentes donnent des résultats différents. La standardisation des méthodes échographiques s'impose. La règle modifiée de Simpson a fait l'objet d'une recommandation récente comme méthode de calcul du LVEF en échographie avec une limite normale inférieure de 55%. Avant de commencer le trastuzumab, le plus souvent après AC, le LVEF devait être supérieur à 50% sauf dans l'étude HERA où la valeur seuil était fixée à 55%. Aucune des études publiées ne mentionnait l'usage d'un électrocardiogramme normal pour exclure la décompensation cardiaque.

Dans les essais B31/9831, on a observé une cardiotoxicité significative du trastuzumab. Cette information fut traduite en une mise en garde de Genentech par lettre adressée aux médecins américains. Dans les 2 études, 30,5% des patients étaient contraints d'arrêter le traitement par trastuzumab pendant au moins 4 semaines après une chute du LVEF (24% des malades B31) ou après des symptômes cardiaques (8% dans B31). Au total, 34% des malades dans le bras trastuzumab de l'étude B31 avait une chute significative du LVEF contre 17% dans le bras contrôle. Ceci survenait alors que 233 des 3497 malades (6,7%) recrutés pour participer aux études B31/N9831 avaient été interdits de participation à cause de la chute du LVEF ou de symptômes cardiaques après doxorubicine. Ceci illustre l'importante cardiotoxicité immédiate et retardée de la doxorubicine. Dans les essais B31 et N9831 (trastuzumab en combinaison, bras C), l'incidence cumulée des décompensations cardiaques de stade 3 et 4 selon la classification de la NYHA et des décès d'origine cardiaque s'élevait à 0,8% et 0% dans le bras contrôle pour 4,1 % et 2,89% après trastuzumab. Dans l'étude B31, tant le LVEF après AC que l'âge du malade étaient chacun prédictifs de la survenue d'une décompensation. L'incidence cumulée à 3 ans de décompensations cardiaques sévères chez les 48 patientes de plus de 50 ans avec LVEF entre 50 et 54 % après doxorubicine s'élevait à 20%. Ce type de malades n'a pas pû participer à l'étude HERA puisqu'un LVEF à 55% au départ était exigé. La décompensation cardiaque associée à l'emploi du trastuzumab s'améliore partiellement après l'arrêt de ce médicament et l'instauration d'un traitement cardiaque approprié.

L'étude HERA ne dit pas combien de patients furent d'emblée interdits de participation à cause de problèmes cardio-vasculaires ou d'un LVEF inférieur à 55% après chimiothérapie. Une comparaison directe de la cadiotoxicité entre cette étude et la précédente est difficile puisque à la fois les méthodes de mesure (échocardiographie ou MUGA), le seuil minimal (50% ou 55%) et l'ampleur relative de la chute de 10% et plus (jusqu'à 55% dans B31 et Fin HER, jusqu'à 50% dans HERA) différent. Ces différences à elles seules peuvent expliquer pourquoi on observait plus souvent une chute significative du LVEF dans l'étude B31 (+17%) que dans l'étude HERA (+4,9%). Dans cette dernière, 1,7% des malades ont développé une insuffisance cardiaque symptomatique accompagnée d'une chute significative du LVEF. Une décompensation cardiaque sévère (classe NYHA 3 ou 4) avec chute significative du LVEF était retrouvée chez 0,5% des malades. La seule étude qui permette une comparaison directe de la toxicité cardiaque entre une administration séquentielle d'un an après chimiothérapie et une combinaison trastuzumab pendant un an et paclitaxel pendant 12 semaines après AC est l'étude N9831. La fréquence des décompensations cardiaques sévères était légèrement plus faible lors de l'administration séquentielle mais s'accompagnait d'une efficacité réduite. Dans l'étude BCIRG006, peu de malades avaient une diminution du LVEF mais à l'aune d'une 3ème définition: une chute d'au moins 15% (au lieu de 10%) sous la limite normale inférieure.

ANALYSE RISQUE-BENEFICE

Le trastuzumab améliore la survie sans rechute de manière significative, chez les patients porteurs d'un cancer du sein HER2+ à un stade précoce pour 6 des 7 bras de traitements pour lesquels les résultats sont publiés. Une augmentation significative de la survie globale de 2,5% a uniquement été observée dans l'analyse groupée B31/ N9831. Le gain de survie sans rechute en valeur absolue varie de 3,0% (bras sous anthracycline du BCIRG 006) à 11,7% (B31 et Fin HER) tandis que le risque relatif s'établit de 0,87 (bras séquentiel N9831) à 0,42 (FinHER). Ceci signifie que la grande majorité des patientes traitées ne tire aucun bénéfice d'un traitement prolongé mais subissent le poids psycho-social d'un long traitement et sont exposés au risque d'effets indésirables sérieux.

Au cours des études B31 et N9831, 2,9% et 4,1% des patients ont développé une insuffisance cardiaque grave ou sont décédés de cause cardiaque endéans les 3 ans. L'incidence de décompensation cardiaque grave après trastuzumab était de 20% chez les malades de plus de 50 ans avec LVEF compris entre 50 et 54 % après doxorubicine. L'avantage procuré par le trastuzumab chez ces malades et chez ceux porteurs d'autres affections cardiovasculaires fond devant les risques encourus. La conséquence en est que les patientes au-delà de 50 ans avec LVEF entre 50 et 54 % après anthracyclines ne devraient idéalement pas recevoir de trastuzumab. Les patients plus âgés ont souvent une fonction cardiaque affaiblie, une tension artérielle élevée ou des lésions coronaires. Le rapport risque-bénéfice du trastuzumab chez les patients au-delà de 70 ans n'a pas été suffisamment étudié.

Les courbes de survie sans rechute dans les bras contrôles sont plutôt similaires, ce qui suggère l'absence de différences majeures entre les populations étudiées et les traitements conventionnels. L'efficacité relative, la sécurité et la robustesse des données qui supportent les 3 concepts de traitement par le trastuzumab sont résumées au tableau III. L'efficacité d'une année de traitement par trastuzumab sur la survie sans rechute dans les stades précoces paraît meilleure lorsque, après les cures d'AC, le trastuzumab est associé au paclitaxel pendant les 12 premières semaines plutôt qu'après le taxane. Le schéma séquentiel est un peu moins efficace mais aussi moins cardiotoxique. De même, l'épirubicine, surtout employée en Europe, est peut-être moins cardiotoxique que la doxorubicine, très souvent utilisée aux Etats-Unis. Le problème de la durée optimale d'administration du trastuzumab après anthracycline n'est pas encore résolu. Les résultats du bras à 2 ans de trastuzumab dans l'étude HERA seront rapidement connus. Une étude comparative entre 6 et 12 mois de trastuzumab débutera incessamment en France sous l'égide de l'Institut National du Cancer. A partir des données déjà connues, il serait aussi possible d'analyser, avec discernement, la survie sans rechute chez les malades qui, à cause d'effets secondaires cardiaques, ont reçu des doses réduites de trastuzumab (jusqu'à 31% des malades traités dans l'étude B31).

Tableau III. Classement de l'efficacité, des effets cardiaques indésirables et de la robustesse des données pour les 3 regimes de traitement par trastuzumab

	Post-anthracycline séquentiel, 1 an (HERA, N9831)	Post-anthracycline combiné, 1 an (B31, N9831, BCIRG006)	Pre-anthracycline combiné, 9 semaines (FinHer)
Efficacité	+	++	++
Sécurité cardiaque	+	+/-	++
Robustesse des données	+ (larges essais mais efficacité variable entre eux)	++ (larges essais, efficacité similaire entre eux)	+ (essai de taille modérée mais un seul pays)

L'inversion de l'ordre d'administration du trastuzumab et l'instauration d'un traitement précoce d'une durée de 9 semaines comme dans l'étude FinHer semble une approche qui, bien que prometteuse du point de vue de l'efficacité et de la sécurité d'utilisation, demande une confirmation rapide. Compte tenu de la susceptibilité du muscle cardiaque vis-à-vis du trastuzumab, vraisemblablement consécutive au prétraitement par anthracyclines, une inversion de l'ordre des 2 médicaments paraît logique. A court terme, l'analyse d'efficacité de l'étude E2198 pourrait apporter un soutien direct à cette approche. Le concept de 52 semaines de traitement par trastuzumab après anthracyclines, comme dans l'étude HERA, n'a pas encore fait l'objet d'une comparaison directe avec le régime inversé de 9 semaines comme dans l'étude FinHer. Sur base d'estimateurs moyens, certes obtenus à partir d'études différentes, le régime court présente de nombreux avantages par rapport au traitement de 52 semaines après anthracyclines. L'impact sur la survie sans rechute et sur la survie globale paraît efficace, sans apparition de la cardiotoxicité associée au trastuzumab. Le traitement est aussi plus court et plus léger pour le patient.

Enfin, si l'on voulait reproduire en pratique journalière les résultats des études cliniques, une standardisation et un contrôle de qualité des mesures HER2 et LVEF s'imposent d'urgence et ce quelque soit la spécialité des médecins qui exécutent ces mesures. La préférence va aux FISH et CISH pour HER2. La scintigraphie (MUGA) est la méthode à préférer pour les LVEF à la limite inférieure ou lorsqu'il est difficile de visualiser le cœur.

Points clés (clinique)

- Le trastuzumab permet une réduction impressionnante des métastase et une amélioration de la survie sans rechute mesurée après 2 à 3 ans qui passe de 75-78% à 86-89% chez les femmes atteintes d'un cancer du sein à un stade non disséminé. Ceci aussi bien pour un traitement de 9 semaines avant anthracyclines que pour un traitement de 52 semaines après anthracyclines. Le « number needed to treat » pour la survie sans rechute après 2 à 3 ans est de 9 et 12 selon les études.
- Malheureusement, le traitement par trastuzumab après anthracyclines est à l'origine de décompensations cardiaques sévères, en particulier chez les patientes de plus de 50 ans avec fraction d'éjection ventriculaire réduite.
- Lorsque le trastuzumab est administré pendant 52 semaines après anthracyclines, la survie sans rechute basée sur les résultats groupés semble moins bonne si le trastuzumab est donné après un taxane plutôt que simultanément. La cardiotoxicité est légèrement réduite si le trastuzumab est administré après le taxane.
- Le traitement de 9 semaines par trastuzumab suivi d'anthracyclines paraît efficace chez les patientes avec fonction cardiaque correcte ou à la limite inférieure de la normale et n'a pas entraîné de décompensation cardiaque.
- Le trastuzumab ne semble pas prévenir le développement de localisations cérébrales.
- Le trastuzumab est encore insuffisamment étudié chez les patients de plus de 70 ans.

EVALUATION ECONOMIQUE

L'évaluation économique du trastuzumab est basée sur une analyse de coût-efficacité et une analyse de l'impact budgétaire, toutes les deux dans la perspective du payeur des soins de santé.

ANALYSE COUT-EFFICACITE

Une évaluation économique digne de ce nom compare aussi bien les coûts que les conséquences d'alternatives précises. Les résultats sont exprimés sous la forme d'un rapport coût-efficacité incrémentiel (ICER). Ce chapitre compare les coûts additionnels en euro par rapport aux années de vie gagnées dans un scénario précis. Un scénario est défini par le mode de traitement, la population de patients décortiquée par âge, le stade du cancer, l'état du cœur, et une série d' hypothèses spécifiques. L'analyse se situe dans la perspective du payeur et compare différents résultats de santé et différents coûts de traitement par trastuzumab en situation adjuvante par rapport à la situation où ce médicament n'est pas administré. Cette analyse coût–efficacité s'inscrit dans une perspective à long terme, jusqu'à la fin de la vie du malade.

L'effet et les coûts du trastuzumab ont fait l'objet d'une modélisation basée sur des essais cliniques (HERA, B31 / N9831 et FinHER) dans le cancer du sein aux stades précoces en respectant le schéma de traitement, l'efficacité et les effets secondaires observés. La durée médiane de survie qui variait de 1 (HERA) à 3 ans (FinHER) ne donne aucune indication sur la survie à long terme. Les résultats à court terme ont été transposés au long terme à partir du risque relatif (HR) encouru par les patients sans métastases. Leur espérance de vie fut calculée à partir des tables belges de mortalité et légèrement réduite en considération du risque de développement d'un cancer secondaire après traitement pour cancer du sein. L'espérance de vie des patients qui présentent une extension à distance correspond à la somme de 2 termes : d'une part, l'intervalle de temps jusqu'à l'apparition de métastase(s) selon l'âge et le stade du cancer et d'autre part, la durée de survie à partir de l'apparition de la métastase selon Berkowitz, 2000. Les années de vie gagnées, qui correspondent à la différence d'espérance de vie entre les 2 situations, sont ensuite multipliées par le risque général de progression vers métastase sans trastuzumab et par le risque relatif sous trastuzumab, risque qui est donné dans chaque étude.

Les coûts incrémentiels comprennent les coûts de diagnostic, traitement et procédures de suivi jusqu'en fin de vie, qu'ils soient habituels dans le traitement du cancer du sein ou inhabituels parce que provoqués par les effets indésirables (décompensation cardiaque) du trastuzumab. Tant la (plus grande) partie des coûts prise en charge par l'Assurance Maladie belge (INAMI/RIZIV) que les coûts directs médicaux supportés par le patient sont ici considérés. Un premier coût incrémentiel est causé par le test FISH de confirmation du statut HER2 des tumeurs trouvées 2+/3+ en immunohistochimie. L'enquête du KCE dans les centres de soins oncologiques belges en 2005 a déterminé la proportion de tumeur HER2 positive en FISH par âge et stade de la maladie. Les coûts incrémentiels nés du traitement par trastuzumab varient selon le schéma d'administration des études HERA, B31/N9831 et FinHER. Ces coûts supplémentaires comprennent le coût du médicament (la quantité injectée comme la quantité perdue) et les séjours supplémentaires en hôpital de jour pour le traitement spécifique par trastuzumab. La durée de traitement varie de 9 semaines à 52 semaines et influence les quantités de médicaments nécessaires et le nombre de séjours supplémentaires. La périodicité de l'administration -hebdomadaire ou toutes les 3 semaines- influence également la quantité de médicament déjetée à chaque administration. Le coût des scintigraphies cardiaques supplémentaires (l'échocardiographie n'étant pas encore standardisée) est également porté en compte pour les patients susceptibles de recevoir le trastuzumab et ensuite, tous les 3 mois pendant la durée du traitement.

Le traitement par trastuzumab n'entraîne pas nécessairement des coûts supplémentaires. Si l'on peut éviter que des malades progressent vers un cancer du sein disséminé, on réalise alors des économies à long terme. Les coûts de traitement des métastases comprennent les coûts de chimiothérapie, d'hormonothérapie, des produits d'épargne calcique, des facteurs hématopoïétiques, etc. mais pas les soins palliatifs. Nous y avons ajouté les coûts de suivi et de diagnostic pendant toute la durée de survie sans rechute. Ces coûts croissent avec la survie. L'incidence de récidives locales a été réduite dans la même proportion que l'amélioration relative de la survie sans rechute après trastuzumab (HR). Le coût de traitement des récidives locales (mastectomie, radiothérapie éventuelle) est également comptabilisé. L'augmentation d'incidence,

les coûts ainsi que la réduction de l'espérance de vie selon l'âge d'apparition de la décompensation cardiaque sont basés sur des données hollandaises.

Nous avons calculé les coûts incrémentiels et les bénéfices de santé (ICERs) pour différents sous-groupes d'âge (tout âge, <50 ans, 50-59, 60-69, 70-79, 80+) et de gravité (stades I, II et III) dans les études HERA et FinHer. Nous avons aussi individualisé les ICERs selon l'âge (tout âge, <50 ans, ≥50) et le LVEF (LVEF compris entre 50 et 54%, ≥55%) au début du traitement par trastuzumab puisque ces éléments sont prédictifs de décompensations cardiaques au cours ou après traitement par ce médicament. La survie sans rechute a été amputée des décès consécutifs à la décompensation cardiaque calculés à partir de la fréquence des décompensations cardiaques détaillées dans l'étude B31.

Analyse de scénarios, modélisation tenant compte de l'incertitude autour des variables introduites et analyse de sensibilité probabilistique

La possibilité que le trastuzumab ne prévienne pas le développement de tumeurs cérébrales pose un problème particulier lors de la modélisation des bénéfices de santé. C'est pourquoi nous avons retenu deux scénarios. Le premier où nous supposons que le traitement est efficace comme pour les autres localisations à distance et le second, le scénario de référence, où le trastuzumab n'empêche pas mais retarde d'environ 1 an le développement de tumeurs cérébrales chez une fraction des malades. Nous avons supposé que l'espérance de vie des patients avec extension cérébrale était identique à celle observée pour les autres localisations à distance. Nous avons également modélisé les scénarios suivants : le traitement sans perte de trastuzumab au moment de l'injection (le scénario de référence tient compte de la perte), la reprise du trastazumab au moment de la dissémination de la tumeur (scénario de référence : pas de reprise), la prise en compte d'un coût supplémentaire de 5000 euro pour le traitement de la dissémination (scénario de référence : pas de coût supplémentaire), différents taux d'actualisation (3% pour les coûts et 1,5% pour les gains de santé (scénario de référence), 3% pour les deux, 5% pour les deux, 5% pour les coûts uniquement, 3% pour les coûts uniquement et finalement aucune actualisation). Tous ces scénarios furent mis en œuvre pour les différents modes de traitement, les 5 sous-groupes d'âge et les 3 stades de gravité.

La plupart des variables entrées dans le modèle, comme celles tirées de la littérature, sont entourées d'incertitude. Lorsqu'il n'existait pas d'intervalle de confiance, nous avons délibérément inclus une incertitude. Nous avons utilisé comme telles les incidences observées lors de la très large enquête épidémiologique auprès des centres de soins oncologiques. La distribution sous-jacente des variables entrées dans le modèle est la plupart du temps normale. Pour n'utiliser que des valeurs réalistes, nous avons réduit l'intervalle à 99%. Pour les proportions, nous avons appliqué une distribution bèta. L'analyse de sensibilité probabilistique reflète l'inclusion simultanée de l'incertitude pour toutes les variables. Pour chacune de celles-ci, l'incertitude du résultat est obtenue par 1000 simulations aléatoires dites de Monte Carlo. Enfin, nous avons effectué un test de rang entre les variables de départ et les résultats calculés pour quantifier l'importance relative de ces variables.

Résultats de l'analyse de coût-efficacité

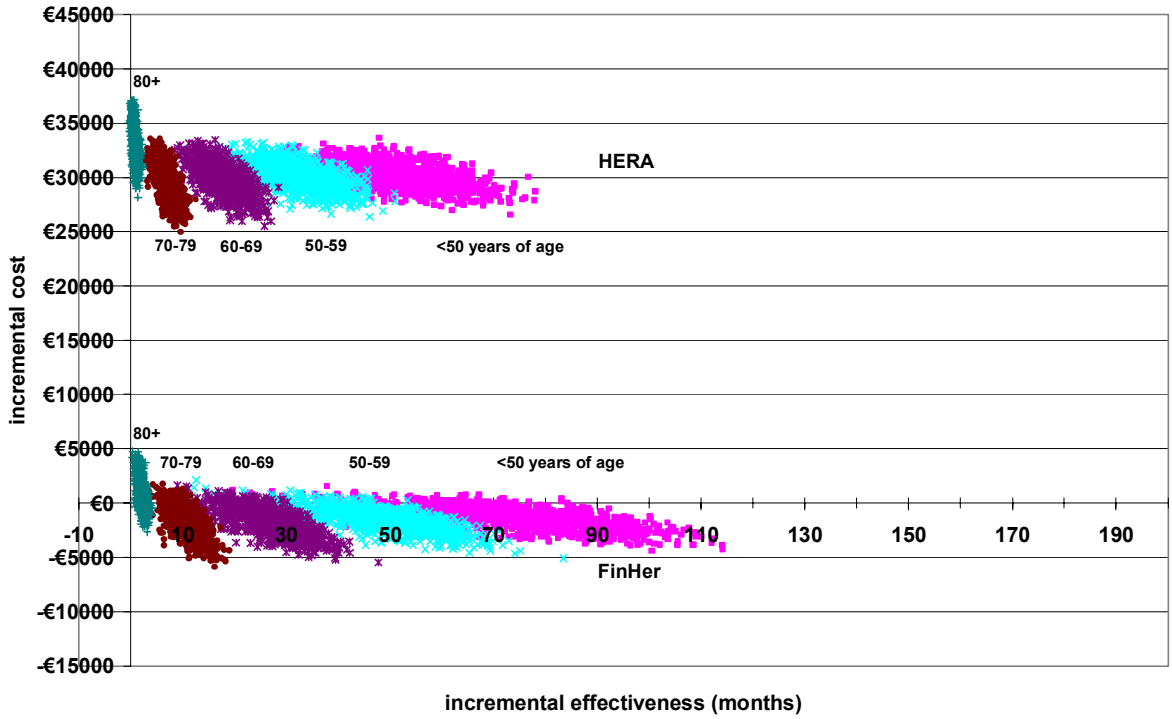
Au taux d'actualisation proposé pour le scénario de référence, le trastuzumab est efficace chez les patientes ayant un LVEF≥55% (HERA) ou ≥50% (FinHer) avant traitement. La seule exception concerne les patientes de plus de 80 ans au stade I dans l'étude HERA. A titre d'exemple, le gain estimé en années de vie pour une patiente de 50-59 ans au stade II de la maldie est de 32,81 mois [21,54 – 44,36] dans le cas de l'étude HERA et de 48,65 mois [26,29 – 65,69] dans l'étude FinHer et ceci pour une population plus importante puisque moins de femmes sont d'emblée exclues pour raison cardiaque. Les bénéfices de santé se recoupent pour les 2 études avec cependant un avantage pour l'étude FinHer bien visible pour les moins de 50 ans (figure III). L'intervalle de confiance du risque relatif, plus important dans l'étude FinHer, se traduit par un nuage de points plus étalé. La comparaison entre les différents sous-groupes fait apparaître un plus grand nombre d'années de vie gagnées chez les patientes plus jeunes et pour les stades avancés de cancers.

Le coût incrémentiel par malade traité selon le schéma court (FinHer) n'est qu'une fraction du coût du régime HERA de 52 semaines. Ces coûts incrémentiels sont même négatifs pour les stades II et III dans l'étude FinHer, ce qui indique une économie nette. Ainsi pour le groupe des patients de 50 à 59 ans souffrant d'un stade II, le coût incrémentiel s'élevait à 30 101 euro

[27 647 - 32 508] dans l'essai HERA et à -1559 euro [-3783 - 527] dans l'essai FinHer (figure III). Dans ce dernier cas, les économies futures dépassent l'investissement initial.

La combinaison de coûts incrémentiels plus faibles et d'estimations plus élevées pour les gains de santé se traduit en général par un bien meilleur ICER pour l'étude Finher que pour l'étude HERA, et ceci à tous les stades de gravité et à tout âge. Dans les 2 études, l'ICER est meilleur chez les patientes plus jeunes (un plus grand pourcentage de femmes tirent avantage du traitement et un plus grand nombre d'années de vie sont gagnées) et dans les stades plus graves (un pourcentage plus important de patientes profite du traitement). Le traitement par trastuzumab du cancer du sein aux stades précoces n'est pas coût-efficace pour 6 des 15 sous-groupes dans le scénario HERA, à savoir le stade I pour les sous-groupes d'âge 60-69, 70-79, 80+, le stade II pour les sous-groupes d'âge 70-79, 80+, et le stade III pour le sous-groupe d'âge 80+. Dans le scénario FinHer, c'est uniquement le cas pour les patientes de plus de 80 ans au stade I.

Figure III. Coût-efficacité incrémentiel pour les études HERA et FinHer par classe d'âge au stade II.



La modélisation des résultats de l'étude B31 était intéressante en raison de l'augmentation de l'incidence des décompensations cardiaques associées au trastuzumab chez les patientes avec une fraction d'éjection ventriculaire entre 50 et 54% après traitement par anthracyclines et avant l'administration de trastuzumab. Celui-ci est efficace chez les patientes de moins de 50 ans, mais pas pour les stades I et II au delà de cet âge lorsque la LVEF se situait entre 50 et 54%. C'est ainsi qu'au stade II, l'incrément d'efficacité s'élevait à 38 mois en moyenne [7,15-61,54] chez les patientes de moins de 50 ans et entrainait une réduction d'espérance de vie de 8,15 mois en moyenne [-28,64-5,95] chez les patientes de plus de 50 ans. Ceci est tout à fait différent de la situation observée dans l'étude FinHer où le trastuzumab provoquait peu ou pas de problèmes cardiaques quelque soit l'âge, même chez les patientes avec LVEF entre 50 et 54%.

ANALYSE DE L'IMPACT BUDGETAIRE

L'incidence annuelle globale des cancers du sein en Belgique a été dérivée directement de l'incidence par tranche d'âge observée en Flandres au cours de l'année 2001 et des données démographiques nationales. Nous supposons que la distribution des cancers par stade de sévérité dans chaque tranche d'âge de notre large enquête est représentative de la situation belge. Pour chaque tranche d'âge, nous avons multiplié le nombre de cancers apparus annuellement par la distribution spécifique observée dans la même tranche et ainsi obtenir le nombre de cancers par âge et par stade pour l'année 2005.

Nous avons ensuite estimé pour chaque stade et chaque tranche d'âge le nombre de patients qui remplissaient 2 conditions: l'expression de neu-HER2 mesurée par FISH et une chimiothérapie. Nous avons ensuite exclu les patients dont la fonction d'éjection ventriculaire gauche trop faible ne leur permettait pas (= avant chimiothérapie) ou plus (après chimiothérapie) d'entamer un traitement par trastuzumab. Enfin, comme les résultats de l'association d'une chimiothérapie et du trastuzumab sont positifs, nous avons posé l'hypothèse que la moitié des patients neu-HER2 positifs non encore traités par chimiothérapie pourrait choisir un traitement plus agressif afin de maximaliser leurs chances de guérison (= plus de chimiothérapie).

Les coûts du trastuzumab et de son administration diffèrent selon les trois études de référence et s'élèvent à 8667, 40 657 et 48 172 euro pour respectivement les régimes FinHer, HERA et B31/N9831. Dans le cas d'un élargissement de la population actuellement traitée par chimiothérapie, la somme des coûts du trastuzumabb et des coûts induits par une chimiothérapie conventionnelle représente pour chaque nouveau malade un coût additionnel de 14 727, 45 537 et 59 223 euro.

Le choix de donner le trastuzumab pendant les 9 semaines avant ou les 52 semaines après les anthracyclines modifie considérablement le nombre de femmes qui peuvent bénéficier de ce nouveau traitement et l'impact budgétaire (tableau IV). Le surcoût du trastuzumab pour les stades I, II et III ensemble s'élèverait aujourd'hui à 5,17 millions d'euro pour 597 patientes traitées dans un scénario 9 semaines et 19,96 millions pour seulement 491 patientes traitées dans un scénario 52 semaines (puisque ce dernier schéma expose davantage de patientes à un risque d'insuffisance cardiaque et entraîne leur exclusion).

Si la moitié des patientes non encore traitées par chimiothérapie optait pour une approche plus agressive, le coût total pour les stades I, II et III réunis pourrait grimper à 9,08 millions d'euro pour 862 patientes traitées dans un scénario 9 semaines et à 29,84 millions d'euro pour 708 patientes traitées dans un scénario 52 semaines. Ce dernier scénario soulage non seulement 19% de patientes en moins, mais implique aussi une durée du traitement de 616 jours au lieu de 189 jours et deux fois plus de journées d'hospitalisation de jour. Ceci signifie également plus d'oncologues, de personnel infirmier très qualifié et davantage de lits. Enfin, le coût réduit d'un traitement de 9 semaines permettrait plus facilement à l'Assurance Maladie de rembourser d'autres traitements innovants.

Tableau IV. Coûts totaux de traitement pour les patients éligibles en 2005

Stade	Chimio & LVEF≥50%	Chimio & LVEF≥55%	Plus de chimiothérapie	Plus de chimiothérapie
	T9 semaines	T52 semaines	T9 semaines	T52 semaines
Stade I	0,85 M	3,25 M	2,82 M	8,26 M
Stade II	2,81 M	10,86 M	4,30 M	14,59 M
Stade III	1,52 M	5,85 M	1,96 M	6,99 M
Stades I, II & III	5,17 M pour 597 patients	19,96 M pour 491 patients	9,08 M pour 862 patients	29,84 M pour 708 patients

Chimio & LVEF ≥50% [ou LVEF ≥55%]: patients neu-HER2 positifs sous chimiothérapie adjuvante et fraction d'éjection ventriculaire ≥50% [ou LVEF ≥55%] au début du traitement par trastuzumab ; coût supplémentaire du trastuzumab.
Plus de chimiothérapie : patients déjà sous chimiothérapie + 50% des patients FISH positifs non encore exposés à une chimiothérapie et avec fraction d'éjection ventriculaire ≥50% [ou LVEF ≥55%] au début du traitement par trastuzumab ; coût supplémentaire du trastuzumab et coût de la chimiothérapie chez les patients non encore exposés.
T9 semaines : cure de 9 semaines de trastuzumab (FinHer).
T52 semaines : cure de 52 semaines de trastuzumab (HERA).

Points clés (Economie de la santé)

- **Selon le modèle pharmaco-économique à long terme, le trastuzumab administré après les anthracyclines semble efficace dans la majorité des sous-groupes définis par âge et stade de gravité tandis que le trastuzumab donné avant anthracyclines est efficace pour tous les sous-groupes étudiés. Pour chacun des scénarios modélisés, le trastuzumab était plus efficace chez les femmes jeunes et dans les stades plus avancés de la maladie.**
- **Lorsque le scénario post-anthracycline est testé chez des patientes dont la fonction cardiaque est à la limite inférieure de la normale (LVEF entre 50 et 54%), le trastuzumab abaisse l'espérance de vie des patientes de plus de 50 ans aux stades I et II.**
- **Dans notre modèle, l'option d'un traitement de 9 semaines avant anthracyclines est plus coût-efficace qu'un traitement donné après anthracyclines, peut même être rentable et permet à 20% de femmes supplémentaires de bénéficier du traitement de leur cancer. Les traitements ne sont pas coût-efficaces pour 6 sous-groupes sur 15 si on applique le schéma de l'étude HERA, tandis qu'avec le schéma de l'étude FinHer, ils sont coûts-efficaces pour 14 des 15 sous-groupes.**
- **Environ 14% des 9564 nouveaux cas estimés de cancers du sein en Belgique expriment HER2. Une fraction seulement de ceux-ci est actuellement traitée par chimiothérapie tout en ayant une fonction cardiaque qui permet l'utilisation de trastuzumab. Un total de 597 et 491 patients au moins pourrait recevoir le trastuzumab respectivement avant et après anthracyclines. Ces traitements coûteraient à l'INAMI respectivement 5,17 et 19,96 millions d'euro.**
- **Ces montants sont des estimations minimales. Devant l'amélioration des résultats thérapeutiques, nous supposons que jusqu'à 50% de femmes supplémentaires pourrait maintenant opter pour le trastuzumab et une chimiothérapie, ce qui alourdirait les coûts en conséquence.**

CONCLUSIONS ET RECOMMANDATIONS

Les résultats partiels déjà prometteurs de l'anticorps monoclonal trastuzumab (Herceptin) dans le traitement des stades précoces du cancer du sein HER2+ (non disséminé) ont été publiés depuis mai 2005. Le dossier n'a été soumis que récemment (février 2006) par la firme pharmaceutique Roche à l'Agence Européenne des Médicaments (EMEA) pour évaluation de l'efficacité et de la sécurité d'utilisation. Après une procédure accélérée, l'EMEA a approuvé en mai 2006 l'extension d'indication du trastuzumab dans le cancer du sein aux stades précoces. Les détails de l'évaluation n'ont été rendus public qu'au moment de la rédaction finale de ce rapport.

Depuis mai 2005, la couverture médiatique a été considérable et dans plusieurs pays des associations de patients ont, parfois avec succès, exigé une mise à disposition anticipée et le financement du trastuzumab pour le traitement des cancers du sein HER2+ à partir des stades précoces. Tout ceci avant que les autorités compétentes n'aient procédé à l'évaluation critique indispensable de l'efficacité et de la sécurité d'emploi. Cette manière d'agir observée dans plusieurs pays n'est pas dénuée de risques.

Le trastuzumab réduit nettement les rechutes à distance et améliore la survie sans rechute à 2 ou 3 ans. Les évaluations en cours suivent le plus souvent un schéma d'administration et une durée de traitement similaires à l'étude HERA. Plusieurs questions subsistent quant au schéma idéal de traitement (pré- ou post-anthracycline) et à la durée optimale de chacun de ces schémas.

Le trastuzumab est un médicament très coûteux. Des estimations minimales indiquent qu'un nombre de 597 et 491 malades par an sont éligibles pour un schéma pré- et post-anthracycline respectivement. Ces traitements au trastuzumab devraient coûter à l'INAMI 5,17 et 19,96 millions d'euro. Si 50% de patients supplémentaires HER2+ devaient choisir le trastuzumab et la chimiothérapie, les coûts pour l'Assurance Maladie pourraient s'élever à respectivement 9,08 et 29,84 millions d'euro.

Selon notre modèle pharmaco-économique à long terme, l'administration de trastuzumab pendant 52 semaines après anthracyclines est coût-efficace pour 9 des 15 groupes de patients tandis que son administration pendant 9 semaines avant anthracyclines est coût-efficace pour 14 des 15 groupes. Pour certains d'entre eux, cette stratégie est même une stratégie dominante, c'est à dire qu'elle procure un gain de santé et des économies. Les estimations les plus coût-efficaces sont basées sur une étude de taille certes plus petite mais exécutée dans un seul pays avec le support des autorités finlandaises.

Tout ceci place les décideurs politiques devant un dilemme épineux. A ce jour, le trastuzumab est exclusivement enregistré pour un traitement de 52 semaines après la fin de la chimiothérapie, ce qui laisse peu de marge aux autorités des pays qui envisagent un financement du trastuzumab. Soit donc on decide de rembourser 52 semaines de traitement après la fin de la chimiothérapie selon le schéma HERA approuvé par l'EMEA et les deniers publics seront pour une part consacrés à des interventions non coût-efficaces. Soit ces décideurs se penchent sur toutes les données cliniques et économiques et ils sont confrontés aux résultats interpellants de la plus petite étude FinHer publiée récemment dans le *New England Journal of Medicine*. Une beaucoup plus courte durée de traitement avant les anthracyclines paraît aussi efficace et dépourvue de cardiotoxicité. De surcroît, 20% de femmes en plus peuvent bénéficier du traitement, y compris celles qui ont une fonction cardiaque légèrement réduite. Ceci a aussi des implications positives pour la qualité de vie et le coût à supporter pour la communauté.

La littérature consultée ne livre aucun argument rationnel en faveur d'une durée minimale de 52 semaines de traitement par trastuzumab comme ce fut le cas dans les 4 grandes études de phase 3. De même, on appréhende mal que le concept d'un traitement court avant anthracycline, comme mis en oeuvre dans les études E2198 et FinHer, n'ait pas été retenu pour une étude de phase 3. Seule une étude comparative, supportée vraisemblablement par les autorités, pourra trancher quel schéma de traitement, avant ou après anthracycline, est le plus efficace. Une telle étude devrait idéalement avoir lieu dans un contexte international.

Cette évaluation d'économie de la santé fournit, sur base des données disponibles, des estimations claires de l'efficacité clinique et du rapport coût-efficacité du trastuzumab. Elle apporte des évidences utiles pour les discussions futures avec les organes compétents de l'INAMI lors de l'extension du remboursement du trastuzumab. Un certain nombre de recommandations basées sur les conclusions actuelles peuvent dès à présent être émises.

Points clés (Conclusions et recommandations)

- La quantité de trastuzumab déjetée peut être réduite par la mise sur le marché de plus petits conditionnements. Ce problème doit être discuté avec le fabriquant.
- Si l'on veut reproduire en pratique journalière les résultats des études cliniques, une standardisation et un contrôle de qualité des mesures HER2 et LVEF s'imposent. La préférence va aux FISH et CISH pour HER2. La scintigraphie (MUGA) est la méthode à préférer pour les LVEF à la limite inférieure ou lorsque le muscle cardiaque est difficile à visualiser en attendant qu'une standardisation de l'échographie voie le jour. Il faut souligner que la scintigraphie est une technique plus coûteuse que l'échographie.
- Le remboursement doit être soumis à des critères stricts d'inclusion et d'exclusion et s'inscrire dans les procédures de qualité des programmes d'oncologie au sein des hôpitaux belges. Si l'on respecte les critères de l'étude HERA, l'administration de trastuzumab pendant 52 semaines est la plupart du temps un traitement efficace sur le plan clinique mais pas toujours coût-efficace chez les femmes qui ont une fraction d'éjection ventriculaire d'au moins 55% et n'ont pas d'autres critères d'exclusion cardio-vasculaires. Pendant le traitement, la fonction cardiaque doit être suivie régulièrement.
- Un enregistrement performant par le Registre du Cancer d'une série de variables pronostiques chez les patients qui souffrent d'un cancer du sein est essentiel pour le suivi du traitement par trastuzumab. De manière générale, un tel registre est nécessaire pour estimer de façon fiable le nombre de malades qui sont susceptibles de bénéficier d'un traitement innovant. Ce rapport mentionne un certain nombre de variables qui peuvent être utilisées.
- Une étude clinique qui compare un traitement de 9 semaines de trastuzumab pré-anthracycline et de 52 semaines post-anthracycline doit être initiée sans délai.

Scientific summary

Table of contents

1 INTRODUCTION 5

1.1 RATIONALE FOR ADJUVANT THERAPY IN ONCOLOGY 5

1.2 DATA SOURCES ON TRASTUZUMAB 5

1.3 DATA SOURCES ON BREAST CANCER 6

1.3.1 Breast cancer incidence in Belgium 6

1.3.2 Epidemiology of breast cancer in Belgium: survey by the KCE 7

1.3.3 Treatment 9

1.3.4 Estimation of the actual distribution of invasive breast cancer in Belgium 10

1.4 RATIONALE FOR TRASTUZUMAB 11

1.5 THE PRODUCT 12

2 EFFICACY 13

2.1 CURRENT INDICATION – METASTATIC BREAST CANCER 13

2.1.1 Dose, administration and treatment duration 13

2.1.2 Detection of HER2 overexpression or HER2 gene amplification 14

2.2 NEW INDICATION – EARLY STAGE BREAST CANCER 15

2.2.1 Dose, administration and duration of treatment 18

2.2.2 Neo-adjuvant use of trastuzumab 18

3 SAFETY PROFILE 26

3.1 CARDIAC SAFETY 26

3.1.1 Metastatic breast cancer indication 26

3.1.2 Early stage breast cancer indication 27

3.2 OTHER SIDE EFFECTS 30

3.2.1 Infusion reactions and hypersensitivity 30

3.2.2 Pulmonary events 30

3.2.3 Haematological toxicity 30

3.2.4 Other common side effects of trastuzumab 31

4 HEALTH-ECONOMIC EVALUATION 32

4.1 COST-EFFECTIVENESS ANALYSIS 32

4.1.1 Methods 32

4.1.1.1 Perspective of the evaluation 32

4.1.1.2 Analytic technique 32

4.1.1.3 Target population 33

4.1.1.4 Comparator 34

4.1.1.5 Time horizon 35

4.1.1.6 Study design 35

4.1.1.7 Calculation of costs 35

4.1.1.8 Estimation and valuation of outcomes 39

4.1.1.9 Modelling 40

4.1.1.10 Discount rate 43

4.1.1.11 Handling uncertainty and probabilistic sensitivity analysis 43

4.1.2 Results 54

4.1.2.1 HERA 54

4.1.2.2 FinHer 59

4.1.2.3 B31-N9831 63

4.1.2.4 Scenario analysis 68

4.1.2.5 Probabilistic sensitivity analysis 71

4.2 BUDGET IMPACT ANALYSIS 72
4.2.1 Number of patients eligible for trastuzumab in early breast cancer 72
4.2.2 Cost of the different trastuzumab regimens 75

5 APPENDICES 80

5.1 APPENDIX 1: ANALYSIS OF BELGIAN BREAST CANCER DATA 80
5.1.1 Data collection 80
5.1.2 Distribution of T, N and M 83
5.1.3 Distribution of number of patients per stage 83
5.1.4 Age at diagnosis per stage 85
5.1.5 Estrogen and Progesteron receptors per age and stage 87
5.1.6 neu-HER2 overexpression by IHC per age and stage 88
5.1.7 Estimated distribution of tumours expressing neuHER2 by FISH, per age and stage 90
5.1.8 Surgery per age and stage 91
5.1.9 Radiotherapy per age and stage 92
5.1.10 Chemotherapy 93
5.1.11 Combinations of Chemotherapies per age and stage 94
5.1.12 Subgroup analysis based on patients stage I – T1c N0 95
5.1.13 Subgroup Analysis based on Patients with T2 N0 M0/X 96
5.2 APPENDIX 2. CHEMOTHERAPY REGIMENS USED IN HERA TRIAL 99
5.3 APPENDIX 3: WASTE OF TRASTUZUMAB 100
5.4 APPENDIX 4: ELIGIBILITY CRITERIA (LVEF) 102
5.5 APPENDIX 5: COST METASTATIC TREATMENT 103
5.6 APPENDIX 6: LIFE EXPECTANCY HEART FAILURE 105

6 REFERENCES 106

List of Abbreviations

AC	Anthracycline + cyclophosphamide
ADCC	Antibody-dependent cell-mediated cytotoxicity
AE	Adverse event
BCS	Breast conserving surgery
BI	Budget impact
BLA	Biological License Application
CBA	Cost-benefit analysis
CEA	Cost-effectiveness analysis
CHF	Congestive heart failure
CISH	Chromogenic *in situ* hybridisation
CNS	Central nervous system
CPMP	Committee for Proprietary Medicinal Products
CUA	Cost-utility analysis
DFS	Disease free survival
EBC	Early breast cancer
EPAR	European Public Assessment Report
ER	Estrogen-receptor
FEC	5FU epirubicin cyclophosphamide
FDA	Food and Drug Administration
FISH	Fluorescence *in situ* hybridisation
G-CSF	Granulocyte-Colony Stimulating Factor
H	Herceptin (trastuzumab)
HER2	Human epidermal growth factor receptor 2
HR	Hazard ratio
IC	Incremental cost
ICER	Incremental cost-effectiveness ratio
IE	Incremental effectiveness
IgG1	Immunoglobulin subtype G1
IHC	Immunohistochemistry
IV	Intravenous
KCE	Federal Health Care Knowledge Centre
LLN	Lower limit of normal
LVEF	Left ventricular ejection fraction
MBC	Metastatic breast cancer
MUGA	Multi-gated acquisition
NCI-CTC	National cancer institute – common toxicity criteria

NYHA	New York Heart Association
NK Cell	Natural Killer Cell
OBC	Operable breast cancer
OS	Overall survival
PR	Progesterone-receptor
SOP	Standard Operating Procedure
TDR	Time to distant recurrence

1 INTRODUCTION

1.1 RATIONALE FOR ADJUVANT THERAPY IN ONCOLOGY

Adjuvant therapy is a treatment which helps (adjuvare = to help) to cure a patient who has been treated by surgery and/or radiotherapy for a primary tumour. The rationale for adding an adjuvant therapy is the fact that in many tumours (breast, colon,…), cells originating from the primary tumour have already invaded, as early as before the diagnosis of cancer, the blood and/or lymph vessels and have already disseminated in distant viscera (liver, lung, brain, bone,…) or loco-regionally (lymph nodes). These foci of a few cells (10, 50 or 100 for example) can not be detected at this time because the now available investigational tools are not sensitive enough to detect such microscopic metastases (as a comparison, a metastasis with a volume of 1 mm - less than the tip of a match – is made of 1.000.000 cells).

Nevertheless, some prognostic factors allow to assess, in a particular patient, the risk of having micrometastases at the time of work up or surgery for the primary cancer (tumour size, histologic grade, nodal invasion or not, presence or absence of hormone receptors, overexpression or not of HER2, …). With these prognostic factors, the risk of relapse (local or at distance) can be characterized and the patient is said to belong to the low, intermediate or high risk category (e.g the so-called St-Gallen 2005 criteria[1]).

The more or less aggressive adjuvant therapy which will be proposed to the patient (eventually no adjuvant therapy will be proposed) is the one that fits the risk level. The proof of effectiveness of an adjuvant therapy requires a follow-up long enough to reach statistically significant differences in disease-free survival and overall survival. The optimal duration of an adjuvant treatment is unknown until trials comparing various durations have shown the one that has the best benefit/risk ratio.

Trastuzumab (Herceptin, Roche), approved since a few years for the treatment of advanced breast cancer, is now proposed in the treatment of node-positive or high risk node-negative, HER2 positive early breast cancer patients.

1.2 DATA SOURCES ON TRASTUZUMAB

In 2005, studies have been reported evaluating the efficacy and safety of trastuzumab after excision of early-stage breast cancer and completion of (neo)adjuvant chemotherapy (HERA trial)[2], or given concurrently with adjuvant chemotherapy for operable breast cancer (trials B31 and N9831).[3, 4] These and other studies had also been presented at the 2005 ASCO[5, 6] and San Antonio[7, 8] conferences. Together with the available data on trastuzumab use for metastatic breast cancer, these reports and presentations form the basis for the evaluation of efficacy and safety of trastuzumab in the adjuvant setting, the KCE having no direct access to the dossiers filed for obtaining marketing approval. Also public clinical trial registry sites (www.controlled-trials.com, www.clinicaltrials.gov and www.roche-trials.com) were searched.

The data on trastuzumab in the metastatic breast cancer indication are based on the European Public Assessment Report (EPAR)[9] and the Summary of Product Characteristics of trastuzumab. The content of the EPAR is derived from the various reports produced during the centralised evaluation procedure, resulting from the review of the documentation submitted by the applicant (Roche), together with the scientific discussion at the Committee for Proprietary Medicinal Products (CPMP) meetings. The scientific discussion of the EPAR was updated throughout until 30 November 2004. It is made available by the EMEA for information to the public, after deletion of commercially confidential information. Other sources consulted are the FDA review of the Biological License Application (BLA) for trastuzumab,[10] submitted in the US by Genentech and approved September 25, 1998, and the transcript of the 58th Meeting of the Oncologic Drug Advisory Committee, September 2, 1998,[11] which includes the discussion of the trastuzumab BLA. Where other sources were used the reference is given.

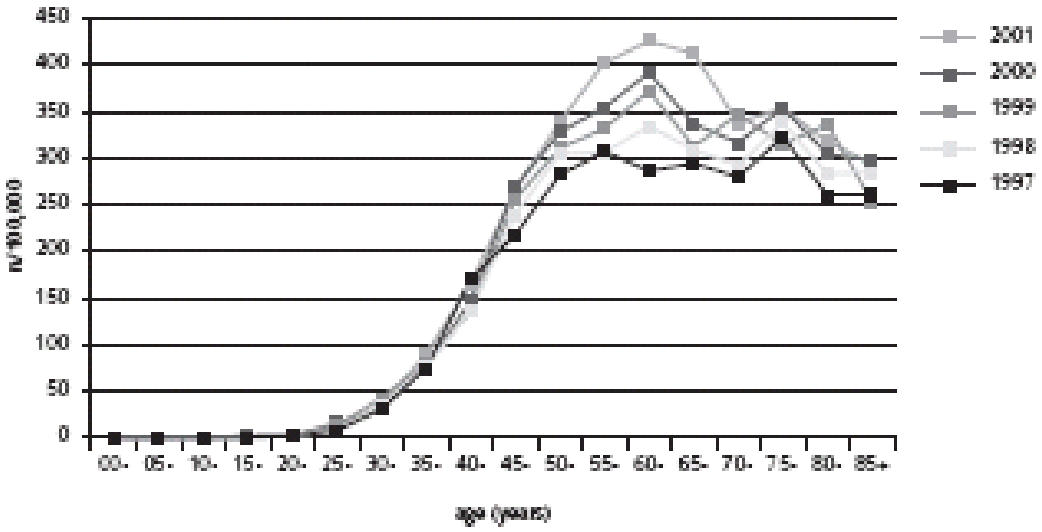
After an accelerated assessment the EMEA Committee for Medicinal Products for Human Use adopted in May 2006 the indication extension of trastuzumab for early breast cancer (www.emea.eu.int).

1.3 DATA SOURCES ON BREAST CANCER

1.3.1 Breast cancer incidence in Belgium

No recent and comprehensive registry of breast cancer incidence is available for Belgium. In July 2005, a new federal structure, the Belgian Cancer Registry Foundation (Stichting Kankerregister), took over the cancer registry role of the Flemish League against Cancer.[12] This initiative should improve the quality of the cancer registration for the whole country. For the period 2000-2001, a total of 10240 cases of breast cancer were registered in Flanders.[12] In the year 2001, 5 337 newly diagnosed invasive breast cancers (of which 3 767 staged) were registered in the Flemish part of Belgium (3 017 612 female inhabitants at January 1st 2001, NIS) by the Flemish Cancer Registry Network (Cancer incidence and survival in Flanders, 2000-2001). This corresponds to a crude incidence rate of 169.6 per 100 000 and an age-standardised incidence rate of 143.5 per 100 000 (figure 1).

Figure 1. Invasive breast cancer: age-specific incidence in women, 1997-2001



The same incidence of invasive breast cancers for every 5-year age class was then applied to the whole female Belgian population at January 1st 2005 (5 334 527, NIS). The calculated figures in table 1 do not incorporate any trend to an increase in the incidence of breast cancer since the year 2001.

Table 1. Invasive breast cancers in Flanders and Belgium

Age-class	Flanders – 2001	Belgium - 2005 (estimated)
<50	1 249	2 213
50-59	1 335	2 557
60-69	1 345	2 128
70-79	958	1 702
80+	450	964
All	5 337	9 564

1.3.2 Epidemiology of breast cancer in Belgium: survey by the KCE

The KCE launched a national survey in February 2006. Thirty-two hospitals agreed to send their data covering the last full year available to the KCE in the requested format. The detailed statistical report can be found in appendix 1.

The TNM (Tumour, Nodal status, Metastasis)) classification system, revised in 2002 by the American Joint Committee on Cancer [13] was used for the staging of breast cancer. A slightly simplified version is given below.

The T classification for primary tumours

- T0: no evidence of primary tumour
- Tis: in situ carcinoma
- T1a: size >0.1cm, <=0.5cm
- T1b: size >0.5cm, <=1.0cm
- T1c: size >1.0cm, <=2.0cm
- T2: size >2cm, <5cm
- T3: size >=5cm
- T4: skin or chest wall extension

Lymph node involvement is often indicated as N+ but can be classified as follows.

- N0: No regional lymph node metastasis
- N1: Metastasis to movable ipsilateral axillary lymph node(s)
- N2: Metastasis to ipsilateral axillary lymph node(s) fixed or matted, or in clinically apparent ipsilateral internal mammary nodes in the absence of clinically evident lymph node metastasis
- N3: Metastasis in ipsilateral infraclavicular lymph node(s) with or without axillary lymph node involvement, or in clinically apparent ipsilateral internal mammary lymph node(s) and in the presence of clinically evident axillary lymph node metastasis; or, metastasis in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement

The M classification indicates whether or not distant metastasis is found.

Stages based on TNM classification are given below.

- Stage 0: Tis, N0, M0
- Stage I: T1, N0, M0
- Stage IIA: T0, N1, M0 or T1, N1, M0 or T2, N0, M0
- Stage IIB: T2, N1, M0 or T3, N0, M0
- Stage IIIA: T0, N2, M0 or T1, N2, M0 or T2, N2, M0 or T3, N1, M0 or T3, N2, M0
- Stage IIIB: T4, N0, M0 or T4, N1, M0 or T4, N2, M0
- Stage IIIC: Any T, N3, M0
- Stage IV: Any T, Any N, M1

Out of 5254 cancers collected, 726 were excluded of the analysis (428 stage 0 and 298 not defined) leaving
4528 staged invasive breast cancers. The distribution of all stages per age group as shown in table 2 was very similar to the distribution observed in 2001 by the Flemish League against Cancer. However, since we used the 6th version of the TNM/AJCC system, there was a higher percentage of stage III.

Table 2. Distribution of invasive breast cancers (KCE survey)

Stage	I	II	III	IV	All
15-49 years old	405	474	192	55	1126
	8.94%	*10.47%*	*4.24%*	*1.21%*	*24.87%*
50-59 years old	527	452	166	64	1209
	11.64%	*9.98%*	*3.67%*	*1.41%*	*26.70%*
60-69 years old	456	353	132	68	1009
	10.07%	*7.80%*	*2.92%*	*1.50%*	*22.28%*
70-79 years old	237	315	138	77	767
	5.23%	*6.96%*	*3.05%*	*1.70%*	*16.94%*
80+ years old	96	198	91	32	417
	2.12%	*4.37%*	*2.01%*	*0.71%.*	*9.21%*
All ages	1721	1792	719	296	4528
	38.01%	*39.58%*	*15.88%*	*6.54%*	*100.00%*

The neu-HER2 status obtained by immunohistochemistry was available for 4151 patients. A positive test (2+ or 3+) was found in 980. For 423 of these, a subsequent fluorescent in situ hybridization (FISH) was performed as shown in table 3. Thirty-four percent of the 2+ by IHC and 81 % of the 3+ showed a gene amplification, to say an estimated 57.35% of the patients found 2+ or 3+ by IHC.

Table 3. Neu-HER2 status determined by immunochemistry and by FISH

IHC	Patients	$FISH^+$ in	$FISH^+$ expected in
0	2561		
1+	610		
2+	496	61/177 (34.46%)	171
3+	484	199/246 (80.89%)	391
All	4151		562

From the number of tumours tested positive for neu-HER2 by IHC (2+ or 3+) we have estimated the expected frequency of FISH+ for the 4 stages as well as for the subgroups T1cN0M0 and T2N0M0 (table 4).

The proportion of FISH positive patients was the highest in the youngest patients and decreased from the age of 60 year. There were relatively twice as much FISH positive patients in stage IV as in stage I except in the group 60 to 69 year old. The lowest proportion of FISH positive tumours was observed in stage I (11%) whatever the tumour size. The estimated proportion of FISH positive tumours was 13.55% for all invasive breast cancers. A same proportion of 13.51% was also found in a large Portuguese population.[14]

Table 4. Proportion of neu-HER2 2+ & 3+ by IHC in invasive breast cancers (KCE survey)

Stage	I	T1c	T2N0	II	III	IV	All
15-49 years old	372	228	171	449	175	46	1042
IHC 2^+ & 3^+	68	49	49	126	54	18	266
FISH+ *estimated*	*10.5%*	*12.3%*	*16.4%*	*16.1%*	*17.7%*	*22.5%*	*14.7%*
50-59 years old	484	268	150	427	150	50	1111
IHC 2^+ & 3^+	85	44	36	116	44	22	267
FISH+ *estimated*	*10.1%*	*9.3%*	*13.8%*	*15.6%*	*16.8%*	*25.3%*	*13.8%*
60-69 years old	417	225	128	333	121	55	926
IHC 2^+ & 3^+	88	43	26	80	40	18	226
FISH+ *estimated*	*12.1%*	*11.1%*	*11.6%*	*13.8%*	*19.0%*	*18.8%*	*14.0%*
70-79 years old	219	128	130	293	124	68	704
IHC 2^+ & 3^+	34	25	28	62	28	19	143
FISH+ *estimated*	*8.9%*	*10.9%*	*12.4%*	*12.1%*	*13.0%*	*16.0%*	*11.7%*
80+ years old	89	53	86	177	78	24	368
IHC 2^+ & 3^+	13	9	18	40	17	8	78
FISH+ *estimated*	*8.4%*	*9.4%*	*12.0%*	*13.0%*	*12.5%*	*19.1%*	*12.2%*
All ages	1581	902	665	1679	648	243	4151
IHC 2^+ & 3^+	288	170	157	424	183	85	980
FISH+ *estimated*	*10.5%*	*10.8%*	*13.5%*	*14.5%*	*16.2%*	*20.1%*	*13.5%*

FISH+ *estimated*: 57.35% of the IHC 2+/3+

1.3.3 Treatment

Surgery and radiotherapy

For women with an invasive breast cancer at stages I, II and III, up to 70 years, surgery and radiotherapy are the major treatments in respectively 99% and 88% of the patients. Surgery and radiotherapy still represent the two major steps for respectively 97% and 80% of the patients who are between 70 and 80 years old (tables 72 & 74 in appendix 1).

Hormone therapy

Hormone therapy in patients with estrogen receptors (79%; table 65) is almost always proposed at any age and stage. However we have no indication with regard to the true duration or the compliance for the long-run treatment with tamoxifen. Some centres have a clear preference for an early use of expensive aromatase inhibitors even when both ER and PR are present.

Chemotherapy

Chemotherapy is the 4th cornerstone of the treatment for patients up to 70 years of age for stage II (71%; table 79) and stage III (86%). In the subgroup of patients tested for neu-HER2 by IHC (4064/4319) the distribution of chemotherapeutic treatments was identical (table 80). However a more aggressive approach was observed in the patients found 2+ or 3+ by IHC whatever their stage (table 5).

Table 5. Frequency of chemotherapy in patients tested for neu-HER2 by IHC

Stage	I		II		III	
Age-class	IHC negative	IHC positive	IHC negative	IHC positive	IHC negative	IHC positive
15-49	29.4%	51.6%	83.8%	90.4%	90.8%	96.3%
50-59	17.6%	28.8%	70.2%	85.2%	86.7%	90.9%
60-69	5.9%	18.8%	43.2%	53.2%	76.5%	85.0%
70-79	1.1%	6.7%	12.8%	15.3%	34.0%	36.0%

IHC negative: 0 or 1+; IHC positive: 2+ or 3+

The principal agent is an anthracycline used in 97% (1744/1793) of the cases in combination with either a taxane or other chemotherapeutic agents. The most frequent combination is a regimen of 5-fluorouracil, epirubicin, and cyclophosphamide (FEC), with eventually several docetaxel cycles given later.

1.3.4 Estimation of the actual distribution of invasive breast cancer in Belgium

The overall yearly incidence of invasive breast cancer in Belgium was directly derived from the age related incidence observed in Flanders in the year 2001 and from the Belgian demographic figures. We assumed that the distribution of tumours by stage of our large survey was representative for the Belgian situation. This distribution was applied to the Belgian age related incidence to give the estimated number of new breast cancers by age and stage for the year 2005. The number of breast cancers was then calculated from the tables 1, 2, and 4. The table 6 shows the expected numbers for the age-classes 15-49, 50-59, 60-69, 70-79 and 80^{+} year old as well as for the 4 stages.

Table 6. Distribution of invasive breast cancers in Belgium in 2005

	N =	I	II	III	IV
Age 15-49 years	2 213	796	932	377	108
FISH+ *estimated*	325	84	150	67	24
FISH+ *estimated* & chemotherapy	256	43	136	64	13
Age 50-59 years	2 557	1 115	956	351	135
FISH+ *estimated*	354	112	149	59	34
FISH+ *estimated* & chemotherapy	241	32	127	54	28
Age 60-69 years	2 128	962	745	278	143
FISH+ *estimated*	299	116	103	53	27
FISH+ *estimated* & chemotherapy	131	22	55	45	9
Age 70-79 years	1 702	526	699	306	171
FISH+ *estimated*	199	47	85	40	27
FISH+ *estimated* & chemotherapy	37	3	13	14	7
Age 80+	964	222	458	210	74
FISH+ *estimated*	118	19	59	26	14
FISH+ *estimated* & chemotherapy	2	0	0	2	0
All breast cancers	9 564	3 621	3 790	1 522	631
FISH+ *estimated*	1 295	378	546	245	126
FISH+ *estimated* & chemotherapy	667	100	331	179	57

FISH+ *estimated*: 57.35% of the observed IHC 2+/3+

1.4 RATIONALE FOR TRASTUZUMAB

The active ingredient of Herceptin is trastuzumab, a humanised IgG1 monoclonal antibody directed against HER2 (human epidermal growth factor receptor 2 protein), which is part of a family of membrane-bound phosphoglycoproteins with tyrosine kinase activity. Overexpression of HER2 makes the affected cell unusually sensitive to mitogenic stimulation by normal (small) amounts of growth factor. Only patients with a strong overexpression (IHC score of 3+) are HER2 positive and thus eligible for trastuzumab treatment. Overexpression of the endogenous receptor protein can occur by genomic amplification or by a mutation in the 'protein-enhancer control region' of the cellular c-*erbB2* proto-oncogene, which can result in increased transcription and subsequently, increased protein formation. In patients the overexpression of the HER2 receptor in breast cancer cells is triggered by amplification of the HER2 gene located on chromosome 17. Therefore, FISH or CISH techniques can also be used for detection of HER2+ breast tumours.

No studies in metastatic breast cancer patients have been included in the EPAR comparing different durations of treatment with trastuzumab. No studies investigating pharmacodynamics were performed in humans. Trastuzumab has been shown, in both *in vitro* assays and in animals (*in vivo* xenograft models), to inhibit the proliferation of human tumour cells that overexpress HER2. In vitro studies with SK-BR-3 cells, a HER2 overexpressing human breast cancer cell line, demonstrated that muMAb 4D5 (the murine parent of trastuzumab) was cytostatic (not cytotoxic). According to the EPAR this is used as an argument for chronic treatment of patients until disease progression. Trastuzumab is also reported as a potent mediator of antibody-dependent cell-mediated cytotoxicity (ADCC) in vitro. Toxicity in HER2 over-expressing tumour cells was increased compared to tumour cells, which express intermediate or low levels of HER2. As a follow-up measure, the company will submit to the CPMP data on HER2 expression as compared to the primary tumour in approximately 100 samples of metastatic sites. In addition to HER2 over-expression, active HER2 signalling, characterized by phosphorylation of intracellular tyroine residues, has been suggested as a condition for cytocidal effects of trastuzumab.[15] In a recent publication, trastuzumab

treatment in neo-adjuvant setting was associated with significantly increased numbers of tumour-associated NK (natural killer) cells compared with chemotherapy alone.[16] An increased NK cell activity has been reported to be associated with a lower incidence of cancer.[17]

1.5 THE PRODUCT

trastuzumab vials marketed in EMEA countries contain 150 mg of trastuzumab. Trastuzumab is produced in recombinant Chinese Hamster Ovary cells using a serum free medium, by continuous perfusion. Cells are expanded using a seed train and fermenters from 80 litres up to 12 000 litres. After harvesting different chromatographic steps are used for purification.

The single dose vial of 150 mg was used for clinical trials outside the US. However in the dossier originally submitted trastuzumab was presented as a multidose formulation of 440 mg trastuzumab to be reconstituted with 20 ml of Bacteriostatic Water for Injection, containing 1.1% benzyl alcohol to yield a multidose formulation at 21 mg/ml trastuzumab. As the use of preservative was contrary to the Ph. Eur. requirements the applicant following a CPMP request changed to 150 mg single dose vials to be reconstituted with sterile water for injections without preservative. Since the manufacturing site and the formulation of the finished product have been changed to Basle and the 150 mg single dose, respectively, a new stability study was necessary to perform. Stability data of three pilot scale batches of 150 mg vials covering 6 months were provided. Supportive data were provided for 36 months from 150 mg vials manufactured at Genentech for clinical trials. As a CPMP follow-up measure, results of an ongoing study to demonstrate stability of full-scale finished product batches produced at Roche, Basle were to be provided. In addition, some methodological issues were identified on the potency assays, which would be clarified by submission of an updated SOP as a follow-up measure.

2 EFFICACY

2.1 CURRENT INDICATION – METASTATIC BREAST CANCER

According to the most recent summary of product characteristics trastuzumab is indicated for the treatment of patients with metastatic breast cancer (MBC) whose tumours overexpress HER2:

a) as monotherapy for the treatment of those patients who have received at least two chemotherapy regimens for their metastatic disease. Prior chemotherapy must have included at least an anthracycline and a taxane unless patients are unsuitable for these treatments. Hormone receptor positive patients must also have failed hormonal therapy, unless patients are unsuitable for these treatments.

b) in combination with paclitaxel for the treatment of those patients who have not received chemotherapy for their metastatic disease and for whom an anthracycline is not suitable.

c) in combination with docetaxel for the treatment of those patients who have not received chemotherapy for their metastatic disease.

Trastuzumab should only be used in patients whose tumours have either HER2 overexpression or HER2 gene amplification as determined by an accurate and validated assay. On the basis of the analysis provided by the applicant, it was concluded that a benefit is only really discernible in the IHC 3+ groups. Accordingly, the indication has been limited to patients whose tumours have HER2 overexpression at a 3+ level.

2.1.1 Dose, administration and treatment duration

Reconstituted trastuzumab solution contains 21 mg/ml of trastuzumab. The required volume of trastuzumab is determined on the basis of a loading dose of 4 mg/kg body weight, or a subsequent weekly dose of 2 mg/kg body weight. The appropriate amount of solution should be withdrawn from the vial and added to an infusion bag containing 250 ml of 0.9% sodium chloride solution. Trastuzumab is administered as a 90-minute intravenous infusion. Patients should be observed for at least six hours after the start of the first infusion and for two hours after the start of the subsequent infusions for symptoms like fever and chills or other infusion-related symptoms. If the initial loading dose was well tolerated, the subsequent doses can be administered as a 30-minute infusion. Trastuzumab should be administered until progression of disease. Some have suggested efficacy for trastuzumab continues beyond the point of disease progression,[18] but there is very little evidence for decision making.[19] Practice pattern surveys suggest that about half of oncologists continue trastuzumab treatment beyond disease progression.[20] We have not studied in depth the local practice with regard to this issue. Local authorities should be aware of this possible practice.

Higher dose

In trial setting, 77 patients received a higher dose (4 mg/kg IV weekly) of trastuzumab either as a single agent or with systemic anti-cancer therapy. Similar types of events occurred during treatment at the higher dose as those seen prior to first disease progression when patients (with few exceptions) were treated with the lower, 2 mg/kg trastuzumab dose.

Anti-trastuzumab antibodies

In the clinical program one patient had a positive, neutralising antibody to trastuzumab. This patient had received nine weekly infusions of trastuzumab and had discontinued the study on day 67 due to progressive disease. This finding was not associated with any clinical symptoms. The induction of antibodies against trastuzumab was also a rare event in monkeys. However, it is recognised that the sensitivity of the detection system of anti-trastuzumab antibodies could be compromised by the presence of trastuzumab in the serum samples of the monkeys.

2.1.2 Detection of HER2 overexpression or HER2 gene amplification

In patients the overexpression of the HER2 receptor in breast cancer cells is triggered by amplification of the HER2 gene located on chromosome 17. Therefore, fluorescence *in situ* hybridisation (FISH) and chromogenic *in situ* hybridisation (CISH) techniques can also be used for detection of HER2+ breast tumours. An excellent overview of HER2 testing techniques is provided in the EPAR,[9] and the summary is given hereafter.

The diagnosis of HER2 expression in the pivotal trials was performed using in-house investigational assays. In parallel to the clinical development, a commercial assay was developed by DAKO, the HercepTest® (DakoCytomation). In the meantime diagnostic developments continued and led to the introduction of HER2 testing methodologies based on the detection of HER2 gene amplification which is the initial genetic event that results in HER2 overexpression. FISH and CISH assays were developed and validated against IHC.

For the individual treatment regimen of a patient with metastatic breast cancer it is essential to determine the HER2 status, because only patients with a strong overexpression (IHC score 3+) that denotes HER2 positivity will benefit from trastuzumab therapy. Therefore reliable and robust methodologies for the determination of the HER2 status are required. All assays described below are for usage on paraffin-embedded tumour tissue samples and assess the HER2 status on a cell-by-cell basis.

Immunohistochemistry (IHC) employs antibodies specifically directed against an epitope of the HER2 protein in the tumour tissue, thereby detecting HER2 on the cell surface. HER2 expression in fixed breast tumour samples is recognized by a typical IHC staining pattern of tumour cells and is interpreted semi-quantitatively by the observer, applying a 0 to 3+ scale, where IHC 3+ indicates the strongest staining intensity. The advantages of IHC are its wide availability, speed, simplicity and relative low cost.

New methodologies like fluorescence *in situ* hybridisation (FISH) and chromogenic *in situ* hybridisation (CISH) detect the genetic event, HER2 gene amplification, which leads to overexpression of HER2 on the cell surface. These DNA-based methodologies directly assess the HER2 gene copy number, and use labelled complementary DNA probes to detect HER2-specific DNA sequences by hybridisation. Interpretation of the testing results is numeric and more quantitative than IHC. DNA is an inherently more stable target compared to protein as it is less susceptible to degradation. With CISH the HER2 gene is detected using a peroxidase enzyme-labelled probe with a chromogenic detection instead of using a fluorescent (FISH) dye to visualize the HER2 gene copies. One advantage is that a standard light microscope can view CISH staining signals and the histopathology of the specimen can be assessed simultaneously.

In the majority of countries IHC is no longer the only methodology for assessing HER2 status of breast cancer patients. This is reflected in national and international HER2 testing guidelines recommending the use of FISH in addition to IHC specimens, eg in the UK.[21] In routine clinical practice CISH gains more and more importance and in Finland has already superseded FISH for HER2 testing. The available concordance data demonstrate that the results of the diagnostic methodologies FISH and CISH are accurate, reliable and robust. There is a strong association between HER2 overexpression and HER2 gene amplification demonstrating that direct determination of the HER2 gene copy number offers a valid alternative for assessing HER2 positivity. Thus FISH or CISH can be used for either primary HER2 testing or for re-testing cases for which the initial test result is difficult to interpret. In Belgium, confirmation of HER2 positivity by FISH in a centre for molecular diagnosis is a condition for reimbursement of trastuzumab in MBC. A recent KCE report describes the organisation, financing and quality assurance of molecular diagnostics in Belgium.[22]

In clinical practice, the quality of HER2 testing will depend on a good validation of the test methodology in the laboratories and an intra- and interlaboratory quality control and quality assurance. To ensure accurate and reproducible results, the testing must be performed in a specialised laboratory, which can ensure validation of the testing procedures. To date, two IHC assays, three FISH assays and one CISH assay are

commercially available. These are CE marked in-vitro diagnostic assays in accordance with Directive 98/79/EC.

IHC assays

HercepTest (DakoCytomation, Glostrup, Denmark) was developed in 1998, in order to have a diagnostic tool to select patients suitable for trastuzumab therapy, as the Clinical Trials Assay (CTA), used in the two pivotal trials for the initial approval of trastuzumab, was too impractical for commercialization and widespread clinical use.

PathWay HER2 assay (for use with the Benchmark® automated System; Ventana Medical Systems Inc., Tucson, USA) was developed in 2000 to aid in assisting the selection of patients for trastuzumab therapy whose tumours overexpress HER2. In Europe, MBC patients are eligible for receiving trastuzumab when their tumours express HER2 at an IHC score of 3+ (on a visualisation scale of 0, 1+, 2+, 3+).

FISH assays for detecting HER2 gene amplification

PathVysion FISH assay (Abbott Laboratories, Abbott Park, USA) uses a 190 Kb DNA probe directly fluorescence labelled with Spectrum Orange. The probe is specific for the HER2 gene locus 17q11.2-q12. In addition to the HER2 specific probe, this assay also includes another DNA probe, which is labelled with Spectrum Green and specific for the centromere region of chromosome 17 (17p11.1-q11.1) known as the CEP17 probe. HER2 scoring is based on the ratio of the average number of HER2 and CEP17 gene copy signals observed per nucleus with a signal ratio of >=2.0 considered to indicate HER2 amplification.

HER2 FISH pharmDx™Kit (DakoCytomation, Glostrup, Denmark) employs a ready-to-use FISH probe mix based on a combination of peptide nucleic acid and DNA technology. The probe mix consists of a mixture of Texas Red labelled DNA probes covering a 218kb region including the HER2 gene on chromosome 17, and a mixture of fluorescein-labelled probes targeted at the centromeric region of chromosome 17 (CEN-17). The specific hybridisation to the two targets results in formation of a distinct red fluorescent signal at each HER2 gene locus and a distinct green fluorescent signal at each chromosome 17 centromere. Using a fluorescence microscope equipped with appropriate filters, tumour cells are located and counting of red (HER2) and green (CEN-17) signals is conducted. HER2/CEN-17 signal ratio >=2.0 indicates HER2 amplification.

INFORM® HER2/neu Probe (for use with the Benchmark® or Benchmark XT automated slide stainers; Ventana Medical Systems Inc., Tucson, USA) includes a biotin-labelled locusspecific HER2 probe. The hybridized HER2 probe is detected by a ligand with a fluorescent label which binds to the biotin label on the DNA probe. The HER2 gene copy number is enumerated without normalizing for chromosome 17 copy number since the INFORM HER2/neu Probe does not include a centromere control probe. A HER2 gene copy number >4 has been established as the optimum cut-point to differentiate amplified versus nonamplified samples.

CISH assays for detecting HER2 gene amplification

Zymed SPOT-Light HER2 CISH Kit (Zymed Laboratories Inc., South San Francisco, USA) includes a double-stranded DNA probe labelled with digoxigenin, which binds specifically to the HER2 gene locus on chromosome 17q12-21. CISH staining results may be assessed with a standard brightfield microscope after visualisation with the conventional peroxidase reactions. Tumour cell nuclei with HER2 gene amplification appear as large peroxidase-positive intranuclear gene copy clusters or as numerous individual peroxidase-positive small signals, where >5 HER2 gene copies per nucleus in >50% of cancer cells indicate amplification.

2.2 NEW INDICATION – EARLY STAGE BREAST CANCER

Four major trials were designed for trastuzumab in early stage breast cancer. Study design, efficacy and safety results reported so far for these and two additional studies in

HER2+ early stage breast cancer are given in Table 7. The HERA trial[2] and the joint analysis of the B31/N9831 trials[3] were both reported in the New England Journal of Medicine, 2005. Both trials show a very significant increase in disease free survival after trastuzumab. The overall survival was not changed significantly in the HERA trial (median follow-up 1 year) but it was in the joint analysis of B31/N9831 (median follow-up 2 years). One should note that in both publications the results were not reported for all study arms. For the HERA trial only the number of events for disease free survival (DFS) in the 2 y trastuzumab arm were reported and these were very similar to the 1 y arm. In trial N9831 the unplanned comparison for DFS between group A (AC→Taxane) and group B (AC→Taxane→H) based on 220 events and a median of 1.5 years of follow-up did not show a significant improvement in DFS for the trastuzumab arm, HR 0.87 (0.67-1.13) versus the observation control arm.[5] Pooled results (fixed effects model, RevMan 4.2) for the two comparisons of sequential trastuzumab after chemotherapy are given in Figure 3 for OS and Figure 4 for DFS. Also for the post-AC trastuzumab combination regimen DFS data from B31/N9831 and BCIRG006 were pooled (Figure 5). The FinHer study, a Finnish study not sponsored for trastuzumab, has been published in the New England Journal of Medicine, 2006.[23] Starting in 2000, the same reverse treatment order used in FinHer (10 weeks of paclitaxel plus trastuzumab before AC, followed or not by one year of trastuzumab) was tested in 2x100 stage II/IIIa patients in the E2198 phase 2 study. Only safety results have so far been made public (http://clinicaltrials.gov/show/NCT00003992).[24] A fifth larger trial, PACS04, is still ongoing and also studies a one year trastuzumab administration post-anthracycline. No efficacy data have yet been published for this trial. (http://www.clinicaltrials.gov/ct/show/NCT00054587?order=1)

Figure 2. Time course of early stage breast cancer treatments from diagnosis to completion in trastuzumab trials

The FinHER study

Cycle	Diag				1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	
Week	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22										
				Mast or Lump	H_4	H_2	H_2	H_2	H_2	H_2	H_2	H_2	H_2	F_{600}			F_{600}			F_{600}			Rx therapy									END
					$D_{100\text{-}80}$			$D_{100\text{-}80}$			$D_{100\text{-}80}$			E_{60}			E_{60}			E_{60}											
														C_{600}			C_{600}			C_{600}											

Herceptin is administered immediately before anthracyclines.

$D_{100\text{-}80}$ = Docetaxel 100-80 mg/m² every 3 weeks
H_4 = Herceptin 4 mg/kg
H_2 = Herceptin 2 mg/kg weekly

Duration of the treatment is 27 weeks (12 day care).

F_{60} 5-fluorouracil 600 mg/m² every 3 weeks
E_{60} = Epirubicin 60 mg/m² every 3 weeks
C_{600} = Cyclophosphamide 600 mg/m² every 3 weeks

The HERA study

Cycle	Diag				1	2	3	4	5	6	7	8	9	10	11	12	1	2	3	4	1	2	
Week	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
				Mast or Lump			Rx therapy						F_{500}			F_{500}			F_{500}			F_{500}			C_{600}	D_{100}		C_{600}	D_{100}	
													E100 or A60			E100 or A60			E100 or A60			E100 or A60			M_{40}	or	or	M_{40}	or	or
													C_{500}			C_{500}			C_{500}			C_{500}			F_{600}		P_{175}	F_{600}		P_{175}

Cycle	3			4			1			2			3			4			5			6			7			8		
Week	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60
	D_{100}	or	C_{600}	D_{100}			H_8			H_6			H_6			H_6			H_6			H_6			H_6			H_6		
	or P_{175}	or	M_{40} or F_{600}	or P_{175}																										

Cycle	9			10			11			12			13			14			15			16			17			18		
Week	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84	85	86	87	88		
	H_6			H_6			H_6			H_6			H_6			H_6			H_6			H_6			H_6			H_6	END	

Mastectomy or breast conservative surgery, radio- and chemotherapy must be completed before starting Herceptin treatment.

Herceptin was administered after anthracyclines.

F_{500} = 5-fluorouracil 500 mg/m² every 3 weeks
C_{500} = Cyclophosphamide 500 mg/m² every 3 weeks
P_{175} = Paclitaxel 175 mg/m² every 3 weeks
M_{40} = Methotrexate 40 mg/m² twice every 4 weeks
H_8 = Herceptin 8 mg/kg

Duration of the treatment is 88 weeks (26 day care).

E_{100} = Epirubicin 100 mg/m² every 3 weeks
D_{100} = Docetaxel 100 mg/m² every 3 weeks
C_{600} = Cyclophosphamide 600 mg/m² twice every 4 weeks
F_{600} = 5-fluorouracil 600 mg/m² twice every 4 weeks
H_6 = Herceptin 6 mg/kg every 3 weeks

The N9831- B31 studies

Cycle	Diag				1			2			3			4			1	2	3	4	5	6	7	8	9	10	11	12	13	14
Week	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
				Mast or Lump	A_{60}			A_{60}			A_{60}			A_{60}			H_4	H_2	H_2	H_2	H_2	H_2	H_2	H_2	H_2	H_2	H_2	H_2	H_2	H_2
					C_{600}			C_{600}			C_{600}			C_{600}			P80	P80	P80	P80	P80	P80	P80	P80	P80	P80	P80	P80		
																													Rx	

Cycle	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44
Week	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60
	H_2	H_2	H_2	H_2	H_2	H_2	H_2	H_2	H_2	H_2	H_2	H_2	H_2	H_2	H_2	H_2	H_2	H_2	H_2	H_2	H_2	H_2	H_2	H_2	H_2	H_2	H_2	H_2	H_2	H_2
	Rx																													

Cycle	45	46	47	48	49	50	51	52		
Week	61	62	63	64	65	66	67	68		
	H_2	H_2	H_2	H_2	H_2	H_2	H_2	H_2	END	

Herceptin is administered immediately after anthracyclines.

A_{60} = Doxorubicin 60 mg/m² every 3 weeks
P_{80} = Paclitaxel 80 mg/m² weekly
Rx = Radiotherapy

Duration of the treatment is 68 weeks (56 day care).

C_{600} = Cyclophosphamide 600 mg/m² every 3 weeks
H_4 = Herceptin 4 mg/kg
H_2 = Herceptin 2 mg/kg weekly

In the HERA trial and in trials B31/N9831 the incidence of isolated brain metastates as first event was higher in the studied trastuzumab group than in the control group (21 vs. 15 in HERA trial, 21 vs. 11 in trial B31 and 12 vs. 4 in trial N9831). This difference could be attributed to earlier failures at other distant sites among patients in the control group. Also in patients with metastatic breast cancer a low efficacy of trastuzumab to block development of CNS metastases has been reported.[25] A possible explanation of these findings could be the low penetration through the blood-brain barrier of trastuzumab, the HER2 expression in brain metastases being highly concordant with the primary tumour.[26]

2.2.1 Dose, administration and duration of treatment

The administration of trastuzumab every three weeks instead of every week was considered when the half-life turned out to be 28 days instead of 8.3 days as initially calculated. The trough concentration using the new schedule was 22% lower but still higher than the theoretical minimum efficacy threshold of 10-20 microg/ml.[27]

The optimal duration of trastuzumab in adjuvant setting is unknown. The data reported cover one year of treatment. Results for the two-year trastuzumab treatment arm in the HERA trial have not yet been reported. A surprisingly high efficacy and safety, after a median follow-up of three years, was reported after only 9 weeks of trastuzumab in the Finher trial.[7, 23] In this study HER2 CISH+ patients were randomized to trastuzumab or no trastuzumab for 9 weeks (together with docetaxel or vinorelbine), followed by epirubicin-based chemotherapy (FEC). Such reversed-order regimen had also been explored in the E2198 phase 2 study, where it was compared with the same regimen plus an additional year of trastuzumab.

Inversing the treatment order and shortening the trastuzumab administration to only 9 weeks as in FinHer is a most promising approach from an efficacy and safety point of view, urgently needing confirmation. In the short term further support for such inversed order and short trastuzumab regimen could come from trial E2198. Also DFS efficacy could e.g. be analysed in those patients who received a shorter regimen of trastuzumab because of cardiac monitoring (31% of trastuzumab treated patients in the B31 trial).

2.2.2 Neo-adjuvant use of trastuzumab

Pre-operative systemic chemotherapy in locally advanced breast cancer aims to reduce the tumour size and may allow for breast-conserving therapy. A number of pilot studies have been reported on the concurrent use of trastuzumab with such chemotherapy.[28, 29] The small sample size of the studies limits the assessment of the reported efficacy and safety results. The reported improvement in pathologic complete response rate is highly significant.[28, 30] More trials evaluating the neo-adjuvant use of trastuzumab in HER2+ breast cancer were identified March 21, 2006 in public trial registries such as www.controlled-trials.com, , www.clinicaltrials.gov and www.roche-trials.com and are listed in Table 8.

Table 7. Major trials reported for trastuzumab (Herceptin) in early-stage breast cancer.

Study Inclusion Reference	Design and patients	Trastuzumab regimen and combination Early discontinuation of trastuzumab	Age median, >=60y, nodal status, AC treated, follow-up		P value, HR	Control arm	H arm	H arm
HERA (39 countries, non-US, mainly Europe) Dec 2001 – Mar 2005 Piccart-Gebhart, 2005[2]	Randomization (5090 patients, 3 arms) of early-stage HER2+ breast cancer (N+ or N0 with >=T1c) after surgery with or without radiotherapy and at least 4 courses of neoadjuvant or adjuvant chemotherapy. 2y H group not reported. LVEF >= 55% (echo or MUGA) at randomization	Sequential, after chemo: H 8 mg/kg + 6 mg/kg every three weeks for 1 or 2 years. Tamoxifen or aromatase inhibitor if receptor+. Trastuzumab stopped early in 8.5% (non relapse).	Age 49 y >= 60y: 16% N0: 32% Anthracycli: 94% FU: 1 y	Arm Pts rand with FU DFS events HR (1y H) TDR events HR (1y H) Mortality HR (1y H) CNS meta LVEF decr CHF any CHF3/4	 P<0.0001 0.54 (0.43-0.67) P<0.0001 0.49 (0.38-0.63) P=0.26 0.76 (0.47-1.23) (to < 50%) P<0.001 P=0.002	Observe 1693 nearly all 220 77.4% (2y) 171 82.8% (2y) 37 95.1% (2y) 15 (0.9%) 34 (2.2%) 1 (0.06%) 0 (0%)	1 y H 1694 nearly all 127 85.8% (2y) 89 90.6% (2y) 29 96.0% (2y) 21 (1.2%) 113 (7.1%) 29 (1.7%) 9 (0.5%)	2 y H 1694 nearly all 128

Joint analysis (B31+N9831) Romond, 2005[3]	Surgically removed HER2+ breast cancer N+ or N0 high-risk. Analysis of groups 1+A versus groups 2+C (n=3387). Group B (N9831) not reported. H started if post-AC LVEF >50% and no decrease >15% after AC, 6.7% excluded for this reason.	AC q3w x 4 → 4 mg/kg H + 2 mg/kg H every week for 51 weeks, with 12 weeks of paclitaxel (P). Tamoxifen or aromatase inhibitor if receptor+. H stopped early in 31.4% (relapse 1.9%, cardiac 19%).	Age: 49 y >= 60y: 16% N0: 6% AC: 100% FU: 2.0 y	Arm Pts rand with FU DFS events HR TDR events HR Mortality HR CNS meta LVEF decr. CHF3/4	 P<0.0001 0.48 (0.39-0.59) P<0.0001 0.47 (0.37-0.61) 2P=0.015 0.67 (0.48-0.93)	1 + A 1843 1679 261 75.4% (3y) 193 81.5% (3y) 92 91.7% (3y) 15 5 (0.4%?)	2 + C 1833 1672 134 87.1% (3y) 96 90.4% (3y) 62 94.3% (3y) 33 30.5%? 51 (3.5%?)	
B31 (US) FEB 2000 – FEB 2005 Romond, 2005[6], Tan-Chiu, 2005[4]	Randomization (1960?, 2 arms) of surgically removed HER2+ breast cancer (N+) LVEF > 50% (MUGA only).	AC q3w x 4 →4 mg/kg H + 2 mg/kg H every week for 51 weeks, with 12 weeks of paclitaxel (P). Hold H if >15% decrease or >10% decrease and <50%. Tamoxifen or aromatase inhibitor if receptor+. H hold in 31%. H stopped early (non-relapse) in 28% (19% cardiac).	Age: 49 y >= 60y: 15% N0: 0% AC: 100% FU: 2.4 y	Arm Pts rand with FU DFS events HR LVEF decr CHF3/4 or cardiac death	 P<0.0001 0.45 (3y cumul., to < 55%) (3y cumul.)	AC→P (group 1) 1024 872 171 17% 0.8%	AC→PH (group 2) 1019 864 83 34% 4.1%	

N9831 (US) MAY 2000 – NOV 2004 Perez, 2005[5]	Randomization (3046 patients, 3 arms) of surgically removed HER2+ breast cancer (N+ or N0 and >2cm, or N0 and >1cm and ER- and PR-. LVEF > 50% (MUGA or echo)	AC q3w x 4 → H (4mg/kg start, then 2mg/kg) qw x 52 after (group B) or combined with (group C) paclitaxel (P) for 12 weeks. Radiotherapy continued. Tamoxifen or aromatase inhibitor if receptor+.	Age: 49 y >= 60y: 17% N0: 12% AC: 100% Follow-up: 1.5 y	Arm Pts rand with FU DFS events HR C vs A DFS events HR B vs A DFS events HR C vs B Mortality HR B vs A HR C vs B CHF3/4	 2p=0.0005 0.55 2p=0.29 0.87 (0.67-1.13) 2p=0.011 0.64 (0.46-0.91) 0.85 (0.55-1.33) 0.74 (0.43- 1.26)	AC→P (group A) 979/971? 807 90 117 0%	AC→P+H→H (group C) 840/814? 808 51 53 20 (2.9%)	AC→P→H (group B) 985/981? ? 103 84 15 (2.2%)
BCIRG006 (global) Slamon, ASCO, 2005[8]	Randomization (3222 patients, 3 arms) of surgically removed HER2+ early breast cancer N+ or high risk N0. Normal LVEF at start.	AC→D: AC q3w x 4 → docetaxel (D) q3w x 4 AC→DH: H (4mg/kg start, then 2mg/kg for 1 year) started with D DCarboH: D+carboplatin q3w x 6, started with H (1 year). LVEF decrease if >15% decrease to below LLN.	2 y (23 months)	Arm Pts rand with FU DFS events HR AC→DH HR DCarboH TDR Mortality LVEF decr. Card. AEs CHF3/4	 0.49 (0.37-0.65) 0.61 (0.47-0.79)	AC→D 1043/1050? 77.0% (3y) 77.0% (3y) NA NA 0.7% 12 (1.2%) 1	AC→DH 1072/1068 86.0% (3y) NA NA 2.7% 25 (2.3%) 18	DCarboH 1056/1056 80.0% (3y) NA NA 0.4% 13 (1.2%) 1

FinHer Joensuu, 2005[7, 23]	Randomization (1010 patients) of EBC pN+ or pN0 (tumour >2cm, PR-) to dectaxel or vinorelbine.	Nine weeks of vinorelbine (plus H or no H if HER2+) or docetaxel (plus H or no H if HER2+), both arms followed by 5FU, epirubicin and cyclophosphamide (FEC), HER2+ patients (23%) H (4mg/kg start, then 2mg/kg) qw x 9 weeks. Tamoxifen for ER+ or PR+ disease.	3 y	Arm Pts rand DFS events HR TDR events HR Mortality HR LVEF decr. CHF3/4	 P=0.008 0.42 (0.21-0.83) P=0.002 0.29 (0.13-0.64) p=0.07 0.41 (0.16-1.08)	No H 58+58 27 77.6% (3y) 26 76.0 (3y) 14 89.7% (3y) 7 (6%) 1 (1%)	Herceptin 57+58 12 89.3% (3y) 8 92.0% (3y) 6 96.3% (3y) 4 (3%) 0 (1%)	
E2198 Sledge, 2001[24]	Randomization (200 planned) of EBC N+ stage II/IIa to receive H for 1 addional year or not (all patients received H pre-AC)	Four cycles of paclitaxel plus H (4mg/kg start, then 2mg/kg) qw x 10 weeks followed by four cycles of doxorubicin/ cyclophosphamide and then randomized to either stop therapy or receive H for 1 addional year	1.3 y (15 months)	DFS TDR Mortality LVEF decr. CHF any		No control arm	NA NA NA 9.3% after 10 weeks of H 13.2% post-AC 0.4% after 10 weeks of H 1.7% post-AC	

NA=Not available; H=Herceptin=trastuzumab; P=paclitaxel; D=docetaxel

Table 8. Trastuzumab in neoadjuvant setting, clinical trials identified in public trial registries.

Clinicaltrials.gov identifier (or other)	Study Title	Patients	Started (or registration date)
NCT00136539	Neoadjuvant Therapy With Herceptin and Taxol for Stage II/III Breast Cancer	41	March 1999
NCT00006110	Phase II Study of Neoadjuvant Doxorubicin, Cyclophosphamide, and Paclitaxel With or Without Trastuzumab (Herceptin) Followed By Local Surgery With or Without Adjuvant Trastuzumab OR Adjuvant Doxorubicin, Cyclophosphamide, Paclitaxel, and Trastuzumab in Women With Stage IIB, IIIA, IIIB, IIIC, or IV Breast Cancer	125	August 2000
NCT00038402	Evaluation of the Addition of Herceptin to Standard Chemotherapy in the Neoadjuvant Setting for Operable Breast Cancer (published 2005)[28]	42	April 2001
NCT00133796	A Phase II Study of the Effects of Herceptin in Patients With Locally Advanced HER-2/NEU Overexpressing Breast Cancer	40	October 2001
MO16432 (Roche)	A randomized, open-label study of the effect of paclitaxel, doxorubicin, and CMF neoadjuvant chemotherapy, with and without Herceptin, on tumour response in women with HER2-positive breast cancer	100-500	May 2002
NCT00068341	Phase II Randomized Study of Neoadjuvant Docetaxel and Carboplatin With Versus Without Trastuzumab (Herceptin®) in Women With Locally Advanced Breast Cancer	75	September 2003
NCT00148668	A Randomized Phase II Study of Preoperative Herceptin/Navelbine Versus Taxotere/Carboplatin/Herceptin in Early Stage, HER-2 Positive Breast Cancer	80	December 2003
NCT00129896	Open-Label Phase I-II Clinical Trial to Evaluate Treatment With Myocet/Taxotere/Herceptin as Primary Chemotherapy Treatment for HER2neu Positive Breast Cancer Patients	59	January 2004
NCT00256243	A Pilot Study of Neoadjuvant Biweekly Doxorubicin and Cyclophosphamide (AC) With GMCSF Followed by Weekly Carboplatin/Paclitaxel With Plus and Minus Traztuzumab (TC ± H) in the Treatment of Breast Cancer	43	April 2004
NCT00118053	Phase II Study of Trastuzumab (Herceptin®), Docetaxel, and Carboplatin in Women With Previously Untreated HER2/Neu-Positive Stage IIB, IIIA, IIIB, or IIIC or Inflammatory Breast Cancer	13-43	July 2005
NCT00232479	Phase II Study of Dose Dense Carboplatin and Taxotere With Herceptin As Primary Systemic Therapy in Breast Cancer	Not given	September 2005
NCT00270894	Pilot Trial of Sequential Dose-Dense Neoadjuvant Chemotherapy Plus Herceptin in HER2 Positive Stage II-III	30	November 2005

Clinicaltrials.gov identifier (or other)	Study Title	Patients	Started (or registration date)
	Breast Cancer Patients		
NCT00288002	Phase III Randomized Study of Neoadjuvant Epirubicin Hydrochloride, Cyclophosphamide, and Docetaxel With Versus Without Capecitabine and/or Trastuzumab (Herceptin®) Followed by Surgery in Women With Stage I-III Primary Breast Cancer	1,042	February 2006
NCT00295893	Phase II Randomized Study of Neoadjuvant Docetaxel, Doxorubicin Hydrochloride, and Cyclophosphamide Versus Doxorubicin and Cyclophosphamide Followed By Paclitaxel and Carboplatin With or Without Trastuzumab (Herceptin®) in Patients With Stage II or III Breast Cancer	105	February 2006

Figure 3. Pooled Analysis of Overall Survival for 1 year of Trastuzumab Sequential Regimen (Fixed Effects)

Review Herceptir
Comparisor 01 Herceptin 1 Y (sequential after chemotherapy) vs chemotherapy alone (observation)
Outcome: 01 Survival

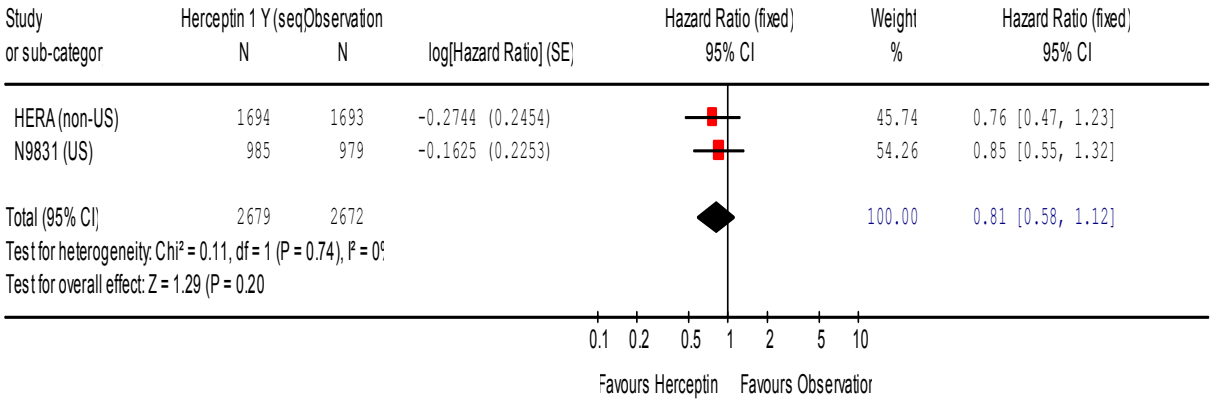


Figure 4. Pooled Analysis of Disease Free Survival for 1 year of Trastuzumab Sequential Regimen (Fixed Effects)

Review Herceptir
Comparisor 01 Herceptin 1 Y (sequential after chemotherapy) vs chemotherapy alone (observation)
Outcome 02 Disease Free Survival

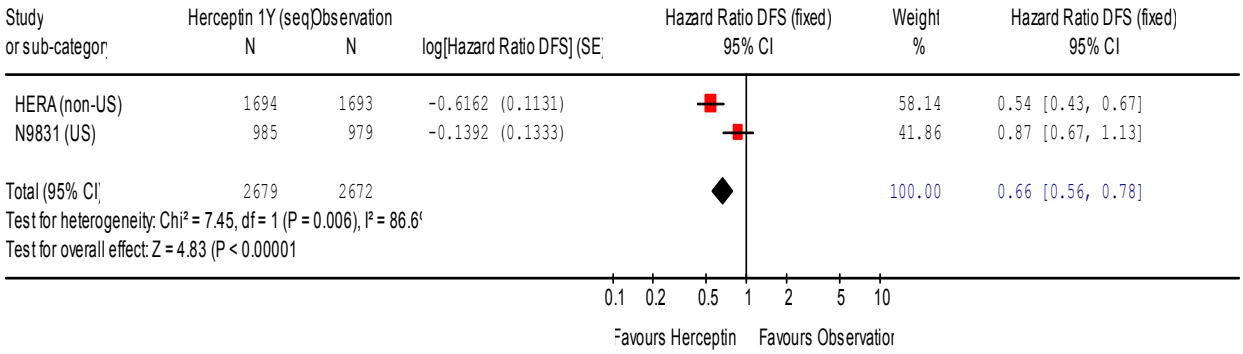
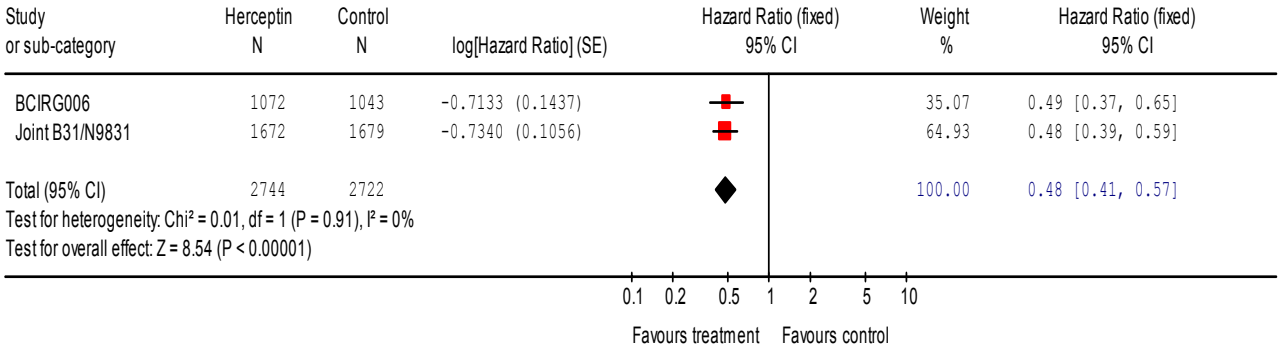


Figure 5. Pooled Analysis of Disease Free Survival for 1 year of Trastuzumab Combination Regimen (Fixed Effects)

Review: Herceptin
Comparison: 02 Herceptin Concomitant vs control
Outcome: 01 DFS



3 SAFETY PROFILE

3.1 CARDIAC SAFETY

3.1.1 Metastatic breast cancer indication

Cardiotoxicity is the main safety concern in patients treated with trastuzumab. Non-clinical data have not yet pointed to the mechanism. Tissue cross reactivity studies with trastuzumab in monkey and human tissue did not reveal localisation to heart tissue. Single-dose studies in rhesus monkeys with the trastuzumab-doxorubicin combination (both at 1.5 mg/kg) had previously shown no evidence for cardiac effects. Enhanced cardiotoxicity was also not observed in a rat model of doxorubicin cardiotoxicity following addition of a surrogate antibody specific for rat c-erbB2. Potential models of anthracycline-induced cardiotoxicity in mice and dogs using trastuzamab were unsuitable due to species specificity of trastuzumab and in consideration of potential immunogenic responses to a humanised protein. Possible anthracycline models in the monkey were considered unsuitable based on ill-defined dose requirements to produce cardiotoxicity.

HER2 is essential for normal embryonic cardiac development, and in mice signalling through HER2 in cardiomyocytes was found essential for prevention of dilated cardiomyopathy.[31] Despite the undetectable or low level expression of HER2 on IHC (not assessed with the trastuzumab antibody),[32] cardiomyocytes seem to be susceptible to trastuzumab. Reliable signal with IHC staining requires >100000 sites per cell, and more in the larger cardiomyocyte. Interestingly, low levels of HER2 mRNA have been reported in two cardiac biopsies from trastuzumab-treated patients who had negative IHC results.[32] Localization of HER2 may be in the transverse tubules of ventricular myocytes, also a target of anthracyclines.[33]. Right ventricular endomyocardial biopsy in nine patients showing a LVEF decrease after trastuzumab did not show any evidence of the typical for anthracycline-related ultrastructural changes on cardiac biopsy material.[34] A most relevant observation was made with radiolabeled trastuzumab tracer in 20 patients with MBC. The 7 patients with scintigraphic evidence of trastuzumab uptake developed cardiotoxicity after trastuzumab versus none of the other patients.[35] Preliminary data suggest cardiotoxicity (5 out of 57 patients) after trastuzumab is only seen in patients with a genetic variant of HER2 (655 val allele, present in 25 out of HER2+ 57 patients).[36] When such pilot studies are confirmed, the identification of patients at increased risk for cardiotoxicity could thus be refined.

Further mechanistic studies on the mode of action and impact of trastuzumab on the enhanced cardiotoxicity are being performed for which the results will be submitted to the CPMP on an ongoing basis.

The decrease in LVEF occurs already during the very first weeks of trastuzumab treatment.[37] However, the FinHer study results suggest that trastuzumab given for only 9 weeks does not result in a LVEF decrease.[23] The risk of cardiotoxicity is greatest when trastuzumab is used concurrently with anthracyclines (doxorubicin or epirubicin). Compared with doxorubicin an 80% higher dose of epirubicin can be given for the same probability of CHF.[38]. This may explain the low frequency of cardiac events in the FinHer study, where trastuzumab was given after a relatively low dose epirubicin regimen (3 FEC cycles, each including 60 mg epirubicin per square meter). Trastuzumab and anthracyclines should not be used currently in combination except in a well-controlled clinical trial setting with cardiac monitoring. Because the half-life of trastuzumab is approximately 28.5 days (95 % confidence interval, 25.5 – 32.8 days), trastuzumab may persist in the circulation for up to 24 weeks after stopping trastuzumab treatment.

The original dossier contained a retrospective analysis of cardiac adverse events, which was made by a cardiac review and evaluation committee. Afterwards, a full reassessment of cardiac-related events was performed using broader search criteria. New events were found, and others were classified differently. In the pivotal trial H0648g symptomatic heart failure after paclitaxel plus trastuzumab was seen in 7.7% (7 out of 91 patients) compared with 4.2% (4 out of 95 patients) after paclitaxel alone. In

the same study H0648g, after anthracycline+cyclophosphamide (AC) plus trastuzumab symptomatic heart failure occurred in 24.5% (35 out of 143 patients) versus in 7.4% (10 out of 135 patients) after AC alone. In study H0649g (trastuzumab alone) symptomatic heart failure was seen in 6.6% (14 out of 213 patients).

In the entire program of trastuzumab for metastatic breast cancer, 84 patients (30 patients in pivotal studies, 54 patients in H0650g) were anthracycline naïve. Three (4 %) of these patients, (one in H0649g and two in trial H0650g), had events of heart failure. All three patients were elderly (aged 71, 76 and 79 years) and two had a documented history of coronary artery disease.

3.1.2 Early stage breast cancer indication

In contrast to the clinical development program of trastuzumab in MBC, cardiac function was monitored prospectively in the trastuzumab studies in early breast cancer (EBC). Left-ventricular ejection faction (LVEF) was assessed using echocardiography or multi-gated acquisition (MUGA) scan. MUGA LVEF measurements are more reliable and reproducible than echo in the unselected population, but are still subject to 5–10% variation, are more time-consuming and costly, and involve radiation. Echo is usually adequate to guide clinical decisions.[39] Different methods of LVEF measurement provide different results.[40] Method standardisation is thus required. A LVEF is considered normal if >=55%, when measured using the recommended echocardiographic 2D method (modified Simpson's rule), based on the summation of 20 elliptical disks.[41] The prevalence of left-ventricular dysfunction, mainly based on the recommended echocardiographic method, was reported for women aged 45 years and older in a population based study in the UK.[42] A definitely impaired (< 40%) and borderline (40-50%) LVEF was seen in 0% and 1.3% of women 45-54 years old, and in 0.5% and 3.0% of women 55-64 years old. Patients could be included in the HERA trial if the LVEF was >= 55% at randomisation (after chemotherapy). In the B31 trial a >= 50% LVEF (MUGA) was required both at baseline and after AC, before starting trastuzumab. Also some other cardiovascular problems, including myocardial infarction, uncontrolled hypertension and clinically significant arrhythmia, were exclusion criteria in trastuzumab adjuvant trials. The proportion of patients to be excluded for cardiovascular problems can be expected to be significant in elderly breast cancer patients. Between studies different definitions were used for significant LVEF decrease. Frequencies of a significant LVEF decrease and severe CHF by trial are given in Tables 9 and 10.

Table 9. Additional cases of significant decrease of LVEF after trastuzumab versus control by treatment strategy and study

	LVEF at start	Significant LVEF decrease	1y sequential post-AC	1y combined post-AC	9-10 weeks combined pre-AC
HERA	≥55% post-AC	≥10% to <50%	+ 4.9% (n=79)	Not studied	
B31 (MUGA)	≥50% post-AC	≥10% to <55%	Not studied	+ 17% (3y cumul)	
N9831	≥50% post-AC		?	?	
BCIRG006	≥50% post-surgery	>15% to <50%		+ 2.0% (n=21, AC) - 0.3% (n=3, no AC)	
Overall			?	?	
FinHer	≥50% post-surgery	≥10% to <50%			- 3% (n=3)
E2198		≥10% to <50%			9.3% after H 13.2% post-AC

Table 10. Additional cases of severe congestive heart failure (NYHA class 3 or 4) after trastuzumab versus control by treatment strategy and study

	1 year sequential	1 year combined	9-10 weeks combined
HERA	+0.5% (n=9) LVEF>=55% epi > doxorubicin	NA	
B31	NA	+3.3% (n=27) 2.6% if LVEF>=55% 12.8% if LVEF 50-54% 20% if LVEF 50-54% and age >50y	
N9831	+2.2% (n=15)	+2.9% (n=20)	
BCIRG006		+1.6% (n=17), AC 0% (n=0), no AC	
FinHer			- 1% (n=1), FEC later
E2198			+ 0.4% (n=1), + 1.7% (n=4) after AC

In trials B31 and N9831 a significant increase in cardiotoxicity was seen in the trastuzumab-containing arm compared with chemotherapy alone. This finding caused Genentech to warn healthcare providers on this issue.[43] Cardiac monitoring in trial B31 was performed after AC and at month 6, 9 and 18 using MUGA scans.[4] In trial N9831 echo could also be used. A significant decrease in LVEF defined as a decrease in LVEF of at least 10 percentage points to <55% was observed in 34% of the patients after trastuzumab and in 17% of the controls in trial B31.[4] In both trials trastuzumab was

withheld (repeat assessment after 4 weeks) if an absolute decrease from baseline in LVEF of >=16% was found or a decrease >=10% together with a LVEF <LLN. 30.5% of the patients required at least one dose delay because of a decrease in LVEF (24% in B31) or cardiac symptoms (8% in B31). Trastuzumab was discontinued if two consecutive holds or a total of three holds occurred. 14.2% of the patients discontinued trastuzumab before 52 weeks because of a confirmed asymptomatic decline in LVEF, and another 4.7% because of symptoms of congestive heart failure or other adverse cardiac effect. In trials B31 and N9831 the cumulative incidence of NYHA class 3 or 4 congestive heart failure or death from cardiac causes at three years was 0.8% and 0% in the control group and 4.1% and 2.9% in the trastuzumab group. In trial B31 both the post-AC LVEF as well as age were found to be independent predictors of trastuzumab-associated CHF.[6, 4] In this trial CHF developed in 2%, 5.4% and 5.3% of patients <50 years, 50-59 years and 60+ years old, respectively. Overall 96 out of 841 patients (11.4%) who started trastuzumab had a LVEF 50-54%, 12 (12.5%) of these patients developed severe CHF. Of the 48 patients with age >=50 years in this group 9 (20%) experienced severe CHF.[4] Note that patients with a LVEF 50-54% were excluded from the HERA trial where a post-chemotherapy LVEF of >=55% was required. Also important to note is that in trials B31 and N9831 after doxorubicin and cyclophosphamide 233 out of 3497 patients (6.7%) did not start trastuzumab because they had a decline in LVEF of at least 16% from baseline or a decline below the lower limit of normal or had cardiac symptoms. In B31, after AC a median decrease of 2% was seen in both arms from an overall median LVEF of 63%. The median decline from baseline after 6 months (5%) and 9 months (6%) of trastuzumab was significantly larger compared with the control arm median decrease at 6 months (3%) and 9 months (2%).[4] At month 18 (6 months after the end of trastuzumab treatment) the median decline was 4% in the trastuzumab arm and 3% in the control arm. In the trial setting (B31), the CHF associated with trastuzumab seemed to be responsive to cessation of trastuzumab treatment and management, with most patients recovering to nearly normal LVEF values, under medical treatment.[4] The reintroduction of trastuzumab under CHF medical treatment may be appropriate for some individuals.[34].

For the HERA trial, it was not reported how many patients were excluded from trial participation for cardiac problems or a LVEF <55% post-chemotherapy. Cardiac monitoring was performed at three months intervals the first year after randomization and every 6 months afterwards. 113 patients (7.1%) on trastuzumab (and 2.2% of the controls) showed a decrease in LVEF, defined as a decrease in the ejection fraction of 10% or more from baseline to a LVEF <50% at any time (which is a lower LVEF cut-off as compared with 55% in B31/N9831). Trastuzumab was stopped before completion of the planned one-year treatment in 143 patients (8.5%) for reasons other than relapse. Adverse events accounted for 5.5%. Patients who developed symptomatic CHF on trastuzumab (1.7%) had a median age of 51 year, which is not significantly older than the study population. 0.5% of the patients developed severe CHF (NYHA class 3 or 4) heart failure in combination with a significant LVEF decrease.

The only study allowing a direct comparison of a sequential regimen of trastuzumab with post-AC combination treatment is N9831, where a somewhat lower frequency of serious CHF is seen in the sequential treatment arm, but associated with a lower efficacy. In BCIRG006 relatively few patients showed a drop in LVEF but yet another definition for a significant LVEF decrease was used in this study: a decrease of at least 15% (instead of 10%) to below the LLN.

The finding of a longer elimination half-life for trastuzumab caused EMEA to warn health care providers on the use of anthracyclines after stopping trastuzumab (http://www.emea.eu.int/pdfs/human/press/pus/169601en.pdf). However, in the FinHer study the anthracycline (epirubicin) was started after 9 weeks of trastuzumab treatment and this resulted in little or no cardiotoxicity. In fact, as the susceptibility of the heart for trastuzumab is most probably linked to the pre-treatment with anthracyclines, reversing the treatment order could make a lot of sense. With respect to cardiotoxicity no conclusions however can be drawn on the relative importance of the trastuzumab-anthracycline treatment order, on the duration of trastuzumab administration, nor on the type of anthracycline and its dose. Multiple variables differ between the pre- and post-anthracycline regimens studied. The low cardiotoxicity observed in FinHer could

e.g. also be explained by the relatively low cumulative dose of of 180 mg/m2 epirubicin while the maximum tolerated cumulative dose of epirubicin is of 720mg/m2. In the B31/N9831 studies doxorubicin was administered at a cumulative dose of 240 mg/m2 while its maximum tolerated cumulative dose is only 500 mg/m2. Epirubicin is generally presented as a less cardiotoxic agent.

Indeed as stated in the FinHer paper[23], the small size and the short duration of the follow-up are limitations of the study and the optimal duration of adjuvant trastuzumab therapy is not known and may be clarified only in further randomized trials.

3.2 OTHER SIDE EFFECTS

3.2.1 Infusion reactions and hypersensitivity

Serious adverse reactions to trastuzumab infusion that have been reported infrequently include dyspnoea, hypotension, wheezing, hypertension, bronchospasm, supraventricular tachyarrythmia, reduced oxygen saturation, anaphylaxis, respiratory distress, urticaria and angioedema. The majority of these events occur during or within 2.5 hours of the start of the first infusion. Should an infusion reaction occur the trastuzumab infusion should be discontinued and the patient monitored until resolution of any observed symptoms. The majority of patients experienced resolution of symptoms and subsequently received further infusions of trastuzumab. In rare cases, these reactions are associated with a clinical course culminating in a fatal outcome. Patients who are experiencing dyspnoea at rest due to complications of advanced malignancy and comorbidities may be at increased risk of a fatal infusion reaction. Therefore, these patients should not be treated with trastuzumab. On very rare occasions, patients have experienced the onset of infusion symptoms or pulmonary symptoms more than six hours after the start of the trastuzumab infusion. Patients should be warned of the possibility of such a late onset and should be instructed to contact their physician if these symptoms occur.

3.2.2 Pulmonary events

Severe pulmonary events have been reported rarely with the use of trastuzumab in the post-marketing setting. These rare events have occasionally been fatal. In addition, rare cases of pulmonary infiltrates, acute respiratory distress syndrome, pneumonia, pneumonitis, pleural effusion, respiratory distress, acute pulmonary oedema and respiratory insufficiency have been reported. These events may occur as part of an infusion-related reaction or with a delayed onset. Patients who are experiencing dyspnoea at rest due to complications of advanced malignancy and comorbidities may be at increased risk of pulmonary events. Therefore, these patients should not be treated with trastuzumab.

Note: In the adjuvant setting (trials B31/N9831) 9 patients on trastuzumab (0.6%) developed interstitial pneumonitis or pulmonary infiltrates. Two patients died.

3.2.3 Haematological toxicity

Haematological toxicity was infrequent following the administration of trastuzumab as a single agent. There was an increase in WHO Grade 3 or 4 haematological toxicity in patients treated with the combination of trastuzumab and paclitaxel compared with patients receiving paclitaxel alone (34% versus 21%). Haematological toxicity was also increased in patients receiving trastuzumab and docetaxel, compared with docetaxel alone (32% grade 3/4 neutropenia versus 22%, using NCI-CTC criteria). Note that this is likely to be an underestimate since docetaxel alone at a dose of 100 mg/m^2 is known to result in neutropenia in 97% of patients, 76% grade 4, based on nadir blood counts. The incidence of febrile neutropenia/neutropenic sepsis was also increased in patients treated with trastuzumab plus docetaxel (23% versus 17% for patients treated with docetaxel alone). The pathophysiologic basis for exacerbation of neutropenia has not been determined; the effect of trastuzumab on the pharmacokinetics of chemotherapeutic agents has not been fully evaluated. No haematological toxicity was reported in the trials of trastuzumab in early-stage breast cancer.

3.2.4 Other common side effects of trastuzumab

The following adverse events occurred in more than 10 out of 100 patients: diarrhoea, weakness, skin rashes, chest pain, abdominal pain, joint pain, and muscle pain.

4 HEALTH-ECONOMIC EVALUATION

4.1 COST-EFFECTIVENESS ANALYSIS

4.1.1 Methods

Policymakers have to take decisions before long-term follow-up data of clinical trials are available. Therefore, intermediate trial results have to be translated to long-term consequences. Due to the short-term follow-up, current published overall survival data cannot be used for a complete economic evaluation. However, most recurrences avoided by adjuvant trastuzumab are distant recurrences.[2] It is very plausible that this reduction will translate after years in a significant reduction of the risk of advanced disease and death. The ability of trastuzumab to prevent cancers from progressing and the subsequent life-years gained and long-term savings form the basis for our model. Which costs were included and how, how side effects were taken into account, etc… is discussed hereafter.

For most methodological aspects, different approaches exist. In this part, we present an overview of the essential elements for a pharmaco-economic evaluation in which the methodological choices for the economic appraisal of trastuzumab are provided. They are based on the "reference case" of the Belgian pharmaco-economic evaluation guidelines, which were set up to improve consistency in these evaluations.[44]

4.1.1.1 Perspective of the evaluation

An important initial step in performing economic evaluations is to determine the perspective of the study. A study can be performed from the point of view of society, the health care provider (hospital or physician), the payer (government or insurer), the patient, etc… The ultimate goal is to assist decision makers in optimizing whatever they want to maximize.[45] In other words, the perspective is determined by the policy decision to be made.

In general, a cost-effectiveness analysis (CEA) is a contributing tool to the discussion on the general allocation of health resources based on the broadest perspective, i.e. the societal perspective, in which the analyst considers everyone affected by the intervention and counts all significant health outcomes and costs that result from it, regardless of who experiences the outcomes or costs. These costs include both medical and non-medical resources, such as transportation costs and the time of patients and unpaid caregivers.[46] The decision maker, however, is usually more interested in the costs of a treatment from the point of view of the health care sector. The aim of the health care decision maker is to maximise health within the constraints of limited resources. In accordance with the Belgian pharmaco-economic guidelines, the analysis is performed from the perspective of the health care payer. This includes both costs paid by the standard health insurance and the patient out-of-pocket contribution.[44]

4.1.1.2 Analytic technique

Well-known methods for economic evaluation are cost-effectiveness (CEA), cost-utility (CUA), and cost-benefit analysis (CBA). In the Belgian guidelines, given the methodological difficulties and controversies associated with this technique, CBA is not accepted as a reference case for pharmaco-economic submissions.[44] The dependence of CBA on the monetary valuation of health benefits and on the reliability of the method for obtaining this monetary valuation has motivated the reliance on CEA in the field of health and medicine.[47]

In our analysis we performed a CEA. A full economic evaluation should look at both costs and effects of alternatives and the outcomes should be expressed in terms of life-years gained. Consequently, the results can be expressed as an incremental cost-effectiveness ratio (ICER), which reflects the additional costs per life-year gained. In the UK, the implicit threshold value is £30 000 per additional quality-adjusted life year with a reference case discount rate of 3.5% for both costs and benefits. [48] In our study, since

there are not yet official thresholds for decision-making, the threshold value was arbitrarily set at 30 000 euro for the reference case discount scenario (costs: 3%, benefits: 1.5%). All the scenarios which had an ICER above this value were even not cost effective with a threshold value off 50 000 euro.

Due to the absence of objective quality of life (QOL) data concerning the use of trastuzumab, no CUA was performed. To do this correctly, objective measures should be available for changes in QOL during trastuzumab treatment, associated with cardiac dysfunction or for metastatic breast cancer. If these objective measures become available, our analysis can be extended. For the moment we thus focus on cost-effectiveness.

4.1.1.3 Target population

The patient population for the pharmaco-economic evaluation should be applied to the patient population studied in the clinical trials.[44] In the first place, only patients with HER2-overexpressing breast cancer are eligible for trastuzumab treatment. Table 11 presents the percentage of Belgian patients being HER2+ using FISH.

Table 11. Percentage of breast cancer patients positive for HER2 using FISH by age and stage (Belgium, 2005)

	All	<50	>50	50-59	60-69	70-79	80+
Stage I	10.5%	10.5%	10.44%	10.1%	12.1%	8.9%	8.4%
Stage II	14.5%	16.1%	13.91%	15.6%	13.8%	12.1%	13.0%
Stage III	16.2%	17.7%	15.65%	16.8%	19.0%	13.0%	12.5%

In case of trastuzumab in early stage breast cancer women were e.g. excluded from participation in the HERA trial if the LVEF was <55% after completion of cytotoxic chemotherapy. However, such patients were included in trials B31/N9831 and FinHer. Some trials also included high-risk stage I patients (see table 7). At the time of writing of this report the target patient population as defined in the EMEA approved label was not yet made public. The specific patients subgroups considered in the model may therefore not match perfectly with the EMEA approved target population.

In our analysis, ICERs were calculated for subgroups defined by prognostic variables such as stage, age, and LVEF.

Difference between LVEF 50-54% en 55%.

Effectiveness and cost-effectiveness are not inherent, unchanging properties of an intervention.[49] They can differ substantially with the characteristics of the population. If the implications of the drug on the effectiveness and/or costs differ between subgroups, separate subgroup analyses should be performed, provided that appropriate justification for subgroup analysis is provided.[44]

As mentioned before, study B31 shows that both the post-AC LVEF and patient age were independent prognostic variables for severe heart failure after trastuzumab. Nine of the 48 patients over 50 years of age with a post-AC LVEF of 50-54% developed severe heart failure. Patients with a LVEF of less than 55% could not enter the HERA trial. Consequently, we make a distinction between LVEF of 50-54% and 55%. The prevalence of left-ventricular dysfunction was reported for women aged 45 years and older in a population based study in the UK.[42] Based on data from this study, the percentage of patients with LVEF less than 50% could be calculated for different age categories based on Belgian age distribution (appendix 4). This was 3.74%, 0.61%, 4.68%, 2.48%, 3.7%, 6%, and 10.39% for respectively all patients, and the age categories younger than 50, older than 50, 50-59, 60-69, 70-79, and older than 80 (table 12). Even if these patients have HER2+ breast cancer, they were not eligible for trastuzumab treatment in any of the trials considered.

Table 12. LVEF <50% according to age

	All	<50	>50	50-59	60-69	70-79	80+
LVEF <50%	3.74%	0.61%	4.68%	2.48%	3.70%	6.00%	10.39%

Source: Davies, 2001[42], Belgium: year 2005, women (appendix 4).

In the HERA trial, patients with a LVEF between 50-54% were excluded. The percentage of patients excluded for this reason is not mentioned in the study publication. In trial B31, 96 out of 841 patients (11.4%) who started trastuzumab had a LVEF 50%-54%.[4] This percentage is used as a proxy for our exclusion criterion of the HERA trial. Furthermore, in trials B31 and N9831 233 out of 3497 patients (6.7%) did not start trastuzumab after doxorubicin and cyclophosphamide because they had a decline in LVEF of at least 16% from baseline or a decline below the lower limit of normal (50%) or had cardiac symptoms.[4] These differences in eligibility criteria are taken into account in our model. More information is provided further (see 'variation on eligibility criteria').

In addition a HER2+ FISH test is considered a selection criterion for trastuzumab treatment. We assume LVEF assessment and HER2 FISH testing take place in parallel. As such, we created four patient groups in our model. First of all, we have the group not being FISH tested because they were IHC 0 or 1+. Second, we have patients being tested with FISH. The result can be negative (2nd group) or positive. In the group with positive study results, patients might (3rd) or might not (4th group) be eligible for trastuzumab treatment based on LVEF.

Difference between stage and age

The clinical report of a trial may indicate that there is no evidence of differences between subgroups in terms of relative treatment effect. Even without any differences noticed between subgroups in the trials for the hazard ratio, subgroup analysis could be important because of differences in baseline risk, i.e. the risk that a certain event happens in the control group. As mentioned by Drummond et al,[47] cost-effectiveness is driven by absolute benefit, and there may be important variation between subgroups in baseline event rates. This assumption of constant relative effects being applied to subgroup-specific baseline event rates is thus common in cost-effectiveness models.[47]

In our analysis, the plausible clinical explanation of subgroup effects is based on the different baseline risk of patients progressing to metastatic breast cancer depending on age and stage of the disease. This probability increases with stage and decreases with age. The following table, adapted from Berkowitz et al,[50] presents the percentage of patients progressing to metastatic disease according to age and stage. These percentages are used in our scenario without trastuzumab treatment.

Table 13. Percentage of patients progressing to metastatic disease according to age and stage

	All	<50	>50	50-59	60-69	70-79	80+
Stage I	32%	47%	28%	39%	31%	23%	14%
Stage II	46%	61%	43%	54%	46%	38%	26%
Stage III	72%	81%	68%	78%	74%	66%	51%

4.1.1.4 Comparator

The drug should be compared with the most relevant alternative treatment for the proposed indication of the drug. The most relevant alternative treatment is either the standard treatment or usual practice if there is no standard treatment.[44] In the HERA trial, randomisation to no trastuzumab or one- or two-year treatment is performed after primary treatment.[2] Trastuzumab does not replace other interventions. In other words, the comparator is current breast cancer treatment. A one year regimen or 9 weeks of trastuzumab are given in addition for respectively the HERA and B31/N9831 trial, and the FinHer trial.

4.1.1.5 Time horizon

The time horizon of a CEA should extend far enough into the future to capture the major health and economic outcomes. Frequently, the appropriate time horizon extends beyond the availability of primary data and modelling must be used.[46] Treatment's intention in adjuvant setting is curative. If more distant recurrence is avoided because of adding trastuzumab to primary treatment, both life-years will be gained and expensive future treatment for metastatic breast cancer will be economized. Consequently, we applied a lifetime horizon for our CEA. Costs for end-of-life care were however not included.

4.1.1.6 Study design

The aim of our economic evaluation is to evaluate trastuzumab under real-world conditions. Modelling is needed because the clinical trials provide insufficient information for an economic evaluation. Models can be constructed to extend the time horizon and extrapolate intermediate outcome parameters to final outcome parameters, take externalities associated with the treatment into consideration, etc…[44] Pharmaco-economic models allow the analyst to combine information from a variety of sources and to link these data to outcomes of interest to decision makers.

4.1.1.7 Calculation of costs

The Belgian guidelines mention the identification, measurement, and valuation of costs should be consistent with the perspective of the Belgian health care payer. Relevant sources should be used for unit costs. Non-health care costs or unrelated health care costs should not be included in the reference case analysis. If non-health care costs or indirect health care costs are deemed important, they could be presented in a separate analysis.[44] In this analysis we focus on direct health care costs.

The identification and measurement of costs is derived from trial data and literature. Concerning the valuation of costs, drug prices are those published by the Belgian health insurance organisation (RIZIV/INAMI). If a generic product exists for certain drugs, the price of the generic is used.[44] For ambulatory and hospital health care services, data from the Belgian reimbursement scheme and standard fees for regularly insured patients are used. For hospitalisation, the average per diem price for Belgian hospitals is applied. Our variables and the source for measurement and valuation of resource use are presented hereafter.

Incremental costs

For a CEA expressing results in ICER, extra attention should be paid to incremental costs and effects. In this part, we discuss the incremental costs. More details on the uncertainty of the estimates are presented separately (see 'handling uncertainty and probabilistic sensitivity analysis').

FISH test

In the first place it concerns the test to determine HER2 overexpression to see whether or not patients can be treated with trastuzumab. As IHC is often already performed for prognostic reasons, one can justify not considering this test as an incremental cost. The FISH test however, is performed additionally to confirm IHC-test results and to be able to obtain reimbursement for trastuzumab in Belgium. This cost should thus be seen as an incremental cost. The following table presents the percentage of patients with IHC 2+ or 3+ test results. In our model, these patients receive a FISH-test. Currently no financing is foreseen for the HER2 FISH test, but the amount of 298.96 euro was taken (DNA hybridization test, code 58 86 96, article 33, in agreed Human Genetic Centres). The assumptions made on (re)testing patients when they progress to metastatic breast cancer are discussed further (see 'modelling').

Table 14. Percentage of patients with IHC 2+ and 3+, and thus tested with FISH, by age and stage (Belgium, 2005)

	All	<50	>50	50-59	60-69	70-79	80+
Stage I	18.22%	18.28%	18.20%	17.56%	21.10%	15.53%	14.61%
Stage II	25.25%	28.06%	24.23%	27.17%	24.02%	21.16%	22.60%
Stage III	28.24%	30.86%	27.27%	29.33%	33.06%	22.58%	21.79%

Trastuzumab treatment

Trastuzumab treatment constitutes an incremental cost. It is important to model correctly who receives this treatment. This depends in the first place on the percentage of patients being FISH-positive, and second, on the percentage of patients being eligible for trastuzumab treatment, i.e. having a sufficient LVEF. Next, the incremental cost due to trastuzumab treatment has to be calculated. This cost depends on the dosage, duration, body weight and price of the product. The dosage and duration are taken from the trial data.[7, 2, 3] The average body weight in a sample of 37 Belgian patients was 63.9kg. The price of trastuzumab was 670.91 euro for a vial of 150 mg.(RIZIV/INAMI) As such, the cost for trastuzumab treatment would on average be 31 439, 30 296, and 5716 euro for respectively the HERA, B31/N9831, and FinHer Trial. However, this amount is an underestimation. When a vial is opened and some drug is left, it is thrown away. This part is not used, but is paid for.

The trastuzumab remaining in vials returned to the central pharmacy of an academic hospital was measured for 37 patients receiving 6 mg/kg (3-week scheme). Individual data can be found in the appendix 3. We have recalculated the amount left for the same patients at start of their treatment (8 mg/kg) and for a weekly scheme, respectively 2 mg/kg and 4 mg/kg for the loading dose (table 15).

Table 15. Mean trastuzumab rest measured or calculated in vials returned to the pharmacy

Dose	Injected dose	Mean rest	Percentage	2.5% - 97.5% CI
8 mg/kg	510.9 mg	60.7 mg	10.6%	8.1% - 13.1%
6 mg/kg	383.2 mg	70.9 mg	15.6%	12.3% - 18.9%
4 mg/kg	255.5 mg	72.9 mg	22.2%	19.0% - 25.4%
2 mg/kg	127.7 mg	46.6 mg	26.7%	23.0% - 30.5%

Taking this into account, trastuzumab-treatment costs increase to 36 229, 38 333, and 7191 euro for the three trials respectively. Furthermore, one has to take into account the incremental cost due to the extra administrations. There are 18 extra administrations for the HERA trial. For the B31/N9831 this is 40 and not 52 since the first twelve administrations are given during the same visit as the paclitaxel and therefore are not an incremental cost due to trastuzumab treatment. Similarly for the FinHer trial, this is 6 and not 9 since visits 1, 4 and 7 are needed for docetaxel administration. The cost per administration is 246 euro. This includes the cost of a one-day hospitalisation (148.96 euro), a lump sum for medical supervision (18.03 euro) and the cost of a blood test (78.99 euro).(RIZIV/INAMI) As such, the total incremental cost due to trastuzumab treatment is 40 657, 48 172, and 8667 euro for respectively the HERA, B31/N9831 and FinHer trials (table 16). The post-surgery period until completion of the cytotoxic chemotherapy and trastuzumab varies by regimen from 22 weeks for FinHer to 83 weeks for HERA. These costs were not discounted.

Table 16. Initial incremental costs due to trastuzumab treatment

	Dosage	Duration	% unused	Administration cost	Total incremental cost
HERA	6 mg/kg 3-weekly (start up: 8mg/kg)	52 weeks	mean: 15.6% (95%CI: 12.3% - 18.9%)	18 x €245.98	€40 657
B31-N9831	2 mg/kg weekly (start up: 4mg/kg)	52 weeks	mean: 26.7% (95%CI: 23.0% - 30.5%)	40 x €245.98	€48 172
FinHer		9 weeks		6 x €245.98	€8667

MUGA scan

Thirdly, due to the possible risk of heart failure, the left ventricular ejection fraction is measured. Awaiting standardisation of echo, MUGA is preferred over echocardiography, certainly in borderline cases. An assessment with MUGA scanning costs 187.74 euro.(RIZIV/INAMI) To reflect real-world conditions, this test would happen after baseline and every three months until completion of trastuzumab treatment. Consequently, only two tests are included for the FinHer regimen, whereas there are 5 tests for the other two regimens, i.e. at baseline and 3, 6, 9, and 12 months after treatment was initiated.

Heart failure

Furthermore, the incremental costs due to heart failure should also be taken into account. In the first place, the incremental percentage of patients confronted with congestive heart failure has to be included. In the HERA trial, symptomatic congestive heart failure, including nine (0.54%) severe cases, occurred in 1.73% of patients in the trastuzumab group and 0.06% of patients in the observation group, i.e. an incremental percentage of 1.67.[2] In the FinHer study, the anthracycline was started after 9 weeks of trastuzumab treatment. This reversed order regimen resulted in little or no cardio toxicity.[7] In trial N9831, the three-year cumulative incidence of NYHA class III or IV heart failure or death from cardiac causes was 0 percent in the control group and 2.9 percent in the trastuzumab group.[3] In trial B31, the cumulative incidence of cardiac event was 0.8% in the control arm and 4.1% among trastuzumab-treated patients. The difference between the arms was 3.3% (95% CI, 1.7% - 4.9%). However, significant differences in CHF were noticed according to post-AC LVEF and age. Consequently, our analysis will make a distinction based on LVEF above or lower than 55% for the analysis of the B31/N9831 trial.

Concerning the costs of heart failure, no data were available for Belgium. As a proxy, Dutch data were used. The Dutch Healthcare insurance costs for heart failure amongst women were 172.4 million euro in 1999. (http://www.rivm.nl/kostenvanziekten/site_nl/index1.htm (accessed 17 March, 2006)) The total number of heart failures could be estimated by multiplying the incidence of heart failure for different age categories of women with population data for the same age categories. (http://www.cbs.nl/nl-NL/menu/themas/dossiers/volkstellingen/cijfers/incidenteel/maatwerk/2003-volkstelling-excel.htm) The incidence data were not available for 1999. As a proxy, the numbers of 2000 were taken into account. (Source: huisartsenregistraties; the estimated incidence in 2000 was the mean of CMR-Nijmegen e.o., Tweede Nationale Studie, RNUH-LEO, RNH-Limburg en Transitieproject. http://www.rivm.nl/vtv/object_document/o1650n17965.html#0 (accessed 17 March 2006)) As such, an estimated number of 24 041 cases of congestive heart failure occurred in 1999, resulting in an estimated cost of 7171 euro per case.

Metastatic breast cancer treatment

We also included metastatic cancer treatment costs. The focus of this HTA report is on trastuzumab treatment in adjuvant setting. However, an economic evaluation should

stand in relation to the health care system as a whole. Treatment with monoclonal antibodies may have higher immediate costs but can have important longer-term benefits. These long-term consequences should be included. Concerning trastuzumab, the initial costs will for sure increase. However, treatment in adjuvant setting is aimed to be curative. If less people progress to metastatic breast cancer, economising on expensive future treatments is possible. Concerning these metastatic treatment costs, we made a distinction on whether or not trastuzumab is (re)administered. Based on a simulation relying on literature data and information from the University Hospital Ghent (appendix 5), we calculated the cost for metastatic breast cancer treatment to be on average 14 050 euro (95%CI: 13 911 – 14 188) without trastuzumab and 31 878 euro (95%CI: 31 173 – 32 582) with trastuzumab. End-of-life care was not included. We refer to the section part 'modelling' for our assumptions concerning this cost and hypotheses on whether or not to include trastuzumab treatment.

Next, the hazard ratio of patients surviving free of distant recurrence, i.e. 0.49 (95% CI: 0.38 – 0.63), 0.47 (95% CI: 0.37 – 0.61), and 0.29 (95% CI: 0.13 – 0.64) for respectively the HERA, B31/N9831, and FinHer trials[2, 3, 23], are multiplied with the baseline risk of progressing to metastatic disease (table 13) to calculate the incremental percentage of patients not progressing to metastatic disease. We assume the reported hazard ratios remain constant. The possibility of trastuzumab not being able to prevent brain metastases is taken into account (see 'modelling: brain metastasis'). The cost savings are calculated by multiplying the incremental percentage with the discounted costs of metastatic breast cancer treatment.

Local recurrence

Cost savings can be realized if local recurrence is avoided. The cost for management of local recurrence is not well documented. According to NCCN guidelines (National Comprehensive Cancer Network), patients initially treated with mastectomy and having local recurrence should have a surgical resection if possible, radiotherapy if possible, and systemic therapy should be considered. For patients initially treated with lumpectomy and radiotherapy, mastectomy should be performed and systemic therapy should be considered. Based on expert opinion, the average treatment cost was varied between the cost of mastectomy (3673 euro) and the cost of mastectomy and radiotherapy (6456 euro). The mastectomy cost is based on the average cost for 5920 mastectomies for Belgium in 2003 (APR-DRG 362, all severity grades).(RIZIV/INAMI) This cost includes the average cost for hospitalization, pharmaceutical products, and fees. The cost for radiotherapy (2783 euro) is also based on Belgian data. Due to the relative short-term nature of local recurrence, these costs were not discounted.

The baseline risk, i.e. without trastuzumab treatment, of local recurrence was based on literature. The 10-year incidence of loco-regional recurrence after mastectomy is about 13% and 12% after breast conserving surgery (BCS) and radiotherapy.[51] A decrease in the 8-year loco-regional recurrence rate from 20.1% to 5.4% was reported in the Netherlands.[52] Tumour size, stage, axillary lymph node involvement, tumour grade, and absence of oestrogen receptor or hormone therapy have all been associated with an increased loco-regional recurrence rate.[51, 53-56] Radiotherapy reduces the 5-year local recurrence rate from 23% to 7% after breast conserving surgery in node-negative tumours and from 23% to 6% after mastectomy in node positive breast cancer.[55] In BCS treated node negative poorly differentiated tumours or ER- tumours radiotherapy reduced the 5-year local recurrence risk from 34% to 12%. As HER2 positive tumours tend to be poorly differentiated, the following frequencies of local recurrence were used by stage: 8%, 10%, and 12% for respectively stage I, II, and III tumours. In the trastuzumab trial publications local recurrence is reported only if it constitutes a first event. In the B31 trial 35 out of 872 control group patients (4%) developed local recurrence as a first event during a median follow-up of 2.4 years, a percentage that seems consistent with the above estimates.

The HERA and B31/N9831 studies report data on local and/or regional recurrence, but only as a first event. As a proxy, the hazard ratio for patients surviving free of disease was used to model the improvement of preventing local recurrence. These ratios were 0.54 (95% CI: 0.43 – 0.67), 0.48 (95% CI: 0.39 – 0.59), and 0.42 (95% CI: 0.21 – 0.83) for

respectively the HERA, B31/N9831, and FinHer trial.[2, 3, 23] Multiplying the hazard ratios with the baseline risk results in the percentage point improvement of preventing local recurrence. The incremental cost saving is then determined by multiplying this percentage point improvement with the cost of treating local recurrence.

Follow-up costs

Changes in life expectancy have an influence on follow-up costs. If patients progress to metastasis, their follow-up becomes again more frequent. Preventing metastatic breast cancer avoids this, but on the other hand, because patients live longer, the follow-up takes longer. If patients have a shorter life expectancy because of CHF the follow-up will also be shorter. With regard to the follow-up schedule, no well defined guidelines are being followed. Different follow-up protocols are available and the evidence-base on which they have been developed is lacking.[57] A plausible follow-up schedule was included in our model. First of all, a doctor's visit (31.28 euro) and blood test (78.99 euro) are performed every three months during the first two years, two times a year the following two years, and once a year afterwards. A mammography in combination with an ultrasound scan (83.99 euro) is performed once yearly. In addition, an X-ray of the thorax (13.57 euro), a bone scan (72.36 euro), and an ultrasound scan of the liver (24.51 euro) are performed once every year for the first five years. Finally, the yearly cost for the Belgian oncology care programme, i.e. 162.60 euro, is also included. The costs for these items are based on RIZIV/INAMI data.

4.1.1.8 Estimation and valuation of outcomes

According to the Belgian guidelines on cost-effectiveness analyses, the outcomes selected should be consistent with the endpoints assessed in the trials. The trials report intermediary outcomes such as patients surviving free of disease or free of distant recurrence. Since the trials contain only short-term outcomes and long-term outcomes are considered important for the pharmaco-economic evaluation, modelling is needed. For chronic diseases outcomes should be expressed in terms of "number of life years gained".[44]

Concerning effectiveness, our model is mainly based on the progression of patients to metastasis. Fewer patients may progress to MBC due to the administration of trastuzumab. To calculate life-years gained, we calculated life expectancy for both patients progressing and not progressing to metastatic breast cancer. For patients progressing to metastasis, life expectancy data are based on a study of Berkowitz and colleagues [50], which mentions the mean time of progressing to metastatic disease (table 17) and the mean survival of patients with metastasis according to age and stage (table 18).

Table 17. Mean time (years) to metastatic disease progression by age and initial stage

	All	<50	>50	50-59	60-69	70-79	80+
Stage I	9.9	15.1	8.4	12.1	9.1	6.7	4.4
Stage II	7.4	11.3	6.4	8.8	6.9	5.1	3.5
Stage III	4.2	5.6	3.7	4.9	4.1	3.3	2.4

Table 18. Mean survival (years) of metastasis according to age and initial stage

	All	<50	>50	50-59	60-69	70-79	80+
Stage I	3.1	4	3.1	3.7	3.3	2.8	2.1
Stage II	3.1	4	3	3.6	3.3	2.8	2.1
Stage III	3.1	4	3	3.6	3.3	2.9	2

For those not progressing to metastatic disease, life expectancy was measured using the age-specific life tables for Belgian women, which are available from the National Institute of Statistics (NIS/INS), and the number of Belgian patients with breast cancer according to age.(NCR, Belgium, 2005) Results are presented in table 19.

Table 19. Life expectancy (years) for Belgian women according to age.

	All	<50	>50	50-59	60-69	70-79	80+
All stages	24.7	40.3	20	29.2	20.7	12.9	6.8

Source: NIS/INS (http://statbel.fgov.be/figures/download_nl.asp#2, accessed: 2006, February 21) and NCR, KCE

As breast cancer patients overall have an increased risk of secondary cancer, the life expectancy obtained from the life tables was slightly decreased in the model (see further 'reduced remaining life expectancy due to risk of second cancer').

As mentioned in the introduction, calculating the consequences of preventing more people to progress to MBC forms the basis of our model.

In the first place, we used the hazard ratio of patients surviving free of distant recurrence, i.e. 0.49 (95% CI: 0.38 – 0.63), 0.47 (95% CI: 0.37 – 0.61), and 0.29 (95% CI: 0.13 – 0.64) for respectively the HERA, B31-N9831, and FinHer trials.[2, 3, 23] Furthermore, cost-effectiveness is not driven by relative benefit but by absolute benefit.[47] As mentioned before, we calculated the incremental percentage of patients not progressing to metastatic disease by combining the hazard ratios with the baseline risk of progressing to metastatic disease (table 13). The difference in life expectancy between patients progressing and not progressing to metastatic breast cancer allows for the calculation of the number of life-years gained. Our scenarios concerning the link between the published intermediary outcomes and the final endpoint are mentioned further (part 'modelling: brain metastasis').

Finally, as mentioned before, trastuzumab treatment may cause congestive heart failure. This not only incurs incremental costs due to extra follow-up costs (MUGA) and treatment of heart failure, but also has its implications on life expectancy. Data were not available for Belgium. Calculations were based on data from a Dutch population.(RIVM data) These numbers were rearranged to age categories (table 20) using the number of Belgian patients with breast cancer according to age (appendix 6).

Table 20. Life expectancy (years) for patients with heart failure according to age

	All	<50	>50	50-59	60-69	70-79	80+
All stages	5.61	6.95	5.21	6.35	5.42	4.43	3.05

Source: RIVM, NCR and own calculations

4.1.1.9 Modelling

In our model, some assumptions were made about (re)testing HER2 overexpression in metastatic breast cancer. Furthermore, several scenarios were worked out concerning re-administering trastuzumab in metastasis, the cost of metastatic breast cancer treatment, taking into account the percentage of unused trastuzumab, and the possible lack of efficacy of trastuzumab in avoiding metastases to the brain.

Retest HER2 in MBC

One may question whether or not HER2 overexpression would be (re)tested if patients progress to metastasis. Zidan and colleagues compared biopsies from primary breast cancer and corresponding metastases.[58] HER2 overexpression was evaluated immunohistochemically. Initially, HER2 was negative for 44 patients. In seven patients, HER2 became positive in metastases. These results were confirmed by fluorescence in situ hybridisation (FISH). Another study also compared HER2 immunohistochemistry of

primary tumours and distant metastases.[59] Initially, 25 cases were IHC 0 or 1+. Three cases showed an increase from score 0 to 3+. Based on expert opinion, only patients with an unexpectedly rapid tumour progression would be retested on HER2 overexpression. They estimated this would be about 15% of patients initially diagnosed with HER2-negative breast cancer that become metastatic. In about one third of these patients the metastatic cancer was assumed to test HER2-positive. These patients would receive trastuzumab in metastatic setting. Since we want to reflect real-world conditions, we applied these assumptions in our model for patients initially being IHC 0 and 1+, and thus not tested with FISH, and patients being tested with FISH and negative test results. Patients who were HER2-positive by FISH in adjuvant setting were assumed to remain HER2-positive and were not retested.

Re-administration of trastuzumab in MBC

One may also question whether or not trastuzumab will be re-administered in metastatic setting if patients already received the drug for treatment of early stage breast cancer. We worked out both situations. As mentioned before, metastatic treatment cost was calculated to be on average 14 050 euro (95%CI: 13 911 – 14 188) without trastuzumab and 31 878 euro (95%CI: 31 173 – 32 582) with trastuzumab.

No data are available on whether or not re-administering trastuzumab in metastatic breast cancer patients has an influence on life expectancy. In our model, life expectancy for MBC patients was not changed. If survival would increase, the influence on incremental effectiveness would be small. First of all, based on current literature on trastuzumab treatment in MBC, life-months gained in this setting would be relatively small. And secondly, these months have to be discounted since we are making an evaluation of trastuzumab in adjuvant setting.

MBC treatment cost

Furthermore, we might also question whether our calculated metastatic treatment costs are not an underestimation of reality. Will and colleagues estimated the average undiscounted lifetime cost was CAD36 340 (1995 prices) for metastatic disease. This included all treatments initiated three months after the diagnosis until three months prior to death, which are considered to be the 'terminal care' phase of the illness.[60] Similar results were reported by Wai and colleagues, i.e. a mean cost of CAD36 474.[61] Another study estimated the total undiscounted life-time cost of treating metastatic breast cancer to be $59 489 a case. Exclusive terminal care cost, i.e. $13 476, this becomes $46 013.[50] Rao and colleagues calculated costs to the health care system from the date of first diagnosis of MBC to the end of follow-up which was on average 16.2 months. Cases of MBC from 1997 to 1999 were included. The mean total costs was $35 164 per MBC patient.[62] Finally, in the United Kingdom, lifetime treatment cost per patient with stage IV breast cancer was estimated to be £12 500 (2000 prices) according to treatment practice in 2000.[63] Since treatment practices and costs in the US and Canada are hard to compare with the Belgian situation, we prefer only to look at the UK cost of £12 500, i.e. 17 933 euro (exchange rate on 27 April 2006: 1 GBP = 1.4346 euro). Trastuzumab treatment was authorised in 2000 (EMEA, 25 May 2000)(www.emea.eu.int). Consequently, the metastatic treatment cost could very probably be compared with our estimates without trastuzumab, i.e. on average 14 050 euro. In our model, follow-up costs were calculated and modelled separately. Adding these costs, which are eg about 1931 euro for two years of follow-up discounted at 3%, the difference would be reduced to less than 2000 euro.

To be able to evaluate the influence of higher metastatic treatment costs, which would be slightly higher taking into account inflation, we included a scenario in which our costs for MBC treatment with and without trastuzumab were increased with 5000 euro.

Unused trastuzumab

Next, we worked out two scenarios taking into account or not the percentage of unused trastuzumab. Multi-dose vials, marketed in the US but currently not approved for marketing in Europe, could provide a solution. If this is not possible, the necessary dose could also more accurately be put together with smaller vials and as such reduce the percentage of unused drug. It is interesting to analyse the influence on the ICER and calculate how much could be economized by avoiding any trastuzumab to be thrown away. More details about the percentage of unused drug, depending on the weekly or 3-weekly schedule, are given further ('handling uncertainty and probabilistic sensitivity analysis').

Brain metastasis

Finally, the possibility of trastuzumab not being able to prevent the development of brain metastases is worked out in a scenario. To be able to perform a useful economic evaluation for decision makers, we have to make an assumption regarding the relationship between the relative short and long-term treatment effect. In our initial analysis, we assume the short-term effect to continue in the long-term, i.e. the hazard ratio of distant recurrence remains the same. For models that extrapolate to longer time periods, it is recommended to present different scenarios to show the impact of different extrapolation approaches on the results.[47] The choice of an extrapolation approach is mainly a judgement. There is no best or worst option. Therefore, it is not possible to recommend one single approach for the reference case.

Concerning trastuzumab treatment, it may be plausible that the initial scenario is too optimistic. Lack of efficacy of trastuzumab to block the development of CNS metastases has been reported in patients with metastatic breast cancer.[25] A possible explanation could be the low penetration through the blood-brain barrier of trastuzumab.[26] As mentioned before, in both the HERA trial and trials B31/N9831 the incidence of isolated brain metastases as first event was higher in the trastuzumab group than in the control group. This difference could be attributed to earlier failures at other distant sites among patients in the control group. Due to the short-term follow-up, the influence of this event on the reported hazard ratios might be minimal. Consequently, we worked out two scenarios assuming the absence or presence of efficacy of trastuzumab to prevent brain metastasis.

Researchers assessed the risk of brain metastases in HER2-positive MBC patients. Out of 173 patients, 45 patients (26%) developed brain metastases including 26.2% and 25.5% who did and did not receive trastuzumab. The median time to brain relapse from diagnosis of MBC was 10 months (range, 0 to 65 months).[64] The mean and its distribution were derived from these data (see 'handling uncertainty and probabilistic sensitivity analysis'). In our first scenario, we included these data. In other words, it may be plausible that trastuzumab prevents the development of metastases, except for brain metastases, i.e. in about 26% of all patients developing metastases. In these cases, brain metastasis would occur but progression to metastatic disease would be delayed by about a year as other metastases were prevented. Consequently, we have four groups of patients on our effectiveness side. First, we identify a group of patients who will not show progression to MBC with or without trastuzumab. Second, there are patients who will progress to MBC with or without trastuzumab. Third, there are patients who will no longer show progression to MBC because of trastuzumab. Finally, we define a group of patients who will still show progression to MBC (brain) but at a slower rate, as we assume trastuzumab can successfully block progression to metastatic disease at non-CNS sites. Changing the time to progression increases life expectancy and decreases metastatic treatment costs since they are discounted over a longer period.

4.1.1.10 Discount rate

Incremental cost-effectiveness ratios should be presented in present values. This means that future costs and benefits should be discounted to reflect the lower value given to future costs and benefits. The choice of the discount rate for costs and benefits is mainly a normative issue. The Belgian guidelines recommend discounting future costs at a rate of 3% and future benefits at a rate of 1.5%. To assess the sensitivity of the results to the discount rate applied, different scenarios should be presented: 3% for benefits and 3% for costs, 0% or 3% or 5% for both benefits and costs and finally 0% for benefits combined with 5% or 3% for costs (table 21).[44] Discounting is applied on treatment costs in the future, i.e. metastatic breast cancer treatment costs, follow-up costs, and on life years.

Table 21. Different scenarios applied on the discount rate for costs and benefits

	Reference case	Scenario 2	Scenario 3	Scenario 4	Scenario 5	Scenario 6
Costs (charges)	3%	3%	5%	5%	3%	0%
Benefits (life-years)	1.5%	3%	5%	0%	0%	0%

4.1.1.11 Handling uncertainty and probabilistic sensitivity analysis

According to the Belgian guidelines, all different aspects of uncertainty in the evaluation should be addressed. This enables us to analyse the robustness of our results. For models, probabilistic sensitivity analyses should be presented.[44] In this section, we discuss the uncertainty placed on our variables and how our probabilistic sensitivity analysis was performed.

Source of Data and Variables' Uncertainty

The model used different sources of data as input parameters. A first source consisted of the published results of clinical trials, which typically present treatment effects expressed as hazard ratios and their associated 95% CI (representing the uncertainty in estimation due to the sampling variability). A second source of data consisted of observational studies, such as registers, which were the basis for the estimates of progression to metastatic disease published by Berkowitz et al. (2000). Presentation of results in these studies is less consistent than clinical trial results, and sometimes no CI was presented around the estimates. To account for the inevitable uncertainty in estimation, some arbitrary prior distributions (leading to probabilistic sensitivity analyses) were set on these parameters (for instance a +/- 10 percentage points range around a distribution). A third source of data consisted of the results of the analyses performed on the Belgian incidence data in 2005, collected by the KCE (appendix 1). As these data represent approximately half of the total population of 2005, estimates were considered as being precise enough to be considered as fixed parameters in the model. A last source of data, the draft Belgian guidelines,[44] was used to address some of the methodological uncertainty, arising from the choice of the discount rate, for instance. These variables are considered fixed parameters in the main model, and their influence is explored in the sensitivity analyses.

The choice is vast for the distributions of the input variables, but fortunately some guidance exists to help justify that choice. Because of the Central Limit Theorem, a normal distribution is the default candidate distribution for parameters based on expected values.[65] Probabilities are constrained on the interval zero to one. Due to the relationship with binomial data, beta distributions can be applied on probability parameters. [66-68, 65]

Table 22 summarizes the information with regard to the source of data used for each input parameter, and how uncertainty was handled.

Table 22. Source of data and variables' uncertainty

Endpoint	Input Variable	Source	Estimate	Uncertainty
Survival free of distant recurrence	Hazard Ratio	Piccart, 2005[2]; Romond, 2005[3]; Joensuu, 2006[23]	Published	Based on published 95% CI
Survival free of disease	Hazard Ratio	Piccart, 2005[2]; Romond, 2005[3]; Joensuu, 2006[23]	Published	Based on published 95% CI
Probability brain metastasis	Percentage	Duchnowska, 2006[64]	Published	Beta distribution: based on 95% CI
Mean time brain relapse	Mean Time to brain relapse	Duchnowska, 2006[64]	Estimation	Computed based on gamma distribution
Progression to MBC	Risk per subgroup (according to age and stage)	Berkowitz, 2000[50]	Published	Beta distribution: range of +/- 10 ppt
Progression to MBC	Mean Time (according to age and stage)	Berkowitz, 2000[50]	Published	Normal distribution: 95% CI +/- 10% above and under mean
Survival of MBC	Mean Time (according to age and stage)	Berkowitz, 2000[50]	Published	Normal distribution: 95% CI +/- 10% above and under mean
Life expectancy with heart failure	Mean Time (according to age)	RIVM, NI	Published	Normal distribution: 95% CI +/- 10% above and under mean
Reduced remaining life expectancy due to risk of second cancer	Percentage	Mellemkjaer, 2006 [69]	Arbitrarily	Asymmetric gamma distribution: min: 90%, mean: 97.5%, max: 100%
MBC treatment cost	Mean cost	Literature study + University Hospital Ghent	Modelled	Normal distribution: variability from model and SE based on a sample of 1000 patients
Unused trastuzumab	Percentage	University Hospital Ghent	Calculated	Normal distribution
Cost Heart Failure	Mean cost	RIVM, NI	Calculated	Normal distribution: 95% CI +/- 20% above and under mean
Incremental risk of heart failure	Percentage	Piccart, 2005[2]; Joensuu, 2006[23]; Tan-Chiu, 2005[4]	Published	Based on published or computed 95% CI
Cost local recurrence	Mean cost	Expert opinion + RIZIV/INAMI	Estimation	Uniform distribution between minimum and maximum value
Probability local recurrence	Risk per subgroup (according to stage)	Literature study	Assumption	Beta distribution: range of +/- 2.5 ppt
Eligibility Criteria	Percentage (according to age)	Davies, 2001[42]; Tan-Chiu, 2005[4]	Published	Beta distribution: range of +/- 2.5 ppt
Retesting HER2	Percentage	Expert opinion	Estimation	Beta distribution: range of +/- 5 ppt

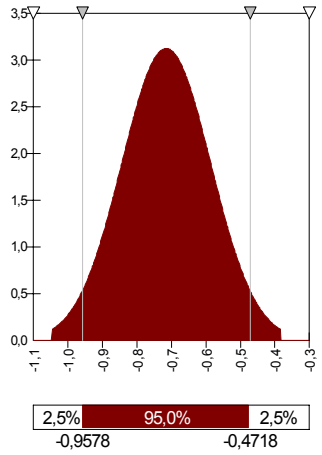
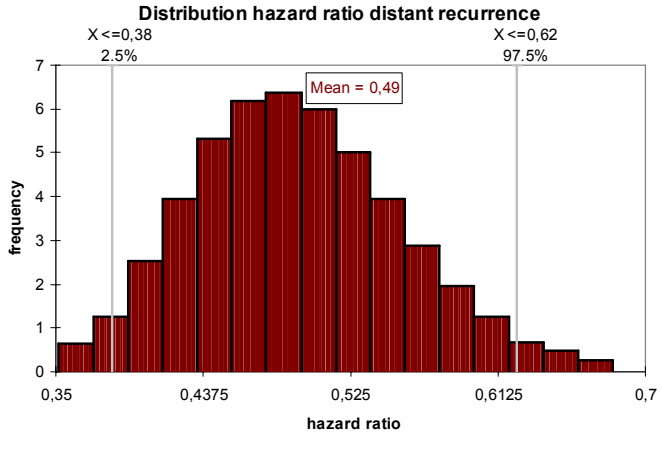
Endpoint	Input Variable	Source	Estimate	Uncertainty
IHC positive	Percentage (according to age and stage)	Belgian Data	See appendix	No distribution
FISH positive after HER2 positive	Percentage (according to age and stage)	Belgian data	See appendix	No distribution
Discount rate	Percentage	Belgian guidelines	Six scenarios	No distribution – explored in sensitivity analysis
Price of trastuzumab	Price	RIZIV/INAMI	670.91 euro	No distribution – explored in sensitivity analysis

The results of this modelling exercise will therefore not only reflect the uncertainty due to sampling variation, but also the uncertainty reflected in the a priori distribution set on selected parameters. In the following part, we discuss our variables individually and provide more information on the applied uncertainty.

Survival free of distant recurrence and Survival free of disease

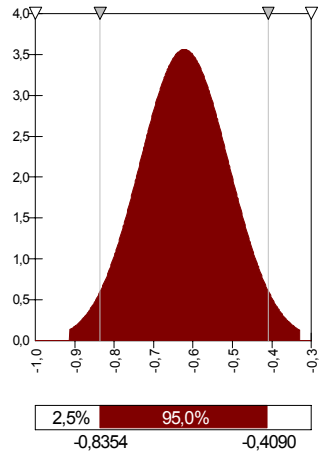
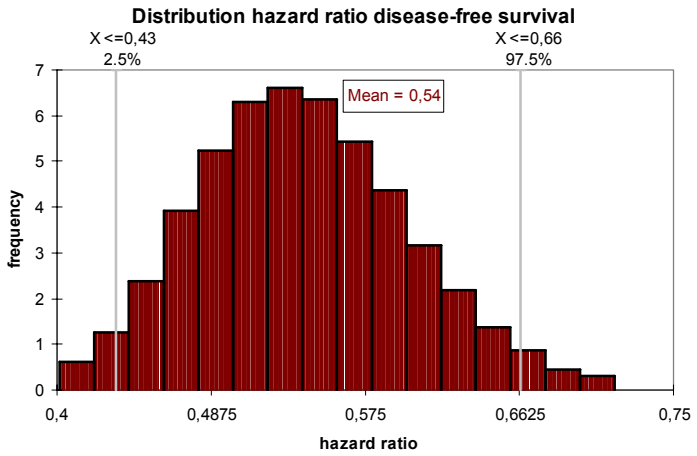
The hazard ratio of patients surviving free of distant recurrence was 0.49 (95% CI: 0.38 – 0.63), 0.47 (95% CI: 0.37 – 0.61), and 0.29 (95% CI: 0.13 – 0.64) for respectively the HERA, B31/N9831, and FinHer trials.[2, 3, 23] The hazard ratio for patients surviving free of disease was respectively 0.54 (95% CI: 0.43 – 0.67), 0.48 (95% CI: 0.39 – 0.59), and 0.42 (95% CI: 0.21 – 0.83). Because the CI of a hazard ratio is symmetrical on the log scale (ln x), simulations were based on that scale, the exponential function was applied to these results, and the resulting distributions were truncated at 99% to avoid any extreme or impossible values. Tables 23 and 24 show the modelled uncertainty for respectively the hazard ratio free of distant recurrence and free of disease for the HERA trial.

Table 23. Hazard ratio free of distant recurrence (HERA)

Ln(0.38) = -0.9676 Ln(0.49) = -0.7134 Ln(0.63) = -0.4620	Exp(-0.9676) = 0.38 Exp(-0.7134) = 0.49 Exp(-0.4620) = 0.63
	

Remark: truncation of the distribution function results in slightly different 95% CI.

Table 24. Hazard ratio free of disease (HERA)

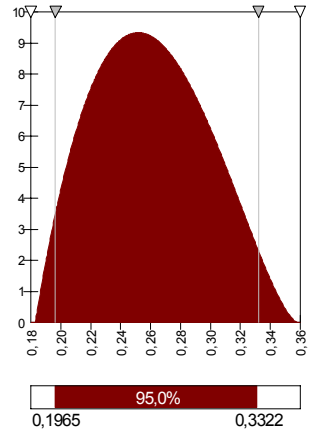
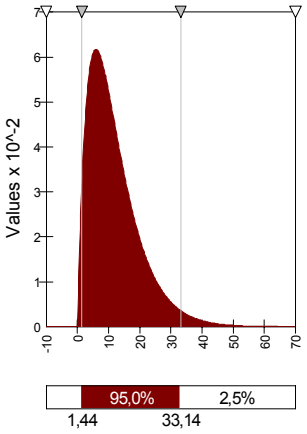
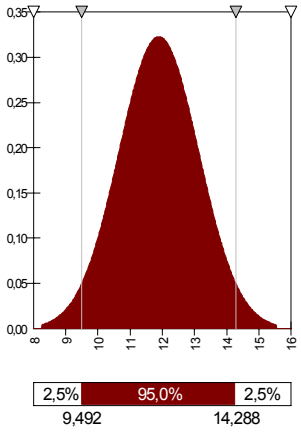
Ln(0.43) = -0.8440 Ln(0.54) = -0.6162 Ln(0.67) = -0.4005	Exp(-0.8440) = 0.43 Exp(-0.6162) = 0.54 Exp(-0.4005) = 0.67
	

Brain metastasis

Concerning brain metastasis, researchers assessed the risk of brain metastases in HER2-positive MBC patients. Out of 173 patients, 45 patients (26%, 95%CI: 19.65% - 33.22%) developed brain metastases including 26.2% and 25.5% who did and did not receive trastuzumab.[64] We applied a beta distribution with these parameters in our model for this probability (table 25, a).

The median time to brain relapse from diagnosis of MBC was 10 months (range, 0 to 65 months).[64] Applying a gamma distribution with these characteristics (table 25, b), the mean and standard deviation could be estimated. A normal distribution for the mean, again truncated at the 99%CI, was used (table 25, c).

Table 25. Brain metastasis

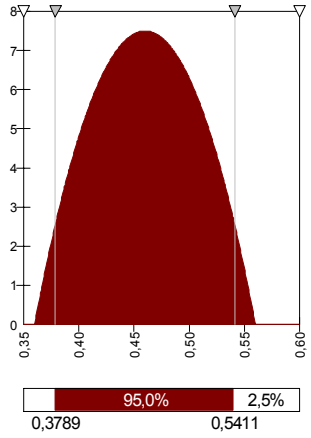
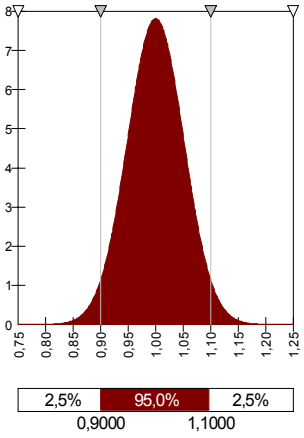
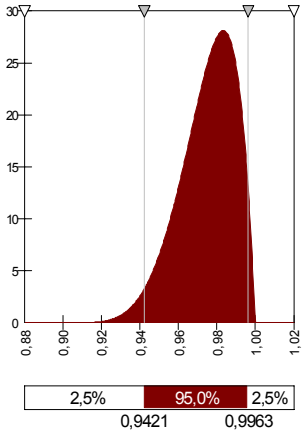
a) probability brain metastase	b) median time brain relapse (patient data)	c) mean time brain relapse (population)
		

Probability of progressing to MBC

One of the reasons to work with subgroups was the difference in baseline risk, i.e. without trastuzumab treatment, of patients progressing to MBC. This probability increases with stage and decreases with age (table 13). As mentioned before, beta

distributions can be used for probability parameters.[66-68, 65] The upper and lower limits were arbitrarily set at 10ppt above and under the point estimate. The graph for patients with stage II breast cancer is presented (see table 26, a).

Table 26. Probability distributions

a) progressing to MBC	b) time to progression, survival of MBC, life expectancy heart failure	c) Reduced remaining life expectancy for women not progressing to MBC due to a higher risk of second cancer
		

TTP, survival of MBC, and life expectancy heart failure

We applied a normal distribution on the following variables: mean time of progressing to metastatic disease (table 17), mean survival of metastasis (table 18), and life expectancy for patients with heart failure (table 20). The distribution was set up so that 95% of the data would be comprised within 10% around the mean, and so that tails were truncated at 20% around the mean (to avoid extreme values). This distribution function is presented in table 26 (b).

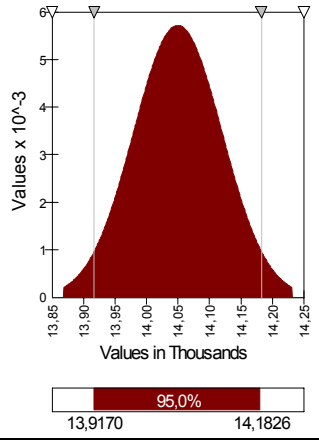
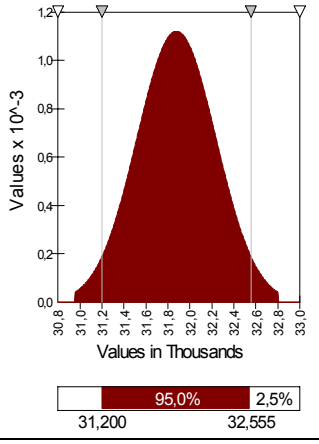
Reduced remaining life expectancy due to risk of second cancer

Next, the excess of cancer after a breast cancer diagnosis is likely to be explained by treatment for breast cancer, by shared genetic or environmental risk factors, or additional explanations such as increased surveillance and general cancer susceptibility.[69] In other words, the mean life expectancy of patients not progressing to MBC could be smaller than life expectancy based on the Belgian life tables. We have not found any data on the exact influence on life expectancy. Therefore, we chose to implement an asymmetric distribution (table 26, c) with a minimum, mean, and maximum of respectively 90%, 97.5%, and 100% of the values from the Belgian life tables (table 19).

MBC treatment cost

As mentioned before, the costs for MBC were modelled resulting in a cost of 31 878 euro (st.dev. 11 371) and 14 050 euro (st.dev. 2228) with and without trastuzumab after 1000 Monte Carlo simulations. Based on a sample a 1000 patients, the resulting 95% CI for the mean was 31 878 euro (95%CI: 31 173 – 32 582) with trastuzumab and 14 050 euro (13 911 – 14 188) without trastuzumab. As before, the tails of the distributions were truncated at 99% CI to avoid extreme outliers. Table 27 presents the applied distributions.

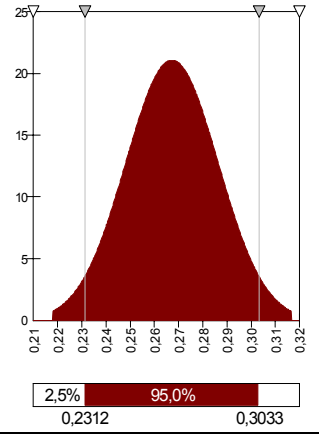
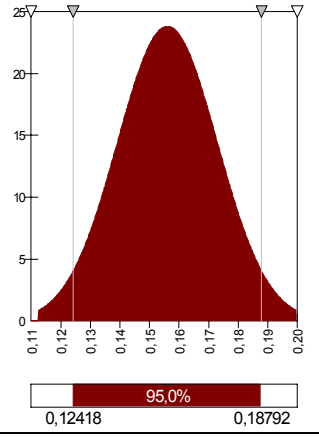
Table 27. MBC treatment cost with/without trastuzumab

without trastuzumab	with trastuzumab
	

Percentage of unused trastuzumab

Trastuzumab is currently marketed as single use vial of 150 mg. Patients receive 2 mg/kg weekly or 6 mg/kg 3-weekly. If a vial is opened and not completely used, the unused part is discarded. This cost should also be taken into account. Instead of working with the percentage of women weighing more than 75kg (i.e. needing more than one vial) or working with a qualified guess of the percentage of people needing more than one unit, we preferred to directly measure the percentage of unused trastuzumab. This estimate is based on data received from 37 patients from University Hospital Ghent. Their average weight was 63.9kg. The dosage of trastuzumab is determined by the body weight, i.e. 2 mg/kg weekly or 6 mg/kg 3-weekly. Consequently, the body weights determined the percentage of unused drugs. On average, this was 26.7% (st.dev. 11.63%) and 15.6% (st.dev. 10.27%) for the weekly and 3-weekly schedules respectively, resulting in a distribution of the mean of respectively 26.7% (95%CI: 23.0 – 30.5) and 15.6% (95%CI: 12.3 – 18.9) (appendix 3). Again tails of the distributions were truncated at 99% to avoid extreme outliers, resulting in slightly different 95% CI. Table 28 presents the applied distribution probabilities.

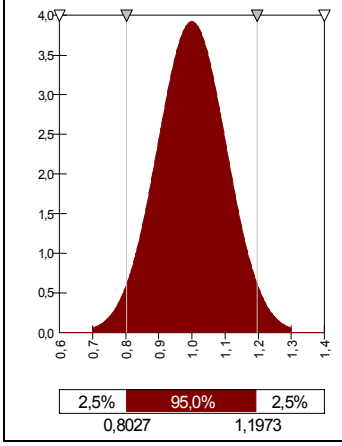
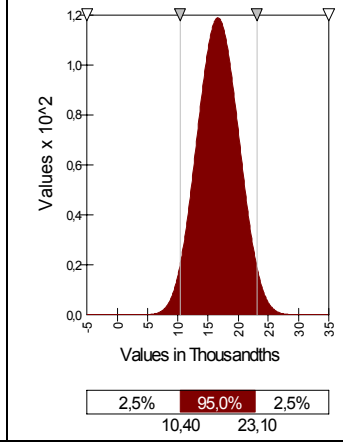
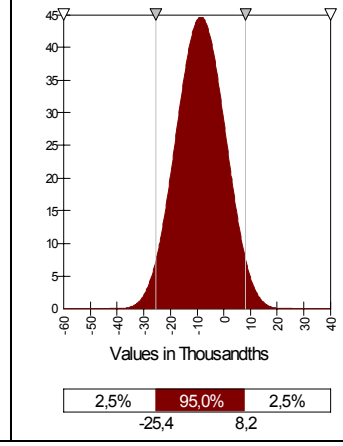
Table 28. Percentage of waste

Weekly	3-weekly
	

Cost heart failure

No data were available for Belgium concerning the cost of heart failure. As mentioned before, as a proxy, Dutch data were used combining the total health insurance cost for heart failure amongst women, the incidence of heart failure for different age categories and population data. This provided an estimated cost of 7171 euro. Since we do not want to reflect individual cost but population data, a normal distribution was used and not an asymmetric gamma distribution that is normally applied to model uncertainty for single costs. Since we have no indications on the uncertainty of this cost, we preferred to set a wide range on this cost, i.e. a normal distribution with a 95% CI 20% under and above the point estimate, with a truncation at +/- 30% around the point estimate (table 29, a).

Table 29. Heart failure

a) cost of heart failure	b) Incremental % heart failure HERA	c) Incremental % heart failure FinHer
		

Incremental percentage of heart failure

In the HERA trial, symptomatic congestive heart failure, associated with a decrease in LVEF (and including severe CHF), occurred in 1.73% of patients in the trastuzumab group and 0.06% of patients in the observation group, i.e. a risk difference of 1.67%. Using the proportions of symptomatic CHF, i.e. 29 out of 1677 patients treated with trastuzumab and 1 out of 1710 patients in the control group,[2] the risk difference and its 95% confidence limits could be estimated, i.e. 1.67% (95% CI: 1.04% - 2.31%). We modelled this using a beta distribution. Assuming a minimum of 0%, i.e. the risk on heart failure with trastuzumab will not be lower in comparison with the treatment schedule without trastuzumab, the maximum of this probability function was 3.48%.

In the FinHer trial, no patients developed severe congestive heart failure after trastuzumab. With none out of 116 in the trastuzumab group and 1 out of 116 in the observation group,[23] the risk difference was estimated at -0.86% (95% CI: -2.54% - 0.82%). The maximum was set at 3.48%, i.e. the maximum applied in the distribution for the HERA trial. In other words, a shorter 9-week treatment schedule will most probably not result in more heart problems than a longer 1-year treatment schedule. If a negative value was drawn from the distribution function, 0 automatically replaced it, i.e. adding trastuzumab will not diminish heart failure. The probability distributions for these risk differences are presented in table 29 (b and c).

In the B31/N9831 trial, significant differences in the incidence of CHF were noticed according to post-AC LVEF and age. Similarly, a distinction was made in our model according to LVEF and age. Among 48 patients older than 50 with an LVEF function of 50-54%, nine experienced severe CHF, i.e. a 3 year cumulative incidence of 20% (95% CI, 11.1% - 35.9%). Among 48 patients younger than 50 with an LVEF of 50-54%, three experienced CHF, i.e. a 3-year cumulative incidence of 6.8% (95% CI, 2.3% - 20.5%).[4]

The frequency of severe CHF after trastuzumab was lower in patients with a LVEF of >= 55%. Six out of 389 and 13 out of 356 patients, respectively younger and older than 50, developed severe CHF. We used these data to define the incremental risk difference due to adding trastuzumab treatment (see table 30).

Table 30. Risk of severe CHF after trastuzumab (B31 study)

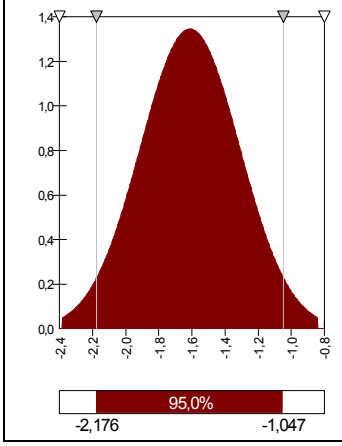
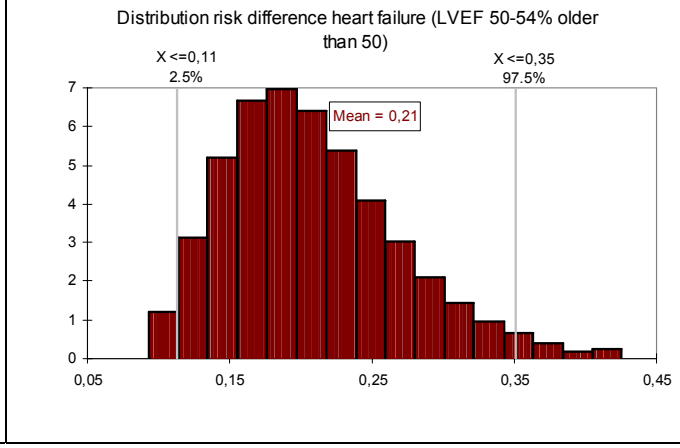
	Younger than 50	Older than 50	All
LVEF 50-54%	6.8%[a] 95% CI: 2.3% - 20.5%	20.0%[a] 95% CI: 11.1% - 35.9%	12/96, i.e. 12.5%[b] 95% CI: 6.63% - 20.82%
LVEF >55%	6/389, i.e. 1.54%[b] 95% CI: 0.57% - 3.33%	13/356, i.e. 3.65%[b] 95% CI: 1.96% - 6.16%	19/745, i.e. 2.55%[b] 95% CI: 1.54% - 3.95%

Source: a: 3-year cumulative incidence [4]; b: [4] and own calculations

On the one hand, one may argue these numbers are an overestimation since the control group had a cumulative incidence of cardiac event of 0.8% (95% CI: 0.3% - 1.9%) and we did not take this into account. We also assumed severe CHF was not completely reversible upon discontinuing trastuzumab. On the other hand, this study defined cardiac event as confirmed class III or IV CHF or possible/probable cardiac death.[4] This description is more limited than symptomatic CHF and therefore these data could even be a more conservative approximation of the real incremental percentage of patients confronted with symptomatic CHF.

To model this uncertainty, and to account for the skewness in the distribution, simulations were based on the log scale, and data were afterwards back transformed with the exponential distribution. Table 31 provides the example for the risk difference for patients older than 50 with a LVEF between 50-54%. The left figure is the initial modelled symmetric distribution of the natural log of the hazard ratios. The right figure presents the resulting distribution after 1000 simulations and applying an exponential function.

Table 31. The modelled risk difference for patients older than 50 and LVEF 50-54%

Ln(0.111) = -2.1982 Ln(0.200) = -1.6094 Ln(0.359) = -1.0244	Exp(-2.1982) = 0.111 Exp(-1.6094) = 0.200 Exp(-1.0244) = 0.359
	

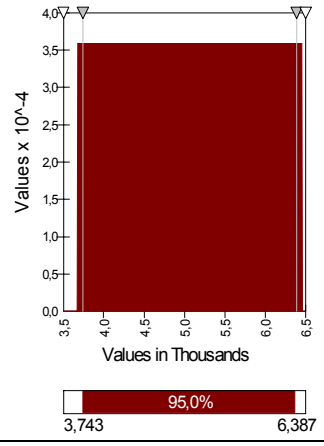
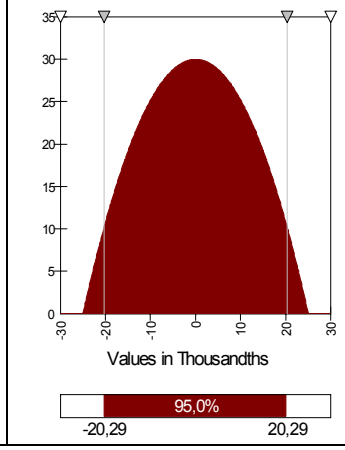
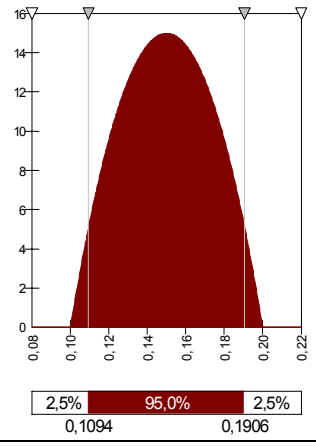
Local recurrence

The short-term cost savings due to preventing local recurrence was also taken into account. Based on expert opinion, the average treatment cost was varied between the cost of mastectomy (3673 euro) and the cost of mastectomy and radiotherapy (6456 euro). Since no further information was found concerning the most appropriate average

point estimate, we applied a uniform distribution on this minimum and maximum value (table 32, a).

Based on literature, the baseline risk, i.e. without trastuzumab treatment, of local recurrence were assumed to be 8%, 10%, and 12% for respectively stage I, II, and III tumours. The uncertainty around these baseline risks was modelled by increasing/decreasing these probabilities with a beta distribution with a maximum/minimum value of +/- 2.5% (table 32, b). The probability distributions of the hazard ratios for patients surviving free of disease were discussed before (see table 24).

Table 32. Probability distributions

a) The cost of treating local recurrence	b) Uncertainty around the baseline risk of local recurrence	c) retesting HER2 if progressing to MBC for patients initially being HER2-negative
		

Variation on eligibility criteria

First of all, based on a study in the UK,[42] we calculated the percentage of patients with LVEF less than 50%. This was 3.74%, 0.61%, 4.68%, 2.48%, 3.7%, 6%, and 10.39% for respectively all patients, and the age categories younger than 50, older than 50, 50-59, 60-69, 70-79, and older than 80 (table 12). Secondly, in trial B31, 233 out of 3497 patients (6.7%) did not start trastuzumab after doxorubicin and cyclophosphamide because they had a decline in LVEF of at least 16% from baseline or a decline below the lower limit of normal (50%) or had cardiac symptoms.[4] Since no such data were provided for the HERA trial, we assumed this probability to be similar. Thirdly, 96 out of 841 patients (11.4%) who started trastuzumab had a LVEF of 50%-54%.[4] As such, the percentage of patients excluded from HERA based on LVEF criteria could be calculated. In the HERA trial, patients were only eligible if they had an LVEF above 55%. For the FinHer trial, the minimum LVEF was 50%. For modelling B31/N9831, we make a distinction between two groups, i.e. 50-54% and more than 55%. Furthermore, we also have to take into account that the second group, i.e. patients not starting trastuzumab after doxorubicin and cyclophosphamide, does not exist in the FinHer trial. The percentage of patients not being eligible for the different trials is presented in table 33.

Table 33. Patients excluded from trial participation based on LVEF, by age

	All	<50	>50	50-59	60-69	70-79	80+
FinHer >=50% LVEF	3.74%	0.61%	4.68%	2.48%	3.70%	6.00%	10.39%
B31 >=50% LVEF	10.44%[a]	7.31%	11.38%	9.18%	10.40%	12.70%	17.09%
HERA, B31 >=55% LVEF	21.08%[b]	17.94%	22.02%	19.82%	21.04%	23.34%	27.72%

a: 10.44% = 3.74% + 6.7%; b: 21.08% = 10.44% + (11.4% x (1-6.7%))

To reflect the uncertainty of these probabilities, we applied a beta distribution on these data with an upper and lower limit of 2.5ppt above and under the point estimate. The graph presenting this uncertainty is presented before in table 32 (b).

Retesting HER2

Several studies have shown that HER2 status might differ between primary breast cancers and corresponding metastases.[59, 58] According to expert opinion, about 15% of patients initially diagnosed with HER2-negative breast cancer and progressing to MBC would be retested. In about one third of these patients the cancer would be HER2-positive. The uncertainty of these probabilities was reflected by applying a beta distribution with an upper and lower limit of 5ppt above and under the point estimate. Table 32 (c) presents the example of the first mentioned probability.

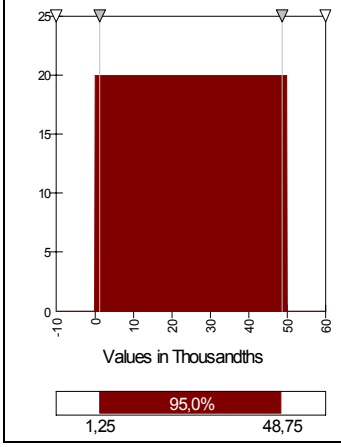
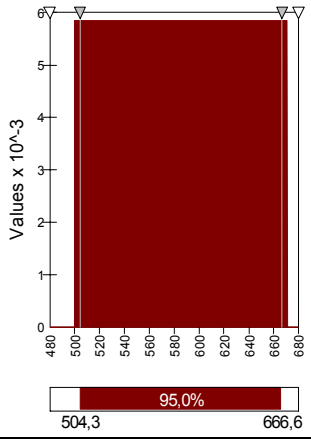
Finally, some correlations were placed on input uncertainties of several variables. In the first place, a perfect correlation of one was implemented on the cost for MBC treatment with and without trastuzumab. In other words, if the average treatment cost for MBC would have been relatively high without trastuzumab, it will also be relatively high with trastuzumab. Secondly, a correlation of 0.8 was placed on the duration of MBC and the cost for treating MBC with and without trastuzumab. In other words, in our opinion, a relatively shorter average duration of MBC is accompanied by a relatively lower average MBC treatment cost.

Probabilistic sensitivity analysis

Probabilistic sensitivity analysis reflects the combined implications of uncertainty in parameters. In the software package '@risk',(DecisionTools Suite 4.5, Palisade, London, UK) the sensitivity analysis can be performed using a rank correlation calculation in which correlation coefficients are calculated between the output values and the sampled input values. This helps determining the importance of the different parameters behind the model on the results.

The uncertainty on the input variables is discussed in the previous part. However, we included also two extra variables in our probabilistic sensitivity analysis. In the first place, we included the discount rate applied on both costs and benefits. Normally, as mentioned before, the choice of the discount rate is mainly a normative issue. To assess the sensitivity of the results to the discount rate applied, different scenarios should and will be presented. However, to be able to provide a more visual presentation of the relative importance of the discount rate, we also included this variable in our probabilistic sensitivity analysis by varying both values uniformly between 0% and 5% (table 34). Secondly, the price of trastuzumab was 670.91 euro per vial of 150 mg. The importance of this price on the ICER could be assessed by varying it in our sensitivity analysis. We applied a uniform distribution with the current price as a maximum and a price reduction of about 25% as a minimum (table 34). Remark that the results of our probabilistic sensitivity analysis will be presented both without and with the inclusion of variability on the discount rates and price of trastuzumab.

Table 34. Extra probability distributions for sensitivity analysis

Discount rate	Price of trastuzumab
	

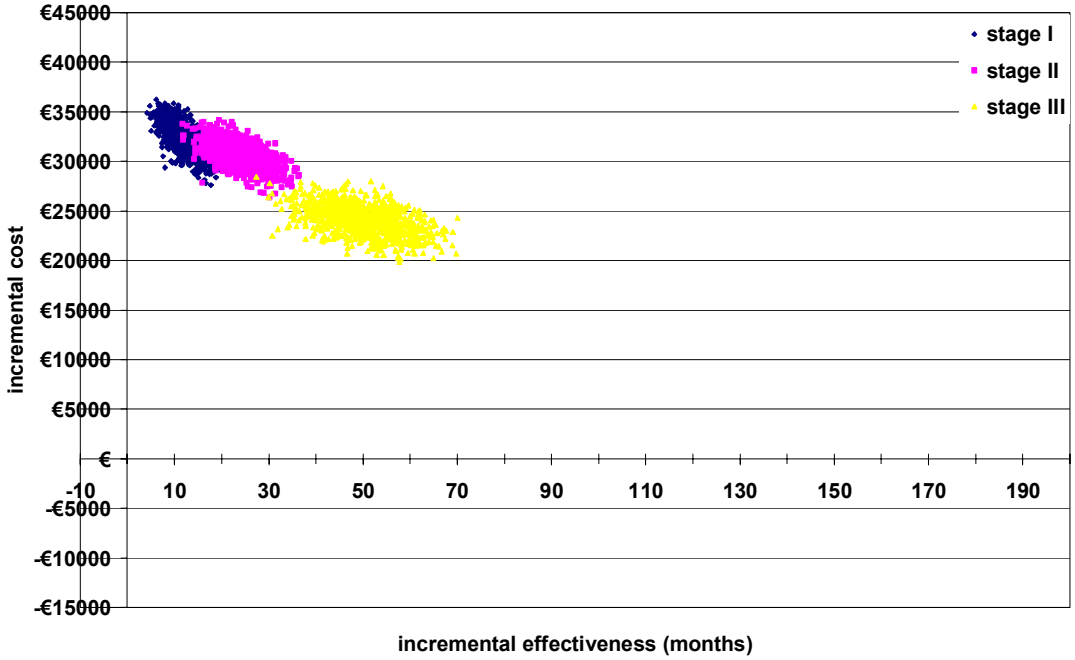
4.1.2 Results

Results of our 1000 Monte Carlo simulations are presented on the cost-effectiveness plane. This shows the incremental costs per trastuzumab treated patient (y-axis) and the resulting incremental effectiveness, i.e. life gained expressed in months (x-axis). Results for HERA, FinHer, and B31/N9831 are discussed respectively.

4.1.2.1 HERA

Figure 6 presents the uncertainty around the costs and effects for trastuzumab treatment as in the HERA trial and for all patients. Each dot represents one of the 1000 simulations. The incremental cost per life-year gained was 34 999 euro (95% CI: 19 493 – 64 322), 16 026 euro (95% CI: 10 553 – 24 064), and 5994 euro (95% CI: 4160 – 8540) for stage I, II, and III breast cancer respectively (table 35). In general, this means that for the HERA trial, trastuzumab treatment is very cost-effective for patients with stage III breast cancer, also cost-effective for stage II, and less cost-effective for stage I.

Figure 6. Cost-effectiveness plane HERA trial (stage I, II, and III; all patients)



The mean number of life-months gained varied from 11.99 months to 23.88 months and 49.74 months for stage I, II, and III. Estimates of the mean incremental cost per trastuzumab treated patient varied from 32 320 euro (95% CI: 29 244 – 35 103) for stage I, to 30 608 euro (95% CI: 28 152 – 33 093) for stage II, and 24 202 euro (95% CI: 21 301 – 26 813) for stage III breast cancer patients (table 35). Even though the same hazard ratios are applied across stages, these differences, both for costs and effectiveness, can be explained by the difference in baseline risk. In stage I, relatively less patients initially, i.e. without trastuzumab treatment, progress to MBC when comparing with stage III breast cancer patients. The same relative benefit is translated in a higher absolute benefit for a higher stage of breast cancer. Consequently, more MBC can be prevented in a higher stage breast cancer population, which results in more life years gained and lower incremental costs.

Table 35. The ICER and 95%CI for the HERA trial (All patients)

	Stage I	Stage II	Stage III
IE (months)	11.99	23.88	49.74
2.5%	6.48	15.91	35.48
97.5%	18.06	32.85	63.98
IC (euro)	32 320	30 608	24 202
2.5%	29 244	28 152	21 301
97.5%	35 103	33 093	26 813
ICER (euro/LY)	34 999	16 026	5994
2.5%	19 493	10 553	4160
97.5%	64 322	24 064	8540

The problem with the previous analysis is that it does not differentiate between age categories. Life-years gained and incremental costs are mean values for the whole population. To be able to provide more clear information, age groups were set up with their own specific characteristics. The following figures present the cost-effectiveness plane for trastuzumab treatment as in the HERA trial according to five age categories, i.e. younger than 50, 50-59, 60-69, 70-79, and older than 80. To be able to compare results across our discussion, the same axis are used on the figures and the incremental effectiveness, incremental cost, and ICER is mentioned in the tables for the general analysis, i.e. without making a difference according to age, and the five subgroups.

Figure 7. Cost-effectiveness plane HERA trial (stage I; according to age)

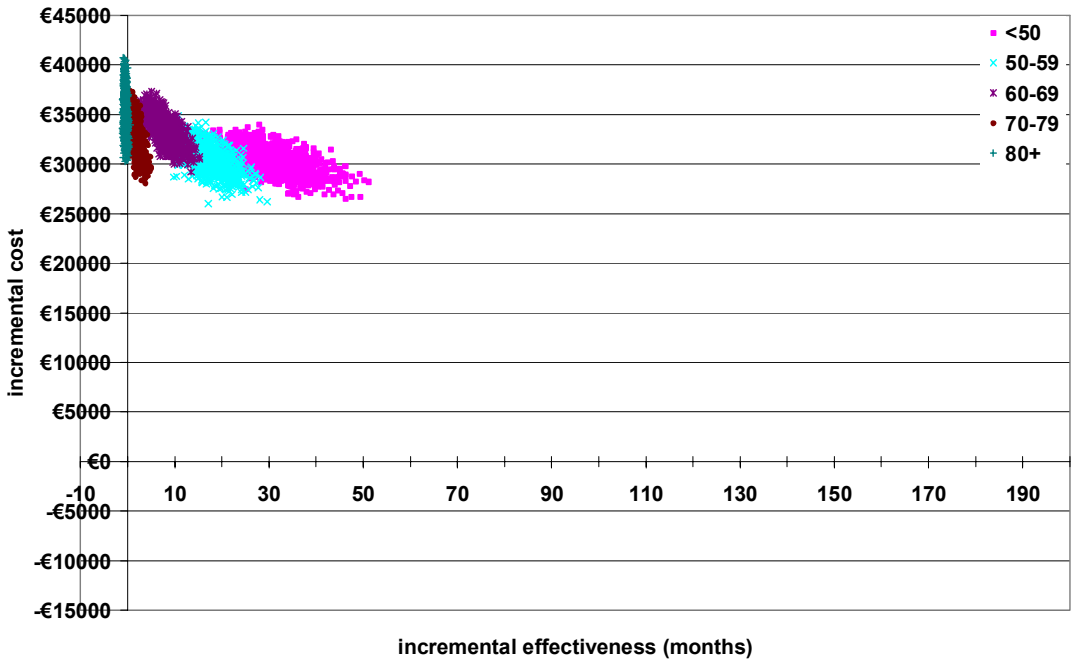


Figure 7 and table 36 show the results for stage I breast cancer patients. It is clear that age is a very important determining factor with better outcomes for younger age categories. In the first place, the baseline risk of progressing to MBC is relatively higher for younger age categories, which results in a higher absolute benefit of patients not progressing due to trastuzumab treatment. Secondly, if patients do not progress to MBC, relatively more life-years are gained when a patients is younger. Whereas cost-effectiveness of trastuzumab for stage I patients is rather borderline when looking at all patients (34 999 euro), it is cost-effective for patients younger than 60, but not cost-effective for the other groups. For patients between 60 and 69 years old, the 1000

simulations provided an ICER of 55 502 euro with a degree of uncertainty as characterized by the 95% confidence interval, which ranged from 28 960 euro to 107 728 euro (table 36). For the age categories 70-79 and older than 80, some dots were even situated in the fourth quadrant, i.e. negative IC with higher incremental costs. On the one hand, due to the small baseline risk of progressing to MBC, the percentage point improvement of patients not progressing to MBC is very small for patients older than 80 with stage I breast cancer eligible for trastuzumab treatment. On the other hand, all these patients are exposed to the danger of heart failure. At the end, the balance of these two factors is on average negative. Furthermore, we have to remark that the risk difference of heart failure was not subdivided according to our age categories. It can be expected that heart problems would be relatively higher in older patients. If this would be the case, our results would be reinforced, i.e. more cost-effective for younger patients and the other way around for older patients categories.

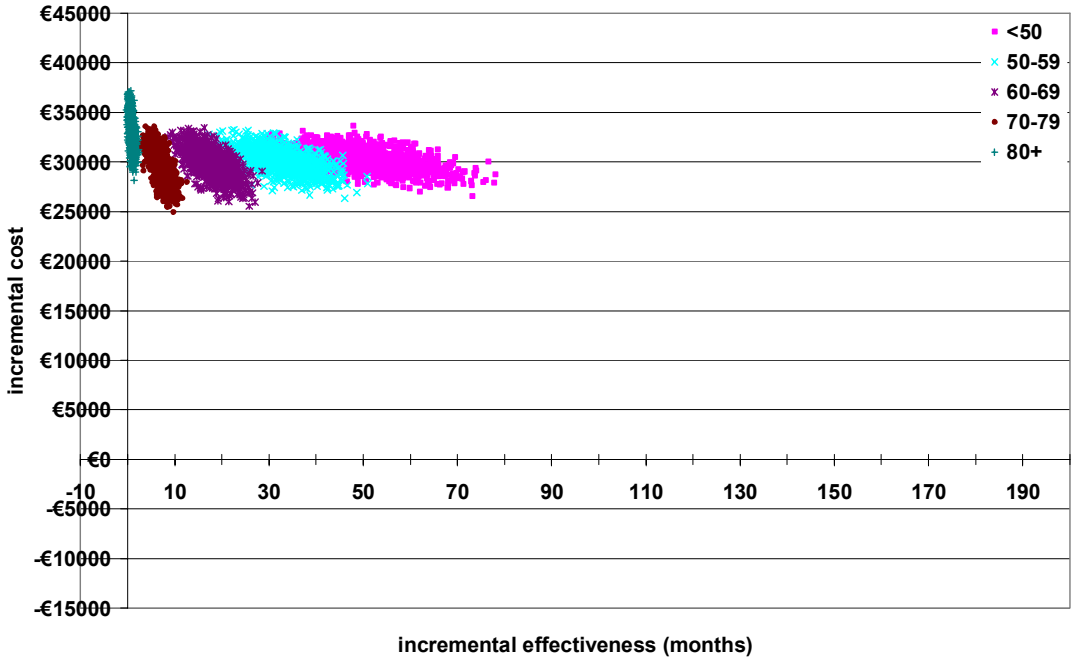
Table 36. The ICER and 95%CI for the HERA trial and stage I breast cancers (all age categories)

	All	<50	50-59	60-69	70-79	80+
IE (months)	11.99	31.06	16.74	8.02	1.88	-0.44
2.5%	6.48	19.58	9.73	3.89	0.19	-0.91
97.5%	18.06	43.86	24.27	12.90	3.94	0.11
IC (euro)	32 320	30 357	30 732	33 472	32 897	35 472
2.5%	29 244	27 774	27 786	30 766	29 349	31 205
97.5%	35 103	32 839	33 440	36 134	36 278	39 635
ICER (euro/LY)	34 999	12 289	23 510	55 502	/[a]	/
2.5%	19 493	7739	14 161	28 960	/	/
97.5%	64 322	18 952	39 736	107 728	/	/

a: since some of the dots cross one of the axis, mean results for the ICER are difficult to interpret. Therefore, only incremental effectiveness and costs are provided.

The shape of the two-dimensional distribution of our 1000 dots is different according to our age categories. Concerning the range of the incremental costs, no big differences are noticed. This is due to a combination of factors. First of all, the initial treatment cost is the same for all patient groups. Secondly, relatively more patients can be prevented from progressing to metastatic breast cancer in a younger population. However, the involved cost savings are discounted over a longer period, resulting in similar incremental costs. On the effectiveness side, the range is relatively larger for a younger population in comparison with older patients. In the first place, an equal distribution on the hazard ratio free of distant recurrence results in a wider distribution of the absolute benefit if the baseline risk is higher. Second, in a population with younger patients, the number of life-years gained due to trastuzumab treatment or lost due to heart failure is also relatively high. This explains the wider distribution of incremental effectiveness for younger patients.

Figure 8. Cost-effectiveness plane HERA trial (stage II; according to age)



As mentioned before, the cost-effectiveness analysis provides better results for stage II in comparison with stage I. Table 37 provides our results more in detail. Similar findings are found concerning the differences across age categories, i.e. much better results for younger populations in comparison with older ones (figure 8). In comparison with stage I breast cancer, treatment becomes cost-effective for more patients, i.e. also for the age category 60-69. Negative incremental effectiveness is only found in 0.9% of our 1000 simulations for the population of patients older than 80.

Table 37. The ICER and 95%CI for the HERA trial and stage II breast cancers (all age categories)

	All	<50	50-59	60-69	70-79	80+
IE (months)	23.88	51.92	32.81	17.78	6.90	0.86
2.5%	15.91	35.57	21.54	11.41	3.83	0.09
97.5%	32.85	69.03	44.36	24.47	10.16	1.78
IC (euro)	30 608	30 247	30 101	29 836	29 809	33 317
2.5%	28 152	27 980	27 647	26 887	26 409	30 174
97.5%	33 093	32 436	32 508	32 548	32 609	36 350
ICER (euro/LY)	16 026	7220	11 426	21 096	55 518	/
2.5%	10 553	4958	7715	13 468	32 248	/
97.5%	24 064	10 623	17 434	32 718	97 978	/

Figure 9. Cost-effectiveness plane HERA trial (stage III; according to age)

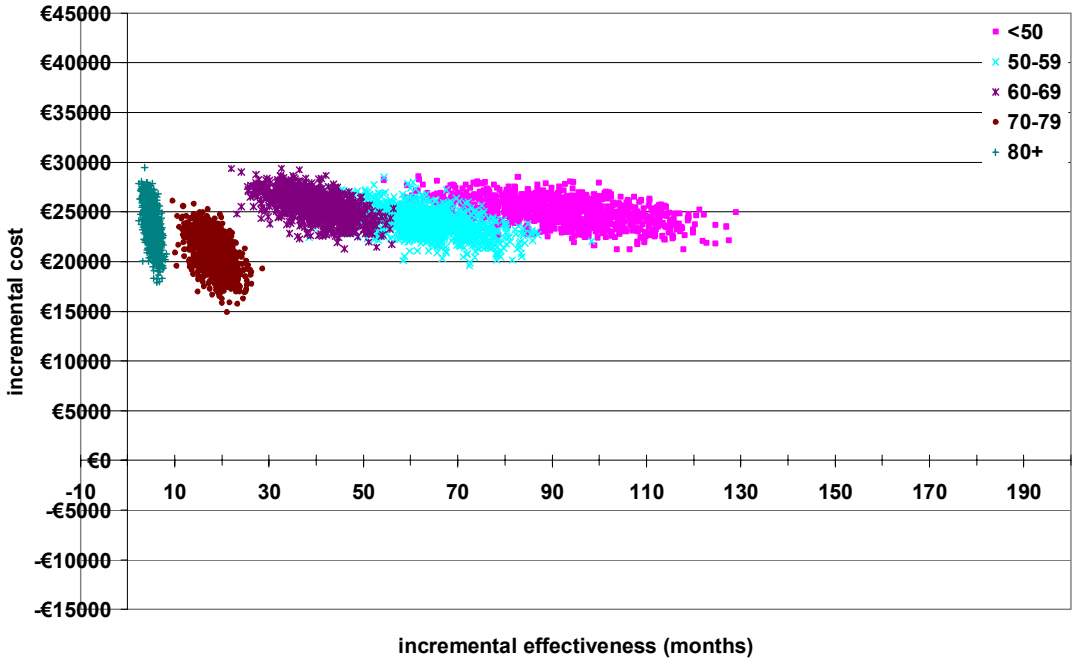


Figure 9 and table 38 show the cost per life-year gained by trastuzumab treatment for stage III breast cancer. Very favourable ICERs are found for all age categories, with exception of patients older than 80 (57 802 euro; 95%CI: 35 276 – 94 291). In contrast with stage I and II breast cancer patients in the age category 70-79, treatment becomes cost-effective with an estimated ICER of 14 197 euro (95% CI: 9069 – 22 041).

Table 38. The ICER and 95%CI for the HERA trial and stage III breast cancers (all age categories)

	All	<50	50-59	60-69	70-79	80+
IE (months)	49.74	91.26	62.84	39.68	18.26	5.18
2.5%	35.48	65.10	45.36	27.83	12.51	3.28
97.5%	63.98	116.86	80.72	51.72	23.77	7.20
IC (euro)	24 202	25 066	23 990	25 604	20 875	23 756
2.5%	21 301	22 529	21 091	22 841	17 298	19 948
97.5%	26 813	27 545	26 754	28 096	24 325	27 187
ICER (euro/LY)	5994	3383	4709	7970	14 197	57 802
2.5%	4160	2400	3242	5466	9069	35 276
97.5%	8540	4864	6700	11 653	22 041	94 291

One may wonder why the relative position of the 1000 simulations of the different age categories on the cost side slightly changes when comparing the figures for stage I, II, and III. Our estimations result from a combination of more than one factor. It is not only the absolute benefit of patients not progressing to MBC, but for example also the period over which these costs have to be discounted. On the one hand, the first factor, i.e. absolute benefit, is relatively smaller in older age categories. On the other hand, the time to progression is also smaller for these populations. As such, the life-years gained and future cost savings have to be discounted over a smaller period. In other words, it is a combination of more than one factor which determines the relative position of our 1000 dots plotted on the cost-effectiveness plane. There are so many factors influencing the ICER, which are listed before. Consequently, only modelling can provide a clear view on the outcomes.

4.1.2.2 FinHer

Figure 10. Cost-effectiveness plane HERA versus FinHer trial (stage I, II, and III; all patients)

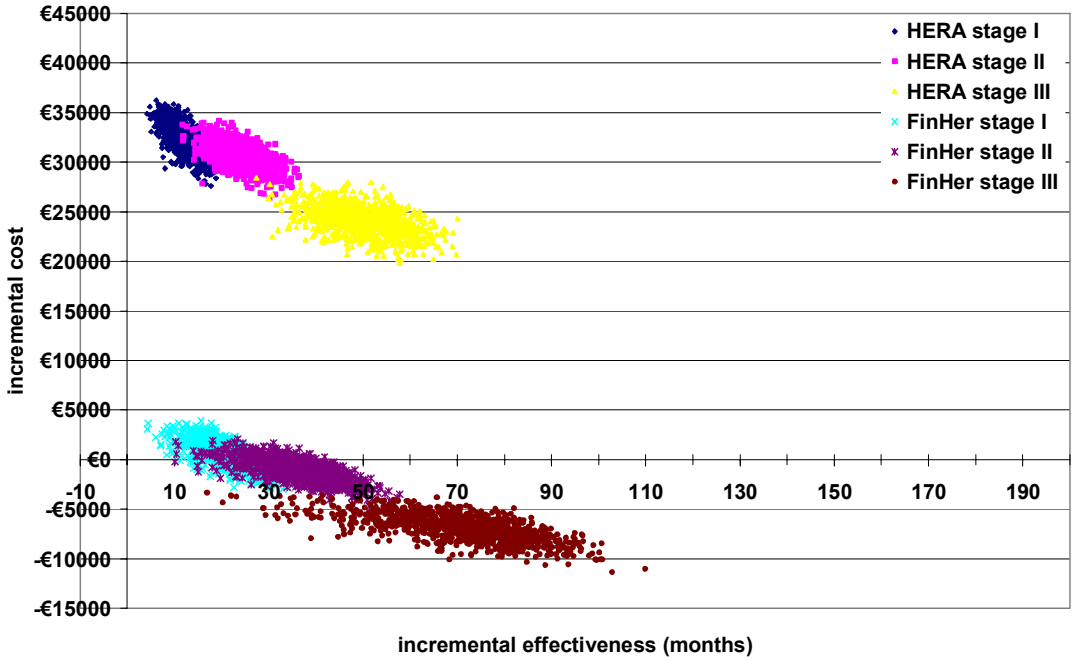
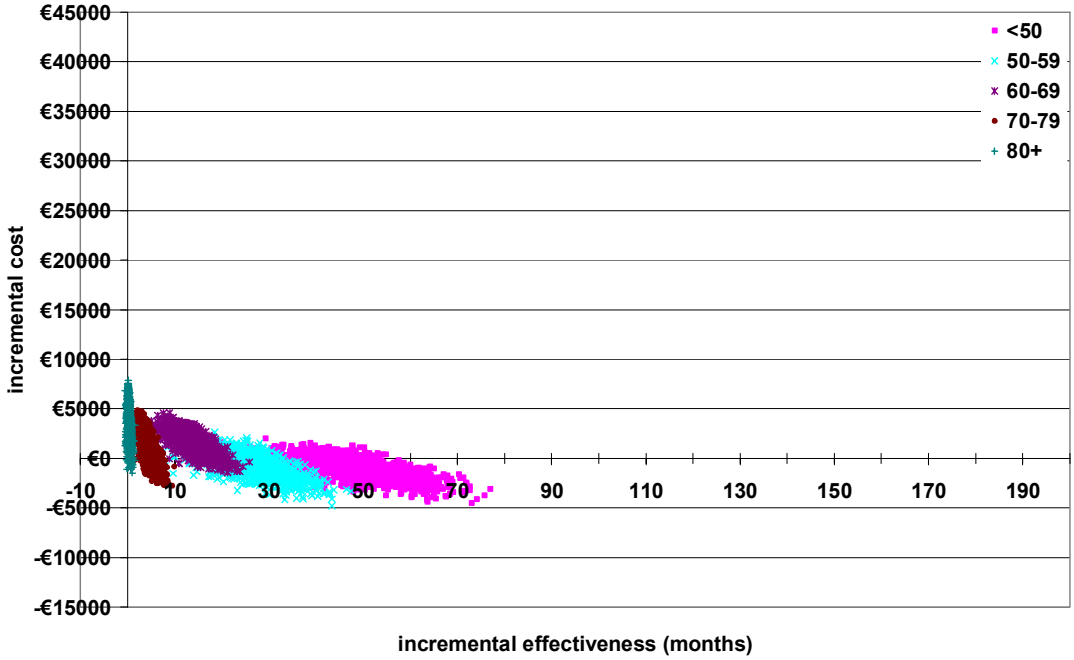


Figure 10 shows the results of our simulations for both the HERA and FinHer trials for stage I, II, and III breast cancer patients. The modelled FinHer trial results provide better cost-effectiveness results in comparison with the HERA trial. First of all, the incremental effectiveness is situated more to the right on the x-axis and has a wider range. The uncertainty on this outcome is higher than in the HERA trial due to the larger confidence interval of the hazard ratio free of distant recurrence for the FinHer trial. Secondly, the incremental cost in the FinHer trial is much lower than in the HERA trial, which is mainly due to the different treatment duration. It is remarkable that a lot of the simulation results for the FinHer trial fall in the dominant quadrant of the cost-effectiveness plane. 30.9%, 79.9%, and 100% of all simulations are situated in this second quadrant for respectively stage I, II, and III breast cancer. In fact, this means that cost savings can be generated. On average, the incremental costs are respectively 668, -1045, and -6869 euro for stage I, II, and III (table 39). The initial 'investment' to administer trastuzumab as in the treatment schedule of the FinHer trial could be counterweighted by the discounted future savings due to preventing more people not to progress to MBC. In the following part, these results are discussed more in detail per stage and according to age.

Table 39. The ICER and 95%CI for the FinHer trial (All patients)

	Stage I	Stage II	Stage III
IE (months)	20.35	36.09	70.33
2.5%	10.21	19.12	38.63
97.5%	30.13	50.15	94.54
IC (euro)	668	-1045	-6869
2.5%	-2033	-3244	-9522
97.5%	3040	1100	-4327
ICER (euro/LY)	/	/	-1195
2.5%	/	/	-1764
97.5%	/	/	-868

Figure 11. Cost-effectiveness plane FinHer trial (stage I; according to age)



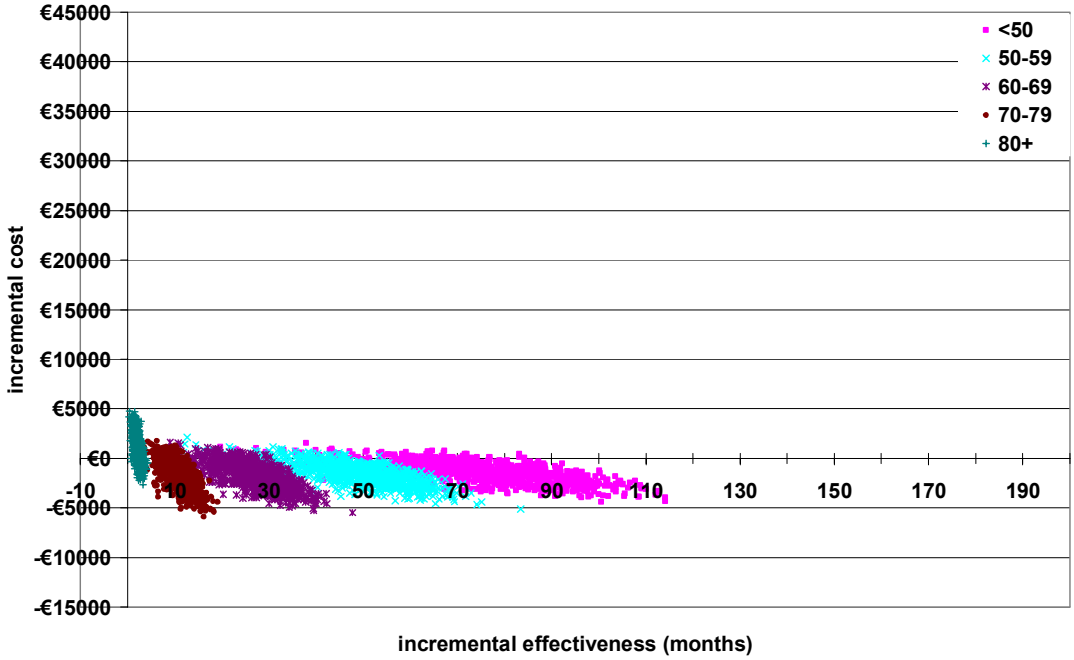
To make simulation results of the FinHer trial comparable with those of the HERA trial, results are presented on a similar cost-effectiveness plane, i.e. with the same axis (figure 11). In comparison with the HERA trial (figure 7), trastuzumab treatment becomes more cost-effective. In the age categories of patients younger than 50 and between 50 and 59, on average, net cost savings could even be generated (table 40). For the HERA trial, treatment of stage I breast cancer patients with trastuzumab was not cost-effective for the three highest age categories, i.e. 60-69, 70-79, and 80+. This is only the case for 80+ with the shorter treatment schedule. The strategy of administering trastuzumab is dominant in 79.5%, 68.5%, 10.6%, 25.1%, and 2.1% of simulations for respectively the age categories younger than 50, 50-59, 60-69, 70-79, and older than 80. When comparing incremental effectiveness and costs for the several age categories, only treatment of patients older than 80 could be questioned due to the small incremental effectiveness of 0.33 months on average (95% CI: -0.24 – 0.97).

Table 40. The ICER and 95%CI for the FinHer trial and stage I breast cancers (all age categories)

	All	<50	50-59	60-69	70-79	80+
IE (months)	20.35	48.34	27.39	14.22	4.54	0.33
2.5%	10.21	25.23	14.18	6.92	2.04	-0.24
97.5%	30.13	67.12	39.95	21.05	7.50	0.97
IC (euro)	668	-1057	-724	1570	1198	3513
2.5%	-2033	-3364	-3262	-718	-1841	56
97.5%	3040	1000	1649	3696	4147	7001

Remark: since simulation results are in different quadrants of the cost-effectiveness plane no ICERs are provided.

Figure 12. Cost-effectiveness plane FinHer trial (stage II; according to age)

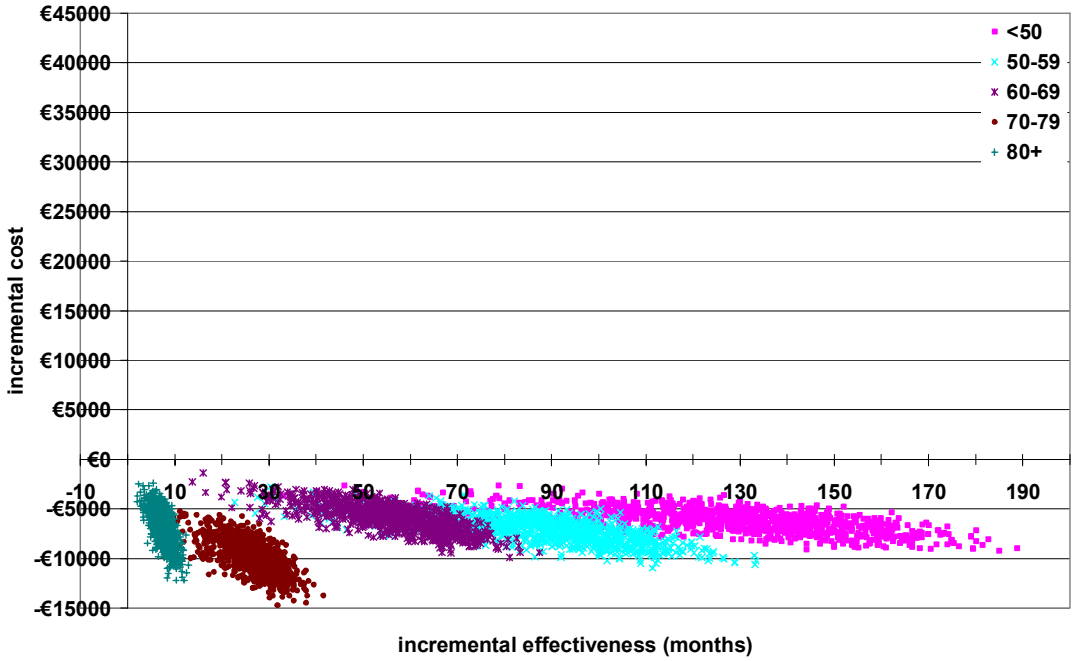


Similarly as for stage I, the short treatment schedule of the FinHer trial is more cost-effective for stage II breast cancer treatment than the longer HERA treatment schedule (figure 12 versus 8). Again, the situation is better for stage II breast cancer patients in comparison with stage I due to the higher baseline risk. Treatment becomes dominant in about 90% of our simulations, i.e. 91.5%, 92.7%, 90.8%, and 86.4% for patients younger than 50, 50-59, 60-69, and 70-79. This results in mean net savings of respectively 1413, 1559, 1766, and 1716 euro (table 41). For patients older than 80 trastuzumab treatment is dominant in 17.8% of our simulations. Even though this subgroup has a relatively low incremental effectiveness of 2.06 months (95% CI: 0.90 – 3.46), treatment can be seen as cost-effective due to the low average incremental costs, i.e. 1427 euro (95% CI: -1296 – 3993).

Table 41. The ICER and 95%CI for the FinHer trial and stage II breast cancers (all age categories)

	All	<50	50-59	60-69	70-79	80+
IE (months)	36.09	75.97	48.65	27.16	11.19	2.06
2.5%	19.12	39.91	26.29	14.11	5.78	0.90
97.5%	50.15	103.12	65.69	38.00	16.18	3.46
IC (euro)	-1045	-1413	-1559	-1766	-1716	1427
2.5%	-3244	-3341	-3783	-4142	-4489	-1296
97.5%	1100	537	527	540	865	3993

Figure 13. Cost-effectiveness plane FinHer trial (stage III; according to age)



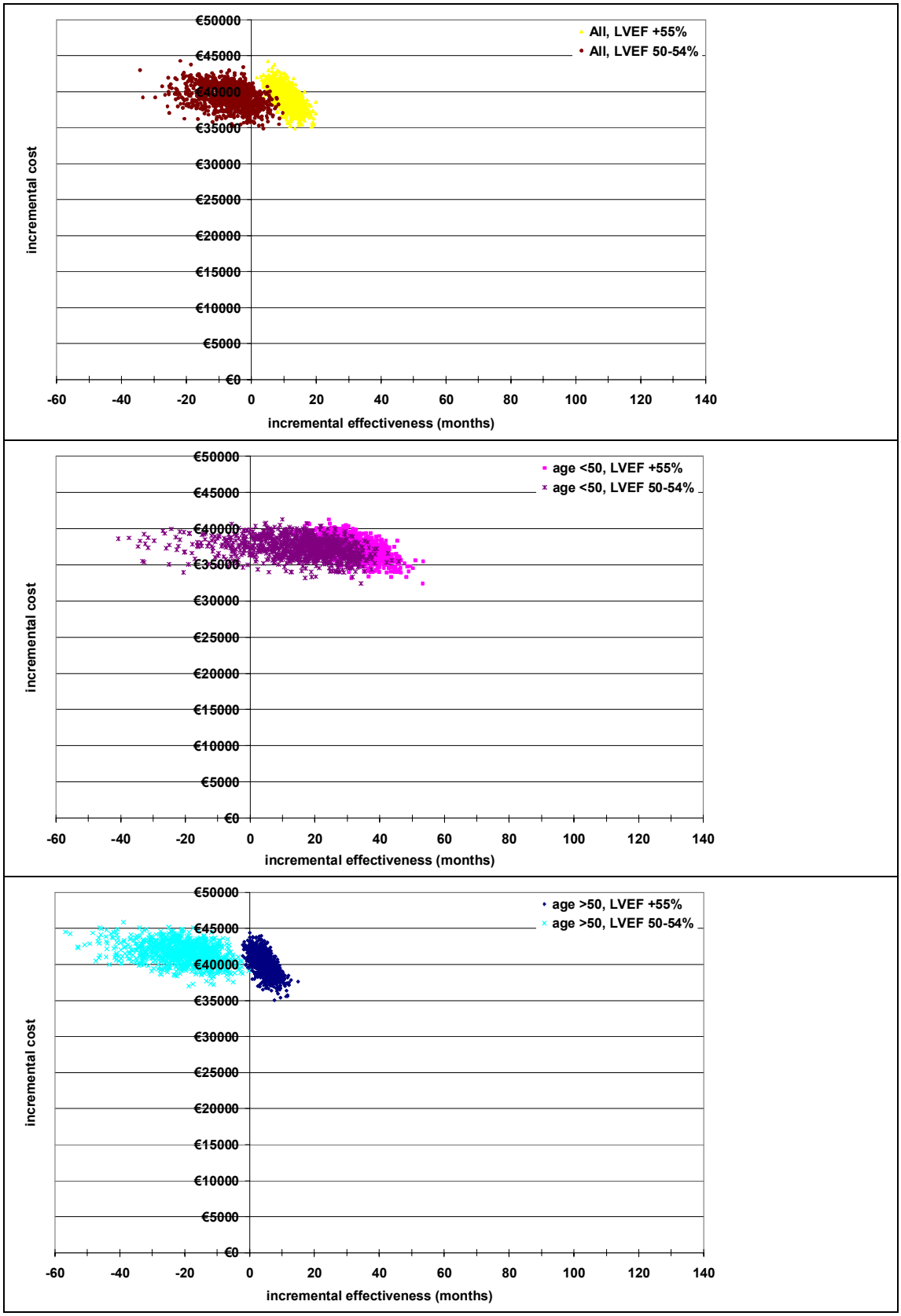
For stage III breast cancer patients, treatment with trastuzumab for 9 weeks is a dominant strategy in 100% of our simulations for all age categories. All dots are distributed over the second quadrant (figure 13). For all age categories of stage III breast cancer patients, positive health gains are generated due to trastuzumab treatment, which are not smaller than in the HERA trial (figure 9). Moreover, the initial higher cost for adding trastuzumab to adjuvant treatment is counterbalanced by the discounted savings due to preventing more people not to progress to MBC. These cost savings range on average form 5887 to 9714 euro (table 42). With results located entirely in the lower right quadrant of the cost-effectiveness plane, decision makers do not have to hesitate.

Table 42. The ICER and 95%CI for the FinHer trial and stage III breast cancers (all age categories)

	All	<50	50-59	60-69	70-79	80+
IE (months)	70.33	127.95	88.44	56.16	26.25	7.80
2.5%	38.63	69.23	47.42	29.95	14.29	3.97
97.5%	94.54	169.53	117.81	74.92	35.26	11.14
IC (euro)	-6869	-6134	-7117	-5887	-9714	-6978
2.5%	-9522	-8474	-9684	-8441	-12 934	-10 341
97.5%	-4327	-3895	-4573	-3322	-6376	-3807

4.1.2.3 B31-N9831

Figure 14. Cost-effectiveness plane B31/N9831 trial (stage I; according to age and LVEF)



Heart failure is the most important side effect of trastuzumab treatment. The B31 trial shows that both the post-AC LVEF and patient age were independent prognostic variables for severe heart failure after trastuzumab. The published data provided us input to analyse the influence of LVEF. Results are discussed in the following part.

First of all, when looking at the 1000 simulated dots for all patients with stage I breast cancer and LVEF above 55% (figure 14) and comparing with the HERA trial (figure 6), incremental effectiveness is very similar between the two trials, i.e. 10.82 (95% CI: 5 – 16.94) versus 11.99 months (95% CI: 6.48 – 18.06). Concerning the costs, the B31/N9831 trial leads to higher incremental costs, i.e. 39 310 (95% CI: 36 269 – 42 124) versus 32 320 euro (95% CI: 29 244 – 35 103). This is due to the fact that the B31 trial applies a weekly schedule, instead of a 3-weekly schedule, resulting in higher incremental administration costs (table 43 versus 35).

When looking at the impact of a lower LVEF on incremental costs, the influence is rather minimal. In contrast, the influence on the incremental effectiveness is of greater importance. In the first graph of figure 14, all patients are regarded, i.e. no distinction is made according to age. Whereas the incremental effectiveness was on average 10.82 months (95% CI: 5 – 16.94) with a LVEF above 55%, this was on average –7.05 months (95% CI: -22.71 – 5.03) with a LVEF of 50-54% (table 43). For the latter, life-years are lost. On the one hand, due to the relative low baseline risk, the absolute benefit of people not progressing to MBC is also low. On the other hand, all treated patients are exposed to the risk of heart failure, which is much higher in the category of patients with a low LVEF.

However, a distinction can be made according to age. In both our groups of patients younger and older than 50, a lower LVEF provides dots which are plotted more to the left. However, this loss is much more obvious for older patients than younger ones. The strategy of administering trastuzumab is even dominated for patients older than 50 with a LVEF lower than 55%, i.e. the incremental effectiveness is on average -20.74 (95% CI: -42.40 – -6.06) whereas the incremental costs are positive (table 43).

Table 43. The ICER and 95%CI for the B31-N9831 trial and stage I breast cancers

	LVEF +55%			LVEF 50-54%		
	All	<50	>50	All	<50	>50
IE (months)	10.82	32.50	4.84	-7.05	14.50	-20.74
2.5%	5.00	19.70	-0.33	-22.71	-20.38	-42.40
97.5%	16.94	44.88	10.12	5.03	34.42	-6.06
IC (euro)	39 310	37 314	40 059	40 565	38 554	41 580
2.5%	36 269	34 502	37 035	37 771	35 892	38 743
97.5%	42 124	39 890	42 977	43 197	40 919	44 471
ICER (euro/LY)	48 881	14 454	/	/	/	/
2.5%	26 222	9411	/	/	/	/
97.5%	98 039	23 651	/	/	/	/

Figure 15. Cost-effectiveness plane B31/N9831 trial (stage II; according to age and LVEF)

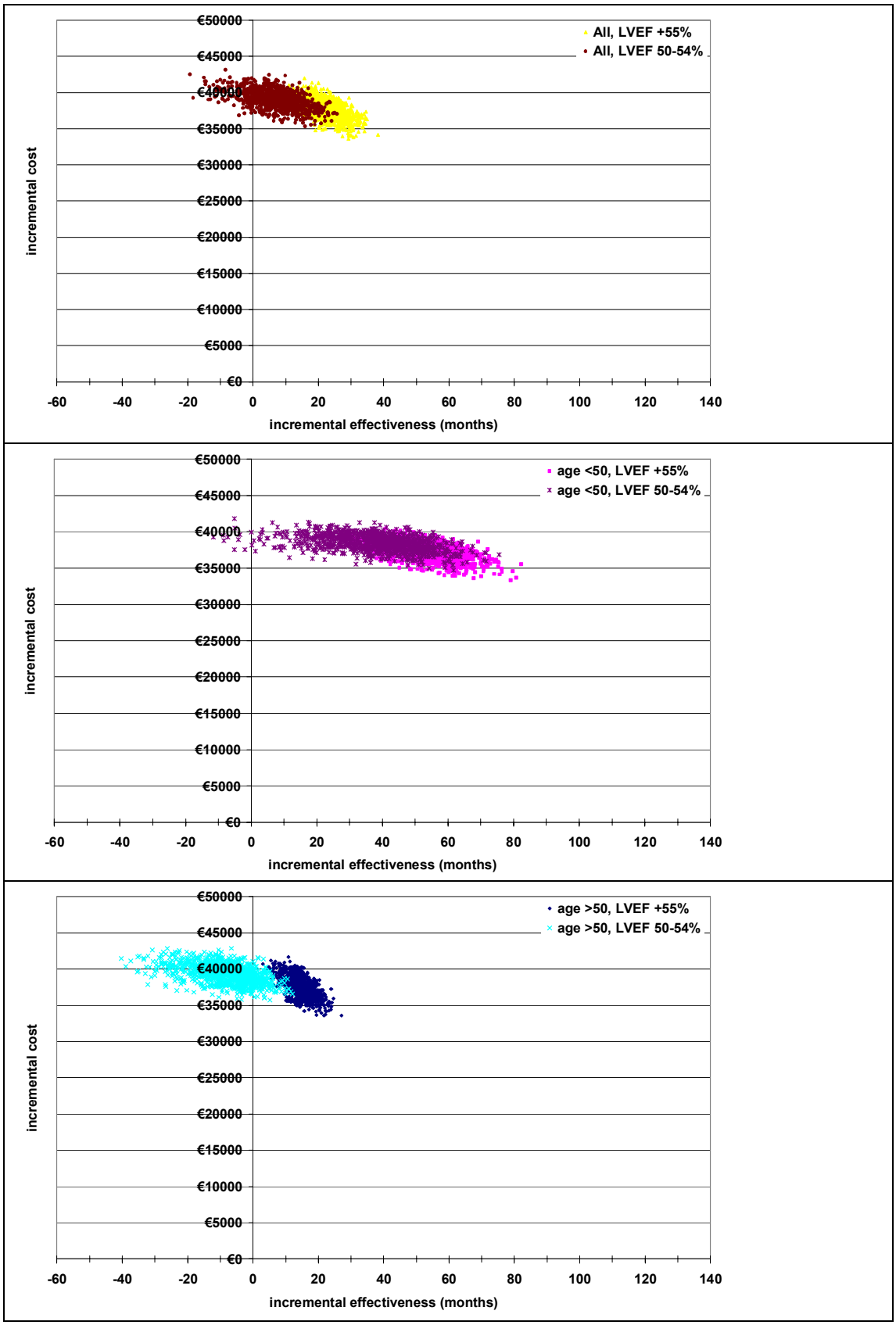


Table 44. The ICER and 95%CI for the B31-N9831 trial and stage II breast cancers

	LVEF +55%			LVEF 50-54%		
	All	<50	>50	All	<50	>50
IE (months)	23.20	53.92	14.65	7.11	38.00	-8.50
2.5%	14.79	36.95	7.57	-9.40	7.15	-28.64
97.5%	32.11	70.81	21.82	20.56	61.54	5.95
IC (euro)	37 579	37 184	37 525	38 993	38 407	39 301
2.5%	34 953	34 627	34 905	36 643	36 036	36 806
97.5%	40 244	39 510	40 245	41 532	40 535	41 901
ICER (euro/LY)	20 328	8543	33 285	/	/	/
2.5%	13 328	5978	19 388	/	/	/
97.5%	31 707	12 519	61 466	/	/	/

Similar conclusions can be drawn for stage II breast cancer patients (figure 15). For patients with a LVEF of more than 55%, incremental effectiveness is always positive. For a lower LVEF, this is not the case. Whereas the incremental effectiveness is clearly positive for younger patients, i.e. on average 38 months (95% CI: 7.15 – 61.54), this is on average -8.5 months (95% CI: -28.64 – 5.95) for older patients (table 44).

As with the results of the other two trials, results are most cost-effective for stage III breast cancer patients. The dots on the cost-effectiveness plane of figure 16 are situated more favourably in comparison with the previous two figures. Even for older patients with a low LVEF, the life-years gained due to preventing progression to MBC are higher than the life-years lost due to heart failure resulting in an incremental effectiveness of 17.78 months (95% CI: -0.09 – 33.45) (table 45). This was not the case for stage I and II breast cancer patients.

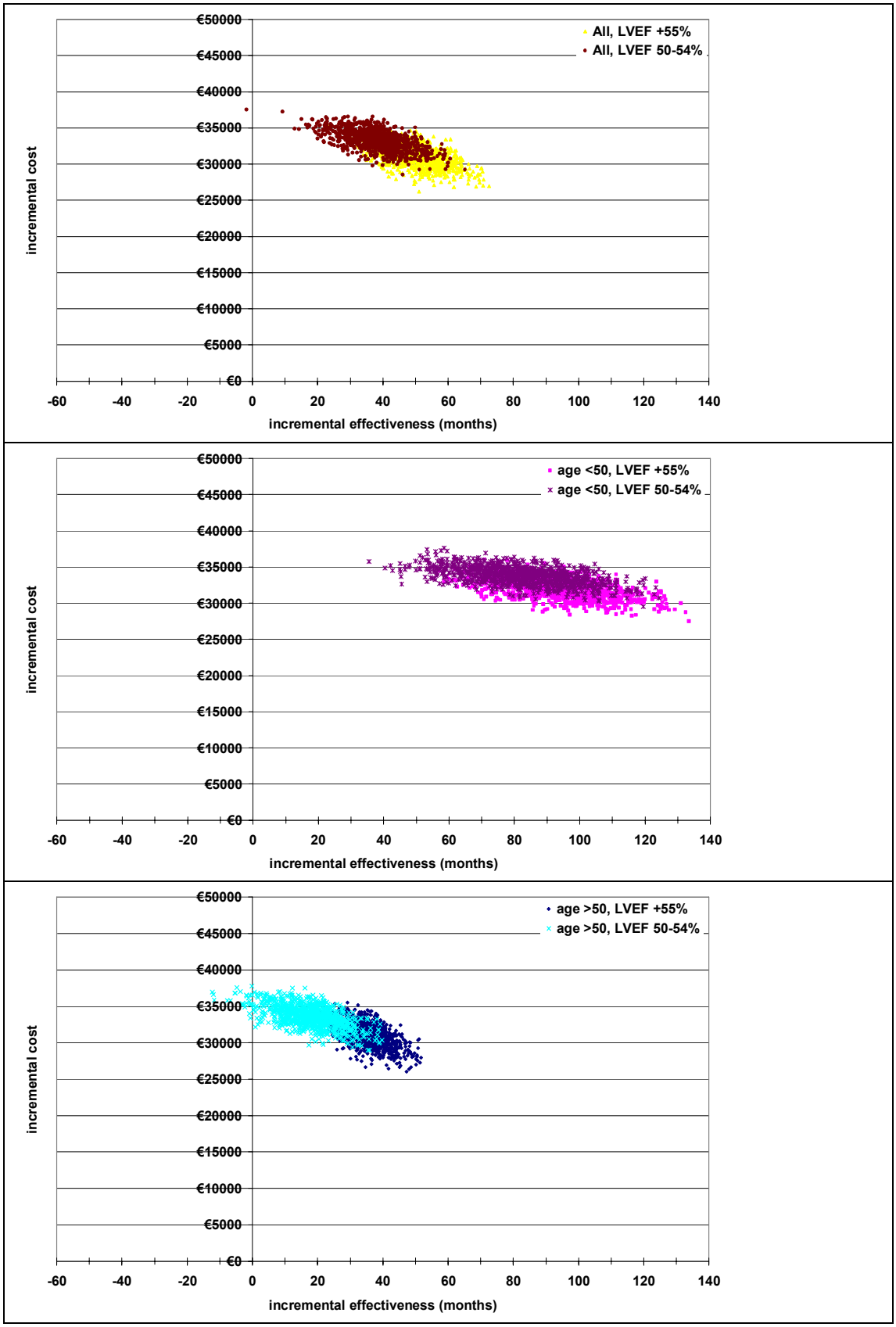
Table 45. The ICER and 95%CI for the B31-N9831 trial and stage III breast cancers

	LVEF +55%			LVEF 50-54%		
	All	<50	>50	All	<50	>50
IE (months)	50.15	94.24	35.66	37.94	82.28	17.78
2.5%	35.64	67.81	24.75	21.46	53.23	-0.09
97.5%	64.48	122.78	47.26	54.28	111.07	33.45
IC (euro)	31 145	31 973	31 095	33 290	33 783	33 649
2.5%	28 193	29 241	27 859	30 580	31 236	30 510
97.5%	33 904	34 394	34 079	35 833	36 104	36 540
ICER (euro/LY)	10 798	4173	7655	/	5132	/
2.5%	7255	3024	5319	/	3430	/
97.5%	15 831	5791	10 823	/	7976	/

In general, administering trastuzumab may do more harm than good in older patients with a low LVEF. For younger patients, trastuzumab treatment could be considered. First of all, the risk on heart failure is lower in comparison with older patients with the same LVEF. Secondly, the baseline risk is higher for younger patients than for older ones, resulting in a higher percentage point improvement, and more life-years can be gained if these patients do not progress to MBC. At the end, especially for stage I and II breast cancer patients, the balance of health gains and losses can be negative for older patients with a low LVEF whereas this is more positive for younger patients.

The HERA trial did not include patients with a LVEF of less than 55%. However, a difference may exist between trial inclusion criteria and real-world conditions. This observation based on B31 published trial results may also be appropriate for the HERA trial which also administers trastuzumab for one year. Decision makers should be aware of this. For the FinHer trial, which did not exclude these patients with a lower LVEF, this does not seem to be a problem.

Figure 16. Cost-effectiveness plane B31/N9831 trial (stage III; according to age and LVEF)



4.1.2.4 Scenario analysis

Scenario analysis is a modelling technique to determine how changes in input data affect the output of the model. As described before (see 'modelling'), we set up four scenarios which are compared with a base case. The base case (or default) scenario is indicated on figure 17 as scenario 1. In this scenario, the following four assumptions are made: trastuzumab is not re-administered in MBC if patients already received the drug in adjuvant setting, MBC treatment costs are not increased, the percentage of unused trastuzumab is taken into account, and finally, the effect of trastuzumab on the development of brain metastases is included.

The following four scenarios each time change one of these assumptions. The results for stage II breast cancer patients for both the HERA and FinHer trial are presented on the cost-effectiveness plane (figure 17) and in table 46 and 47.

In the second scenario, the influence of re-administering trastuzumab in MBC is analysed. For these patients, the undiscounted MBC treatment cost increases on average with 17 828 euro, i.e. the difference between 31 878 and 14 050 euro, due to adding trastuzumab treatment. This is smaller than the cost of a complete one-year treatment since trastuzumab is administered until disease progression (appendix 5). However, the influence on incremental costs is clear. Compared with the baseline scenario, incremental costs are much higher, i.e. 36 764 euro (95% CI: 34 729 – 38 698) versus 30 608 euro (95% CI: 28 152 – 33 093) for the HERA trial (table 46). As mentioned before (part 'modelling: re-administration of trastuzumab in MBC'), incremental effectiveness did not change since we do not know whether re-administering trastuzumab after progression would increase survival of MBC. Altering this assumption would not have a large influence on our results because the relatively small amount of life-months gained in MBC also has to be discounted since we are making an evaluation of trastuzumab in adjuvant setting.

The third scenario increases the cost of MBC treatment with 5000 euro. This results in a slightly better incremental cost-effectiveness ratio. If the modelled MBC treatment costs are higher, preventing women from progressing will result in higher cost savings. The impact is much less than the increase of 5000 euro. First of all, the absolute percentage point improvement of patients not progressing to MBC has to be taken into account. And secondly, these costs savings are discounted since they occur in the future. The impact would be higher for subgroups with a higher baseline risk and a shorter time to progression. Changing the cost of MBC treatment of course does not have an impact on incremental effectiveness.

Figure 17. Scenario analysis (HERA and FinHer trials)

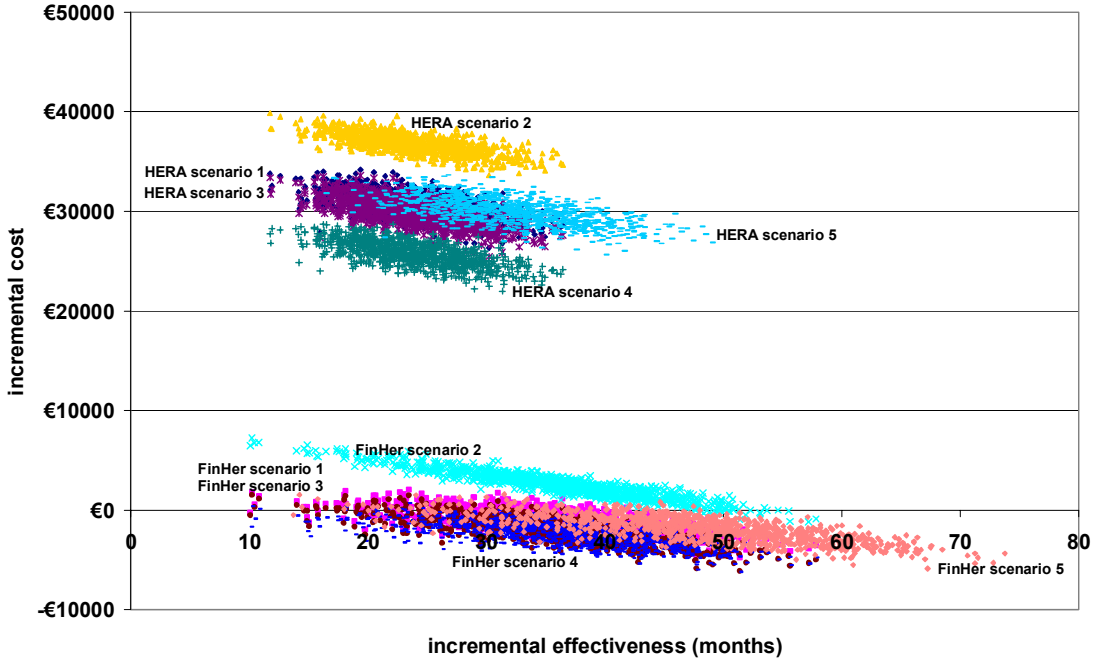


Table 46. Scenario analysis (HERA trial, stage II, all patients)

	Scenario 1	Scenario 2	Scenario 3	Scenario 4	Scenario 5
IE (months)	23.88	23.88	23.88	23.88	32.16
2.5%	15.91	15.91	15.91	15.91	21.91
97.5%	32.85	32.85	32.85	32.85	43.10
IC (euro)	30 608	36 764	29 908	25 791	30 034
2.5%	28 152	34 729	27 346	23 386	27 511
97.5%	33 093	38 698	32 522	28 052	32 532
ICER (euro/LY)	16 026	19 226	15 672	13 516	11 620
2.5%	10 553	12 898	10 206	8733	7770
97.5%	24 064	28 673	23 695	20 612	16 957

In the fourth scenario, the influence of not taking into account the percentage of waste is analysed. About 15% and 25% was not administered in respectively a 3-weekly and weekly schedule. As for the previous scenarios, this does not change effectiveness. However, it has a relatively big influence on incremental costs. These cost savings arise immediately, i.e. they do not have to be discounted. Even though the percentage of waste is larger in a weekly schedule, the incremental cost savings are larger in monetary terms for the HERA trial due to the longer treatment schedule. Incremental costs are on average 25 791 (95% CI: 23 386 – 28 052) instead of 30 608 (95% CI: 28 152 – 33 093) for the HERA trial and -2473 (95% CI: -4679 – -402) instead of -1045 (95% CI: -3244 – 1100) for the FinHer trial. In general, a lot of money could be economized if this problem of unused drugs is (partly) resolved.

Table 47. Scenario analysis (FinHer trial, stage II, all patients)

	Scenario 1	Scenario 2	Scenario 3	Scenario 4	Scenario 5
IE (months)	36.09	36.09	36.09	36.09	47.53
2.5%	19.12	19.12	19.12	19.12	25.34
97.5%	50.15	50.15	50.15	50.15	65.31
IC (euro)	-1045	2588	-1996	-2473	-1822
2.5%	-3244	19	-4539	-4679	-4247
97.5%	1100	5443	447	-402	528

Next, the fifth scenario presents the influence of not taking into account the possible problem of trastuzumab not being able to prevent the development of brain metastasis. As shown on the cost-effectiveness plane (figure 17), this would increase the number of life-years gained resulting in a more favourable cost-effectiveness ratio. Incremental costs slightly decrease since MBC could also be prevented for this proportion of our population. Secondly, more life years are gained if progression to MBC is not just postponed but avoided. Longer-term follow-up will provide more information. We preferred to apply the more conservative approach in our reference case analysis.

Finally, six scenarios were modelled with respect to the applied discount rate for costs and benefits. Figure 18 presents the cost-effectiveness acceptability curves for these scenarios for the HERA trial and stage II breast cancer patients. This curve presents the probability (y-axis) that treatment is cost-effective depending on the value of a life-year (x-axis). Curves more to the left indicate a more favourable cost-effectiveness ratio.

According to the Belgian guidelines, future costs are discounted at a rate of 3% and benefits at 1.5% for the reference case. This provides an ICER of 16 026 euro (95% CI: 10 553 – 24 064) (table 48). The confidence interval of this scenario is indicated on the graph. The acceptability curves show that cost-effectiveness strongly depends on the applied discount rate. Not discounting both costs and benefits results in much more favourable cost-effectiveness ratios, i.e. on average 5791 euro (95% CI: 3395 – 9121). In this scenario, with a ceiling ratio set to 10 000 euro, 98.8% of our 1000 simulations provide a cost-effective outcome. The opposite is true when 5% discount rates are considered, which increases the ICER to 34 445 euro (95% CI: 22 952 – 51 757). In this scenario, with a higher ceiling ratio of 20 000 euro, our intervention is not cost-effective with a probability of 99.9%. This observation is completely rational since health gains and cost-savings due to preventing more people to progress to MBC are situated in the future. The discount rate has a large impact on both incremental effectiveness and costs. IC changes from 11 948 (95% CI: 9347 – 14 408) to 39 657 euro (95% CI: 37 102 – 42 273) with respectively discount rates of 0% and 5%. IE changes from 14.41 (95% CI: 9.48 – 19.88) to 25.92 months (17.26 – 35.74) with respectively discount rates of 5% and 0%.When comparing results with other studies, it is obvious that discount rate is an important determining variable. This report provides results for the reference case.

Figure 18. Cost-acceptability curves according to the applied discount scenario (HERA trial, stage II, all patients)

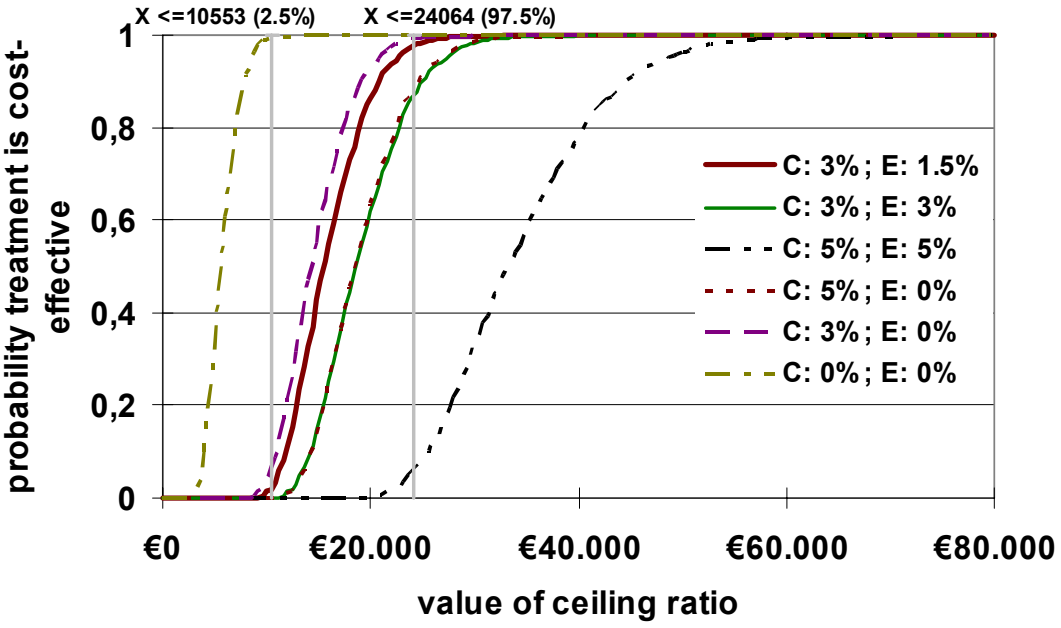


Table 48. Discount rate scenarios (HERA trial, stage II, all patients)

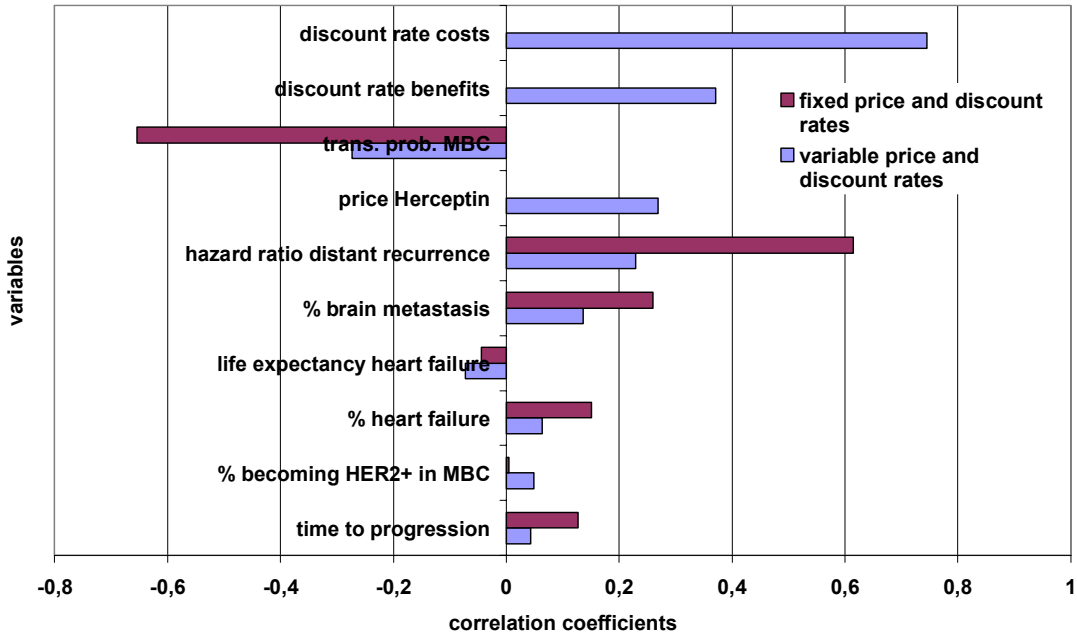
	C: 3%; E: 1.5%	C: 3%; E: 3%	C: 5%; E: 5%	C: 5%; E: 0%	C: 3%; E: 0%	C: 0%; E: 0%
IE (months)	23.88	19.90	14.41	25.92	25.92	25.92
2.5%	15.91	13.21	9.48	17.26	17.26	17.26
97.5%	32.85	27.37	19.88	35.74	35.74	35.74
IC (euro)	30 608	30 608	39 657	39 657	30 608	11 948
2.5%	28 152	28 152	37 102	37 102	28 152	9347
97.5%	33 093	33 093	42 273	42 273	33 093	14 408
ICER (euro/LY)	16 026	19 239	34 445	19 110	14 762	5791
2.5%	10 553	12 676	22 952	12 913	9716	3395
97.5%	24 064	29 038	51 757	28 290	22 120	9121

4.1.2.5 Probabilistic sensitivity analysis

The rationale for probabilistic sensitivity analysis is primarily based on a consideration of the needs of decision makers in assessing the consequences of decision uncertainty. If health technology assessment is to be based on a correct analysis of all available data, then probabilistic methods must be used both for sensitivity analysis and for estimation of expected costs and benefits.[70]

The results of our probabilistic sensitivity analysis after 1000 Monte Carlo simulations are presented in figure 19 for two scenarios. In contrast with the second scenario, discount rates and the price of trastuzumab are fixed in the first scenario. Longer bars represent the more important input variables. Only the 10 most important variables are shown.

Figure 19. Sensitivity analysis (HERA trial, stage II, all patients)



In the first scenario, i.e. with a fixed price for trastuzumab and the reference case discount rates, the transition probability of progressing to MBC and the hazard ratio of distant recurrence are the most important variables. The combination of these two variables determines the absolute improvement of people not progressing to MBC. The correlation coefficient of the transition probability of progressing to MBC has a negative sign. The higher the baseline risk, the more people can be cured in absolute numbers, which results in a better (lower) ICER. Incorporating discount rates as variables

decreases the importance of these variables. As shown in our previous scenario analysis, the discount rates determine the present value of future health gains and cost savings. As expected, the correlation coefficient of the price of trastuzumab is also relatively large. A lower price would have a very positive effect on the ICER and budget impact. Furthermore, it is important to notice that the percentage of brain metastasis and heart failure are also important determining variables which should not be omitted. Finally, it should be remarked that results of a probabilistic sensitivity analysis depend on the uncertainty placed on the input variables. For example, our scenario analysis on waste (see 'scenario analysis') showed that avoiding drugs to be thrown away does have a large impact on outcomes. Nevertheless, this variable does not appear in the list of top ten most important variables. This is because the distribution of the mean was included and not an uncertainty starting at 0%. In other words, the distribution of the input variables is of importance for the outcome of such an analysis and therefore should be interpreted with caution.

4.2 BUDGET IMPACT ANALYSIS

4.2.1 Number of patients eligible for trastuzumab in early breast cancer

For each stage and age-class, we have estimated the numbers of patients fulfilling 2 conditions: expression of neu-HER2 assayed by FISH and treatment by chemotherapy. The results were previously shown in table 6.

We have then accounted for the risk of heart failure either before or after anthracycline treatment (table 49). The incidence of heart failure in the general population and the risk of severe congestive heart failure after anthracyclines and trastuzumab according to the age were calculated for the age structure of the breast cancer population and have already been detailed in part 'Variation on eligibility criteria'.

Table 49. Percentage of Belgian women not eligible for trastuzumab due to heart problems

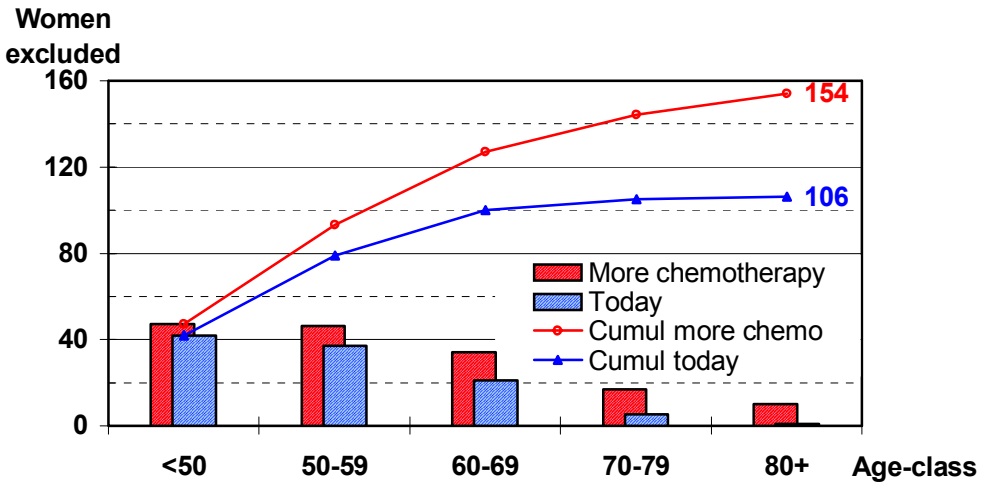
Age-class	LVEF ≥50%§	Before anthracyclines LVEF ≥50%	After anthracyclines* LVEF ≥55%
<50	0.61%	0.61%	17.94%
50-59	2.48%	2.48%	19.82%
60-69	3.70%	3.70%	21.04%
70-79	6.00%	6.00%	23.34%
80+	10.39%	10.39%	27.72%
ALL	3.74%	3.74%	21.08%

§LVEF : left ventricular ejection fraction assessed by echocardiography or multiple gated acquisition; from Davis, Lancet, 2001, recalculated for the 2005 Belgian age-distribution of invasive breast cancers

*After a cumulative dose of 240 mg/m^2 doxorubicin, 6.70% had a strong LVEF drop and 11.40% x (1- 6.70%) or 10.64% had a LVEF of 50-54%.(Romond, 2005)

The choice to start trastuzumab before or after anthracyclines has important consequences with regard to the number of women who are at risk of heart failure and thus would lead to the exclusion of many patients if the trastuzumab treatment starts after completion of the chemotherapy. Since chemotherapy is far more frequent in women under the age of 60, it is in that group that most of the exclusions will occur. The figure 20 shows how many women are not eligible in the actual pattern of care (today) and in the hypothesis where more of them start chemotherapy (more chemotherapy). A minimum of 106 out of 597 women will loose the benefit of a trastuzumab treatment if this drug is proposed after completion of the chemotherapy.

Figure 20. Patients with stages I, II and III to be excluded for insufficient LVEF after previous anthracycline treatment



Today: Patients neu-HER2 FISH positive, treated with adjuvant chemotherapy.
More chemotherapy: Actual chemo + 50% of the chemo naïve FISH positive patients with LVEF ≥50% at start of trastuzumab treatment.

Finally, as the results of the association of chemotherapy and trastuzumab are quite positive, we have arbitrarily assumed that 50% of the neu-HER2 positive patients who are not yet treated by chemotherapy could choose a more aggressive therapy in order to maximize their chances of cure (= more chemotherapy). The next three tables (50, 51 and 52) give the detailed figures for the stages I, II and III.

Table 50. Number of eligible patients with stage I in 2005

Stage I	FISH positive	Chemo today*	Chemo & LVEF ≥50%	More chemo-therapy	Chemo & LVEF ≥55%	More chemo-therapy
Age			T 9 weeks	T 9 weeks	T 52 weeks	T 52 weeks
<50	84	43	43	63	35	52
50-59	112	32	31	70	26	58
60-69	116	22	21	66	17	54
70-79	47	3	3	24	2	19
80+	19	0	0	9	0	7
ALL	378	100	98	232	80	190

*Chemo today: Patients neu-HER2 FISH positive, treated with adjuvant chemotherapy.
Chemo & LVEF ≥50% (or ≥55%): Patients neu-HER2 FISH positive, treated with adjuvant chemotherapy and LVEF ≥50% (or ≥55%) at start of trastuzumab treatment.
More chemotherapy: Actual chemo + 50% of the chemo naïve FISH positive patients & LVEF ≥50% (or ≥55%) at start of trastuzumab treatment.
T 9 weeks: trastuzumab 9-week schedule
T 52 weeks: trastuzumab 52-week schedule

Table 51. Number of eligible patients with stage II in 2005

Stage II	FISH positive	Chemo today*	Chemo & LVEF ≥50%	More chemo-therapy	Chemo & LVEF ≥55%	More chemo-therapy
Age			T 9 weeks	T 9 weeks	T 52 weeks	T 52 weeks
<50	150	136	135	142	112	117
50-59	149	127	124	135	102	111
60-69	103	55	53	76	43	62
70-79	85	13	12	46	10	38
80+	59	0	0	26	0	21
ALL	546	331	324	425	267	349

Table 52. Number of eligible patients with stage III in 2005

Stage III	FISH positive	*Chemo today	Chemo & LVEF ≥50%	More chemo-therapy	Chemo & LVEF ≥55%	More chemo-therapy
Age			T 9 weeks	T 9 weeks	T 52 weeks	T 52 weeks
<50	67	64	64	65	53	54
50-59	59	54	53	55	43	45
60-69	53	45	43	47	36	39
70-79	40	14	13	25	11	21
80+	26	2	2	13	1	10
ALL	245	179	175	205	144	169

4.2.2 Cost of the different trastuzumab regimens

The figures 21, 22 and 23 illustrate the costs of drugs and of use of a day-care facility from a societal perspective (reimbursement rates applied by the INAMI-RIZIV and personal contribution if any) for the 3 analyzed trials.

Figure 21. Detailed costs of chemotherapy in the FinHer setting

Cycle	Diag				1	2	3	4	5	6	7	8	9	1			2			3							
Week	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	
				Mast	H4	H2	H2	H2	H2	H2	H2	H2	H2	F600			F600			F600								E
				or	D100-80			D100-80			D100-80			E60			E60			E60								N
				Lump										C600			C600			C600			Rx therapy					D

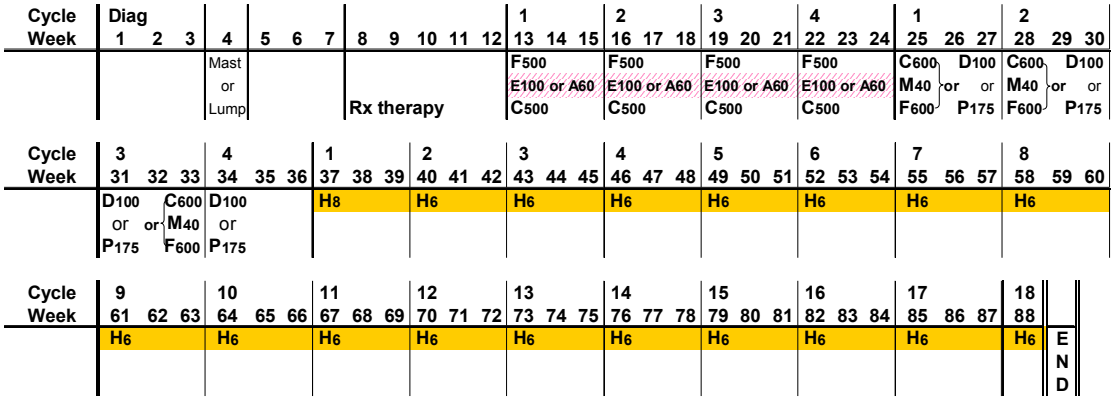
Herceptin is administered immediately before anthracyclines.
$D_{100\text{-}80}$ = Docetaxel 100-80 mg/m² every 3 weeks
H_4 = Herceptin 4 mg/kg
H_2 = Herceptin 2 mg/kg weekly

Duration of the treatment is 27 weeks (12 day care).
F_{60} 5-fluorouracil 600 mg/m² every 3 weeks
E_{60} = Epirubicin 60 mg/m² every 3 weeks
C_{600} = Cyclophosphamide 600 mg/m² every 3 weeks

Surface	1,75m²
Weight	63,9 kg

	Dose	Cost/cycle	Cost per regimen		Cost per regimen
3 cycles					
docetaxel 90 mg/m²	157,5 mg	1.311,00 €	**3.933,00 €**		
dexamethasone	45,0 mg	5,13 €	**15,39 €**		
daycare (3)		245,98 €	**737,94 €**		
9 cycles of which 3 concurrent with docetaxel					
1 x trastuzumab 4 mg/kg	255,6 mg	1.143,23 €			**1.143,23 €**
1 x unavoidable waste 22,2%	56,7 mg	253,80 €			253,80 €
8 x trastuzumab 2 mg/kg	127,8 mg	571,62 €			**4.572,92 €**
8 x unavoidable waste 26,7%	34,1 mg	152,62 €			1.220,97 €
daycare (6)		245,98 €			**1.475,88 €**
3 cycles					
5-fluorouracil 600 mg/m²	1.050 mg	10,00 €	**29,99 €**		
epirubicin 60 mg/m²	105,0 mg	196,32 €	**588,96 €**		
cyclophosphamide 600 mg/m²	1.050 mg	5,77 €	**17,32 €**		
daycare (3)		245,98 €	**737,94 €**		
TOTAL DRUGS			**4.584,66 €**		**7.190,92 €**
Daycare stays			**1.475,88 €**		**1.475,88 €**
TOTAL			**6.060,54 €**		**8.666,80 €**
GRAND TOTAL FinHER				**14.727,34 €**	

Figure 22. Detailed costs of chemotherapy in the HERA setting



Mastectomy or breast conservative surgery, radio- and chemotherapy must be completed before starting Herceptin treatment.

Herceptin was administered after anthracyclines.

Duration of the treatment is 88 weeks (26 day care).

F500 = 5-fluorouracil 500 mg/m² every 3 weeks
C500 = Cyclophosphamide 500 mg/m² every 3 weeks
P175 = Paclitaxel 175 mg/m² every 3 weeks
M40 = Methotrexate 40 mg/m² twice every 4 weeks
H8 = Herceptin 8 mg/kg

E100 = Epirubicin 100 mg/m² every 3 weeks
D100 = Docetaxel 100 mg/m² every 3 weeks
C600 = Cyclophosphamide 600 mg/m² twice every 4 weeks
F600 = 5-fluorouracil 600 mg/m² twice every 4 weeks
H6 = Herceptin 6 mg/kg every 3 weeks

Surface	1,75m²
Weight	63,9 kg

	Dose	Cost/cycle	Cost per regimen		Cost per regimen
4 cycles					
5-fluorouracil 500 mg/m²	875 mg	7,83 €	**31,33 €**		
epirubicin 100 mg/m² (67% of patients) or	175 mg	324,12 €	**864,32 €**		
doxorubicin 60 mg/m² (33% of patients)	105 mg	131,56 €	**175,41 €**		
cyclophosphamide 500 mg/m²	875 mg	4,29 €	**17,17 €**		
daycare (4)		245,98 €	**983,92 €**		
4 cycles for 25% of patients					
docetaxel 100 mg/m² (10% of patients)	175 mg	1.480,23 €	**592,09 €**		
or					
paclitaxel 175 mg/m² (15% of patients)	306 mg	1.202,07 €	**721,24 €**		
daycare (4*25%)		245,98 €	**245,98 €**		
or					
3 cycles for 75% of patients					
2 x cyclophosphamide 600 mg/m²	1.050 mg	5,77 €	**25,98 €**		
2 x méthotrexate 40 mg/m²	70 mg	15,70 €	**70,65 €**		
2 x 5-fluorouracil 600 mg/m²	1.050 mg	10,00 €	**44,98 €**		
daycare (6*75%)		245,98 €	**1.106,91 €**		
18 cycles					
1 x trastuzumab 8 mg/kg	511,2 mg	2.286,46 €			**2.286,46 €**
1 x unavoidable waste 10,6%	54,2 mg	242,36 €			242,36 €
17 x trastuzumab 6 mg/kg	383,4 mg	1.714,85 €			**29.152,38 €**
17 x unavoidable waste 15,6%	59,8 mg	267,52 €			4.547,77 €
daycare (18)		245,98 €			**4.427,64 €**
TOTAL DRUGS			**2.543,17 €**		**36.228,98 €**
Daycare stays			**2.336,81 €**		**4.427,64 €**
TOTAL			**4.879,98 €**		**40.656,62 €**
GRAND TOTAL HERA				**45.536,60 €**	

Cost per regimen = cost per cycle x number cycles x percentage of patients treated in that way

Figure 23. Detailed costs of chemotherapy in the N9831 & B31 settings

The N9831- B31 studies

Cycle	Diag				1			2			3			4			1	2	3	4	5	6	7	8	9	10	11	12	13	14
Week	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
				Mast or Lump	A60 C600			A60 C600			A60 C600			A60 C600			H4 P80	H2 P80	H2 P80	H2 P80	H2 P80	H2 P80	H2 P80	H2 P80	H2 P80	H2 P80	H2 P80	H2 P80	H2 Rx	H2

Cycle	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44
Week	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60
	H2	H2	H2	H2	H2	H2	H2	H2	H2	H2	H2	H2	H2	H2	H2	H2	H2	H2	H2	H2	H2	H2	H2	H2	H2	H2	H2	H2	H2	H2
	Rx																													

Cycle	45	46	47	48	49	50	51	52	
Week	61	62	63	64	65	66	67	68	
	H2	H2	H2	H2	H2	H2	H2	H2	END

Herceptin is administered immediately after anthracyclines.

A60 = Doxorubicin 60 mg/m² every 3 weeks
P80 = Paclitaxel 80 mg/m² weekly
Rx = Radiotherapy

Duration of the treatment is 68 weeks (56 day care).

C600 = Cyclophosphamide 600 mg/m² every 3 weeks
H4 = Herceptin 4 mg/kg
H2 = Herceptin 2 mg/kg weekly

Surface	1,75m²
Weight	63,9 kg

	Dose	Cost/cycle	Cost per regimen		Cost per regimen
4 cycles					
doxorubicin 60 mg/m²	105,0 mg	131,56 €	**526,24 €**		
cyclophosphamide 600 mg/m²	1.050 mg	5,77 €	**23,09 €**		
daycare (4)		245,98 €	**983,92 €**		
12 cycles					
paclitaxel 80 mg/m²	140,0 mg	547,12 €	**6.565,44 €**		
daycare (12)		245,98 €	**2.951,76 €**		
52 cycles of which 12 concurrent with paclitaxel					
1 x trastuzumab 4 mg/kg	255,6 mg	1.143,23 €			**1.143,23 €**
1 x unavoidable waste 22,2%	56,7 mg	253,80 €			253,80 €
51 x trastuzumab 2 mg/kg	127,8 mg	571,62 €			**29.152,38 €**
51 x unavoidable waste 26,7%	34,1 mg	152,62 €			7.783,69 €
daycare (40)		245,98 €			**9.839,20 €**
TOTAL DRUGS			**7.114,77 €**		**38.333,09 €**
Daycare stays			**3.935,68 €**		**9.839,20 €**
TOTAL			**11.050,45 €**		**48.172,29 €**
GRAND TOTAL	**N9831 - B31**			**59.222,75 €**	

The costs of trastuzumab administration differ according to the 3 reference trials and amount 8667, 40 657 and 48 172 euro for respectively the FinHer, the HERA and the N9831/B31 courses. In case of an enlargement of the population actually treated with chemotherapy, the cost of trastuzumab and the costs induced by a classical chemotherapy for every new patient represent an additional cost of respectively 14 727, 45 537 and 59 223 euro.

Since more than 85% of the patients younger than 60 year are already treated by chemotherapy at stages II and III, there is not much room left for a broader intervention in these patients. At stage I, far more new treatments could be expected: from + 50% in patients younger than 50 year to + 300% in patients older than 50.

The choice to administer trastuzumab before or after anthracycline brings major financial consequences in budgetary terms at every stage (tables 53, 54 & 55 for stages I, II and III).

Table 53. Cost of treatment for eligible patients with stage I in 2005

Stage I	Chemo & LVEF ≥50%	More chemotherapy	Chemo & LVEF ≥55%	More chemotherapy
	T 9 weeks	T 9 weeks	T 52 weeks	T 52 weeks
<50	0.37 M€	0.67 M€	1.42 M€	2.20 M€
50-59	0.27 M€	0.84 M€	1.06 M€	2.51 M€
60-69	0.18 M€	0.84 M€	0.69 M€	2.38 M€
70-79	0.03 M€	0.34 M€	0.08 M€	0.86 M€
80+	0.00 M€	0.13 M€	0.00 M€	0.32 M€
ALL	0.85 M€ for 98 patients	2.82 M€ for 232 patients	3.25 M€ for 80 patients	8.26 M€ for 190 patients

Chemo & LVEF ≥50% (or ≥55%): Patients neu-HER2 FISH positive, treated with adjuvant therapy and LVEF ≥50% (or ≥55%) at start of trastuzumab treatment; cost of added trastuzumab therapy.
More chemotherapy: Actual chemo + 50% of the chemo naïve FISH positive patients with LVEF ≥50% (or ≥55%) at start of trastuzumab treatment; cost of added trastuzumab therapy and new chemotherapy in naïve pats.
T 9 weeks: trastuzumab 9-week schedule.
T 52 weeks: trastuzumab 52-week schedule.

Table 54. Cost of treatment for eligible patients with stage II in 2005

Stage II	Chemo & LVEF ≥50%	More chemotherapy	Chemo & LVEF ≥55%	More chemotherapy
	T 9 weeks	T 9 weeks	T 52 weeks	T 52 weeks
<50	1.17 M€	1.27 M€	4.55 M€	4.78 M€
50-59	1.07 M€	1.24 M€	4.15 M€	4.56 M€
60-69	0.46 M€	0.80 M€	1.75 M€	2.61 M€
70-79	0.10 M€	0.60 M€	0.41 M€	1.68 M€
80+	0.00 M€	0.38 M€	0.00 M€	0.96 M€
ALL	2.81 M€ for 324 patients	4.30 M€ for 425 patients	10.86 M€ for 267 patients	14.59 M€ for 349 patients

Table 55. Cost of treatment for eligible patients with stage III in 2005

Stage III	Chemo & LVEF ≥50%	More chemotherapy	Chemo & LVEF ≥55%	More chemotherapy
	T 9 weeks	T 9 weeks	T 52 weeks	T 52 weeks
<50	0.55 M€	0.57 M€	2.15 M€	2.20 M€
50-59	0.46 M€	0.49 M€	1.75 M€	1.84 M€
60-69	0.37 M€	0.43 M€	1.46 M€	1.60 M€
70-79	0.11 M€	0.29 M€	0.45 M€	0.90 M€
80+	0.02 M€	0.18 M€	0.04 M€	0.45 M€
ALL	1.52 M€ for 175 patients	1.96 M€ for 205 patients	5.85 M€ for 144 patients	6.99 M€ for 169 patients

The last table (table 56) summarizes the added costs for trastuzumab in the stages I, II and III. It would today represent an expense of 5.17 million euro in a 9-week scenario and of 19.96 million euro in a 52-week scenario. The cost for the stages I, II and III together could rise up to 9.08 million euro in a 9-week scenario and to 29.84 million euro in a 52-week scenario if a more aggressive approach is preferred. The last figure is furthermore a higher price for treating 18% less women, the women exposed to a high risk of heart problems, than in a 9-week scenario. On top, a treatment with a total duration of 616 versus 189 days and twice as much day-care stays requires also more oncologists, more cancer nurses and more beds in outpatient settings.

Table 56. Total cost of treatment for eligible patients in 2005

	Chemo & LVEF ≥50%	Chemo & LVEF ≥55%	More chemotherapy	More chemotherapy
	T 9 weeks	T 52 weeks	T 9 weeks	T 52 weeks
Stage I	0.85 M€	3.25 M€	2.82 M€	8.26 M€
Stage II	2.81 M€	10.86 M€	4.30 M€	14.59 M€
Stage III	1.52 M€	5.85 M€	1.96 M€	6.99 M€
Stages I, II & III	5.17 M€ for 597 patients	19.96 M€ for 491 patients	9.08 M€ for 862 patients	29.84 M€ for 708 patients

5 APPENDICES

5.1 APPENDIX 1: ANALYSIS OF BELGIAN BREAST CANCER DATA

5.1.1 Data collection

The KCE launched a national survey in the early days of February 2006. For each female patient diagnosed with a new breast cancer, the centre had to mention (figure 24):

- Age at diagnosis,
- Menopausal status,
- TNM classification, (6th revised edition),
- Histologic grade,
- Presence of estrogen and progesteron receptors,
- Neu-HER2 status assayed by immunohistochemistry and by gene amplification,
- Type of surgery,
- Radiotherapy,
- Anthracyclines,
- Taxanes,
- Other chemotherapeutic agents,
- Tamoxifen,
- Aromatase inhibitor

Figure 24. Questionnaire sent to the centres

Intern. ID	Age in yr at diag.	Menopausal status	T	N	M	Histol. grade	ER	PR	HER2/neu IHC	HER2/neu FISH/CISH	Surgery	Radiotherapy	Anthracycline	Taxane	Other	Tamoxifen	Arom. Inhibitor

Menopausal status **A**nte, **P**ost, **U**nknown

T 0, is, 1a, 1b, 1c, 2, 3, 4, x
N 0, 1, 2, 3, x
M 0, 1, x

Histologic grade **1** = well
2 = moderately
3 = poor / anaplastic
Unknown

ER -, +, Unknown
PR -, +, Unknown

HER2/neu **IHC** -, **1+**, **2+**, **3+**, **U**nknown
HER2/neu **FISH** -, +, Unknown
or **CISH** -, +, Unknown

Surgery **M**astectomy, **L**umpectomy

Radiotherapy -, +, **U**nknown

Anthracycline **D**oxorubicin, **E**pirubicine

Taxanes **P**aclitaxel
Docetaxel

Other **C**yclophosphamide
5-**F**luorouracil

Tamoxifen -, +, Unknown

Arom. inhibitor **A**nastrozol, **L**etrozol, **E**xemestan

Primary tumor (T)

Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1a	Tumor more than 0,1 cm but not more than 0,5 cm in greatest dimension
T1b	Tumor more than 0,5 cm but not more than 1 cm in greatest dimension
T1c	Tumor more than 1 cm but not more than 2 cm in greatest dimension
T2	Tumor more than 2 cm but not more than 5 cm in greatest dimension
T3	Tumor more than 5 cm in greatest dimension
T4	Tumor of any size with direct extension to chest wall or skin

Regional lymph nodes (N)

Nx	Regional lymph nodes cannot be assessed (e.g., previously removed)
N0	No regional lymph node metastasis
N1	Metastasis in 1-3 axillary lymph node(s)
N2	Metastasis in 4-9 axillary lymph node(s)
N3	Metastasis in ≥10 axillary lymph node(s)

Distant metastasis (M)

Mx	Presence of distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis {not including ipsilateral supraclavicular lymph node(s)}

Eighty centres were invited to fill in our questionnaire. Out of the 7 academic centres, only one (ULB Erasme) was able to produce a complete picture of the newly diagnosed breast cancers for the year 2005 by the 15th of May in spite of a request at the 9th of February. Eleven large centres with >149 patients, to say OLV-Aalst, Middelheim-Stuyvenberg, Antwerpen, KLINA-Braschaat, St Jan-Brugge, ZOL-Genk, Jolimont-Haine St Paul, Groeninge-Kortrijk, Citadelle-Liège, St Elisabeth-Namur, HH-Roeselare, St Elisabeth-Turnhout, complied with our request On the other hand, 18 centres of small or median size made this effort (table 57). Finally, 32 hospitals agreed to send their data to the KCE in the requested format. These data (KCE files closed at May 15th) covered the year 2003 for 1 hospital, the year 2004 for 3 hospitals and the year 2005 for 29 hospitals, one centre sent his data for the years 2004 and 2005.

Patients who had 2 breast cancers diagnosed in the same year, either in the same breast or a contralateral tumour, were counted once, with the most advanced stage of both. Incomplete files were returned to the centres for data clarification until no further improvement could still be achieved. The staging was performed at the KCE in accordance with the 6th edition of the TNM/AJCC classification 2002 (http://www.cancer.gov/cancertopics/pdq/treatment/breast/HealthProfessional/page3#Section%2030).

Table 57. Number of data received per hospital

Participating centres	Frequency	*Percent*
BORDET-BXL (2003)	474	*9.02*
ZOL-GENK (2004)	128	*2.44*
UZG-GENT (2004)	209	*3.98*
KUL-LEUVEN (2004)	752	*14.31*
OLV-AALST (2005)	220	*4.19*
ST JOSEPH-ARLON (2005)	72	*1.37*
IMELDA-BONHEIDEN (2005)	130	*2.47*
KLINA-BRASSCHAAT (2005)	237	*4.51*
ST JAN-BRUGGE (2005)	197	*3.75*
CHU-CHARLEROI (2005)	148	*2.82*
CITADELLE-LIEGE (2005)	155	*2.95*
ERASME-BXL (2005)	138	*2.63*
CLINIQUES EUROPE-BXL (2005)	146	*2.78*
ZOL-GENK (2005)	165	*3.14*
MM-GENT (2005)	125	*2.38*
GODINNE (2005)	38	*0.72*
ND-GOSSELIES (2005)	48	*0.91*
GROENINGE-KORTRIJK (2005)	210	*4.00*
CHR-HUY (2005)	48	*0.91*
JOLIMONT (2005)	184	*3.50*
HH-LIER (2005) (+ no data received for 92 patients)	63	*1.20*
IXL-MOLIERE (2005)	86	*1.64*
ST ELISABETH-NAMUR (2005)	246	*4.68*
MM-ST-NIKLAAS (2005)	58	*1.10*
ST DAMIAAN-OOSTENDE (2005)	109	*2.07*
HH-ROESELARE (2005)	157	*2.99*
STEDELIJK-ROESELARE (2005)	49	*0.93*
GLORIEUX-RONSE (2005)	37	*0.70*
SERAING-WAREMME (2005)	57	*1.08*
MIDDELHEIM-STUIVENBERG-ANTWERPEN (2005)	222	*4.23*
ND-TOURNAI (2005)	116	*2.21*
ST ELISABETH-TURNHOUT (2005)	181	*3.44*
YPERMAN-IEPER (2005)	49	*0.93*
TOTAL	5254	

5.1.2 Distribution of T, N and M

The tumour characteristics are presented below (tables 58, 59 & 60). In general, the proportion of missing data was relatively low (5% for the size of the tumour T, 10% for the regional lymph nodes N and 10% for the distant metastasis M).

Table 58. Distribution by tumour size

T	Frequency	Percent	Cumulative frequency	Cumulative percent
0	3	*0.06*	3	*0.06*
Ia	185	*3.52*	188	*3.58*
Ib	582	*11.08*	770	*14.66*
Ic	1434	*27.29*	2204	*41.95*
Ix	142	*2.70*	2346	*44.65*
2	1564	*29.77*	3910	*74.42*
3	337	*6.41*	4247	*80.83*
4	310	*5.90*	4557	*86.73*
X	271	*5.16*	4828	*91.89*
is	426	*8.11*	5254	*100.00*

Table 59. Distribution by node

N	Frequency	Percent	Cumulative frequency	Cumulative percent
0	2922	*55.61*	2922	*55.61*
1	1250	*23.79*	4172	*79.41*
2	389	*7.40*	4561	*86.81*
3	164	*3.12*	4725	*89.93*
X	529	*10.07*	5254	*100.00*

Table 60. Distribution by metastasis

M	Frequency	Percent	Cumulative frequency	Cumulative percent
0	4437	*84.45*	4437	*84.45*
1	296	*5.63*	4733	*90.08*
X	521	*9.92*	5254	*100.00*

5.1.3 Distribution of number of patients per stage

The TNM staging system for breast cancer, 2002 revision (6th edition) approved by the AJCC, was applied. It is important to note that the revised classification takes into account the number of involved nodes, the macroscopic involvement of the internal mammary nodes and the extension to the supraclavicular nodes.

Details on this procedure, and on the conventions that were used to deal with missing data, are provided in addendum.

On the 5254 patients, staging could be defined for 4528, after exclusion of patients with stage 0 (428 patients, 8%), or patients for which there was not enough information to determine the stage (298 patients, 6%; table 61).

Table 61. Staging definition for all patients

Stage	Frequency	Percent	Cumulative frequency	Cumulative percent
0	428	*8.15*	428	*8.15*
I	1721	*32.76*	2149	*40.90*
IIa	1171	*22.29*	3320	*63.19*
IIb	621	*11.82*	3941	*75.01*
IIIa	400	*7.61*	4341	*82.62*
IIIb	182	*3.46*	4523	*86.09*
IIIc	137	*2.61*	4660	*88.69*
IV	296	*5.63*	4956	*94.33*
Undefined	298	*5.67*	5254	*100.00*

Table 62 presents the distribution of patients by staging, and compares these data with the data of the Flemish Cancer Registry Network (year 2001) (Breast cancer incidence in Flanders, 2000-2001, Flemish League against Cancer, Brussels). Although there is good agreement for stages I and 4, patients from stage 3 are more represented in our sample than in the NCR data (16% vs 9%). This might be explained by the difference in TNM classification used (6th version vs 5th version). The 6th edition classifies some nodal categories as Stage III that were previously considered Stage II.[a]

Table 62. Stages observed in the KCE survey and in the NCR registry

	KCE 2005 * (N=4528)			NCR 2001 **(N=3767)	
Stage	Frequency	Percent	Cumulative Percent	Frequency	Percent
I	**1721**	***38.01***	*38.01*	1470	*39.02*
IIa	1171	*25.86*	*63.87*		
IIb	621	*13.71*	*77.58*		
Total II	**1792**	***39.58***		1755	*46.59*
IIIa	400	*8.83*	*86.42*		
IIIb	182	*4.02*	*90.44*		
IIIc	137	*3.03*	*93.46*		
Total III	**719**	***15.88***		333	*8.8*
IV	296	*6.54*	*100.00*	209	*5.55*

* staging definition based on TNM classification 2002 (6th edition)
** staging definition based on TNM classification 1997 (5th edition)

[a] Singletary SE, Allred C, Ashley P, et al: Revision of the American Joint Committee on Cancer staging system for breast cancer. J Clin Oncol 20 (17): 3628-36, 2002.

5.1.4 Age at diagnosis per stage

Table 63. Age at diagnosis per stage

	Analysis Variable : Age at diagnosis					
Stage	N	Mean	Median	Std deviation	Minimum	Maximum
I	1721	58.9	58.0	12.0	21.0	93.0
II	1792	59.9	59.0	14.6	25.0	98.0
III	719	60.8	60.0	14.7	26.0	94.0
IV	296	62.8	63.5	13.4	32.0	92.0

Figure 25. Number of women per age and stage

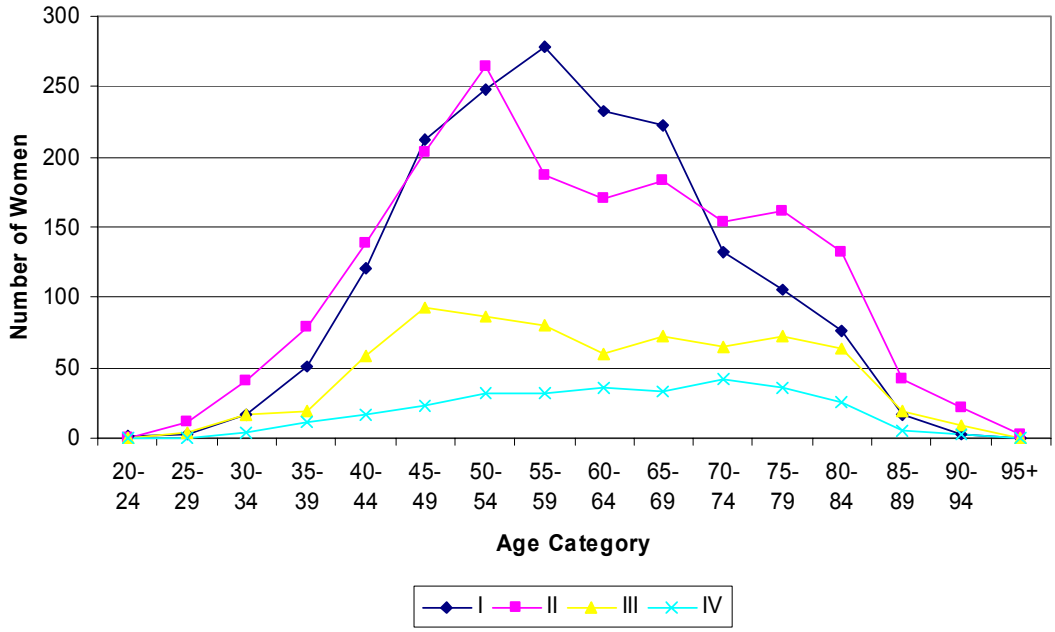
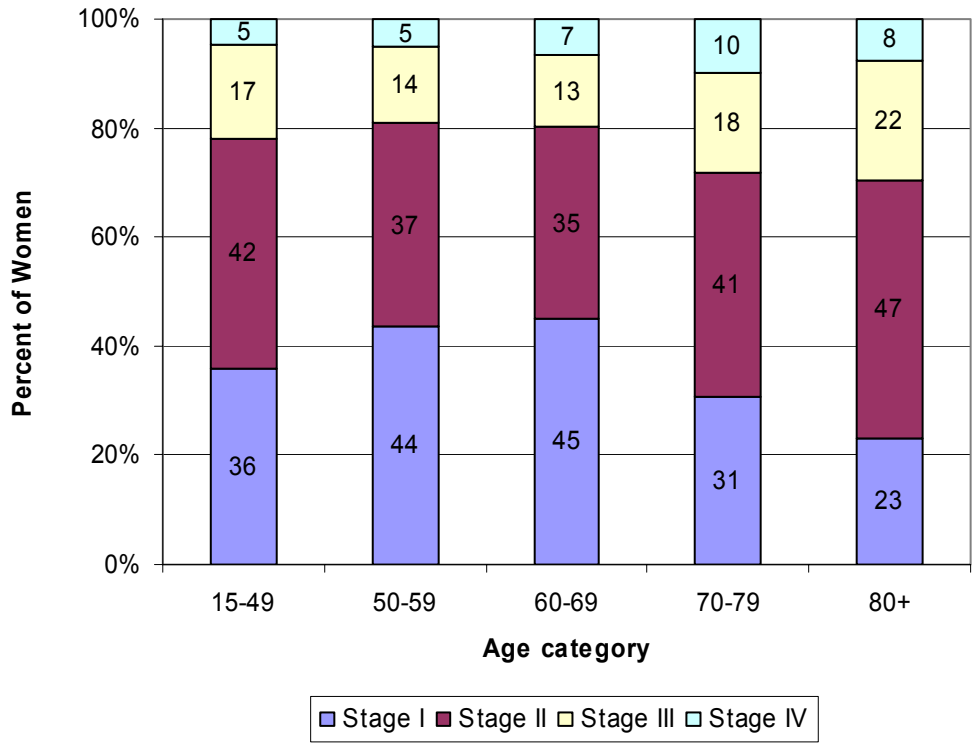


Table 64. Number and percent of patients per age and stage

Table of age by stage					
Age at diagnostic	Stage				Total
Frequency Percent	I	II	III	IV	
15-49	405 *8.94*	474 *10.47*	192 *4.24*	55 *1.21*	1126 *24.87*
50-59	527 *11.64*	452 *9.98*	166 *3.67*	64 *1.41*	1209 *26.70*
60-69	456 *10.07*	353 *7.80*	132 *2.92*	68 *1.50*	1009 *22.28*
70-79	237 5.23	315 *6.96*	138 *3.05*	77 *1.70*	767 *16.94*
80+	96 *2.12*	198 *4.37*	91 2.01	32 *0.71*	417 *9.21*
Total	1721 *38.01*	1792 *39.58*	719 *15.88*	296 *6.54*	4528 *100.00*

Figure 26. Age at diagnosis per stage



5.1.5 Estrogen and Progesteron receptors per age and stage

Table 65. Presence of Estrogen Receptors (ER) per age and stage

Age		stage I ER +	stage I ER -	stage I N	stage II ER +	stage II ER -	stage II N	stage III ER +	stage III ER -	stage III N	stage IV ER +	stage IV ER -	stage IV N	ER + All	ER - All	All
15-49	N	318	74	392	327	139	466	132	55	187	39	13	52	816	281	1097
	%	*81.12*	*18.88*		*70.17*	*29.83*		*70.59*	*29.41*		*75.00*	*25.00*		*74.38*	*25.62*	
50-59	N	428	85	513	332	113	445	119	42	161	39	19	58	918	259	1177
	%	*83.43*	*16.57*		*74.61*	*25.39*		*73.91*	*26.09*		*67.24*	*32.76*		*77.99*	*22.01*	
60-69	N	379	64	443	281	66	347	89	38	127	49	15	64	798	183	981
	%	*85.55*	*14.45*		*80.98*	*19.02*		*70.08*	*29.92*		*76.56*	*23.44*		*81.35*	*18.65*	
70-79	N	214	22	236	249	60	309	96	38	134	55	20	75	614	140	754
	%	*90.68*	*9.32*		*80.58*	*19.42*		*71.64*	*28.36*		*73.33*	*26.67*		*81.43*	*18.57*	
80+	N	84	10	94	151	38	189	68	17	85	26	4	30	329	69	398
	%	*89.36*	*10.64*		*79.89*	*20.11*		*80.00*	*20.00*		*86.67*	*13.33*		*82.66*	*17.34*	
All ages	N	1423	255	1678	1340	416	1756	504	190	694	208	71	279	3475	932	4407
	%	*84.80*	*15.20*		*76.31*	*23.69*		*72.62*	*27.38*		*74.55*	*25.45*		*78.85*	*21.15*	

Table 66. Presence of Progesteron Receptors (PR) per age and stage

Age		Stage I PR +	Stage I PR -	Stage I N	Stage II PR +	Stage II PR -	Stage II N	Stage III PR +	Stage III PR -	Stage III N	Stage IV PR +	Stage IV PR -	Stage IV N	PR + All	PR - All	All
15-49	N	300	92	392	310	153	463	120	66	186	33	18	51	763	329	1092
	%	*76.53*	*23.47*		*66.95*	*33.05*		*64.52*	*35.48*		*64.71*	*35.29*		*69.87*	*30.13*	
50-59	N	361	152	513	277	166	443	98	61	159	34	22	56	770	401	1171
	%	*70.37*	*29.63*		*62.53*	*37.47*		*61.64*	*38.36*		*60.71*	*39.29*		*65.76*	*34.24*	
60-69	N	301	136	437	215	127	342	74	52	126	30	32	62	620	347	967
	%	*68.88*	*31.12*		*62.87*	*37.13*		*58.73*	*41.27*		*48.39*	*51.61*		*64.12*	*35.88*	
70-79	N	163	71	234	193	114	307	79	55	134	42	30	72	477	270	747
	%	*69.66*	*30.34*		*62.87*	*37.13*		*58.96*	*41.04*		*58.33*	*41.67*		*63.86*	*36.14*	
80+	N	77	15	92	124	65	189	56	29	85	14	13	27	271	122	393
	%	*83.70*	*16.30*		*65.61*	*34.39*		*65.88*	*34.12*		*51.85*	*48.15*		*68.96*	*31.04*	
All ages	N	1202	466	1668	1119	625	1744	427	263	690	153	115	268	2901	1469	4370
	%	*72.06*	*27.94*		*64.16*	*35.84*		*61.88*	*38.12*		*57.09*	*42.91*		*66.38*	*33.62*	

5.1.6 neu-HER2 overexpression by IHC per age and stage

Table 67. neu-HER2 overexpression assayed by immunohistochemistry (IHC)

HER2-neu IHC	Frequency (N=4151)	Percent
-	2561	*61.70*
1+	610	*14.70*
2+	496	*11.95*
3+	484	*11.66*
Total Positive tests (2+, 3+)	**980**	**23.61**

(N = 377 missing IHC tests)

Table 68. neu-HER2 overexpression in IHC by age

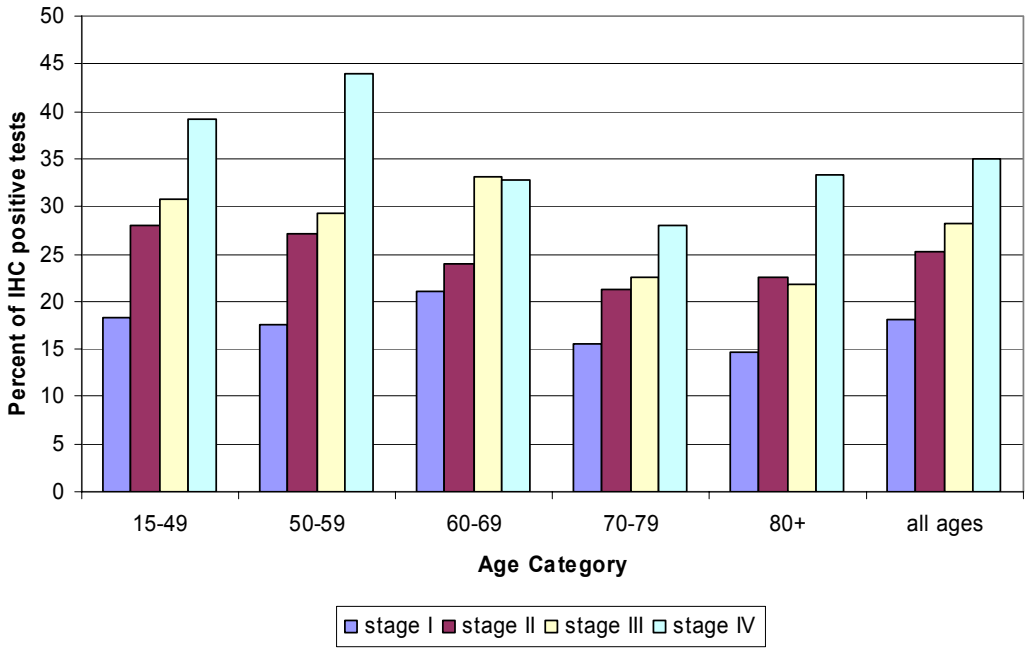
Table of age by IHC			
Age / HER IHC Frequency Row Pct	-, 1+	2+, 3+	Total
15-49	776 *74.47*	266 *25.53*	1042
50-59	844 *75.97*	267 *24.03*	1111
60-69	700 *75.59*	226 *24.41*	926
70-79	561 *79.69*	143 *20.31*	704
80+	290 *78.80*	78 *21.20*	368
Total	3171	980	4151
Frequency Missing = 377			

Table 69. neu-HER2 overexpression in IHC by age and stage

Age		stage I HER 2+ 3+ n	N	stage II HER 2+ 3+ n	N	stage III HER 2+ 3+ n	N	stage IV HER 2+ 3+ n	N
15-49	N	68	372	126	449	54	175	18	46
	%	*18.28*		*28.06*		*30.86*		*39.13*	
50-59	N	85	484	116	427	44	150	22	50
	%	*17.56*		*27.17*		*29.33*		*44.00*	
60-69	N	88	417	80	333	40	121	18	55
	%	*21.10*		*24.02*		*33.06*		*32.73*	
70-79	N	34	219	62	293	28	124	19	68
	%	*15.53*		*21.16*		*22.58*		*27.94*	
80+	N	13	89	40	177	17	78	8	24
	%	*14.61*		*22.60*		*21.79*		*33.33*	
All ages	N	288	1581	424	1679	183	648	85	243
	%	*18.22*		*25.25*		*28.24*		*34.98*	

n, % = patients with IHC 2+ or 3+

Figure 27. Percent of IHC positive tests, per age and stage



5.1.7 Estimated distribution of tumours expressing neuHER2 by FISH, per age and stage

A total of 460 FISH tests were performed (for one patient only, there was no corresponding IHC test, and therefore this data was excluded from the following tables). 57% of these tests were positive.

Table 70: Gene amplification by FISH test, per IHC results

IHC result / Frequency / Row Pct	FISH result: Positive	FISH result: Negative	Total
-	0 *0.00*	22 100.00	22
1+	2 *14.29*	12 85.71	14
2+	61 *34.46*	116 *65.54*	177
3+	199 *80.89*	47 *19.11*	246
Total	262	197	**459**
%	*57.08*	42.92	

5.1.8 Surgery per age and stage

Table 71. Type of surgery

Surgery	Frequency	Percent	Cumulative Frequency
No	230	*5.17*	230
Yes	4221	*94.83*	4451
Lumpectomy	2603	*58.48*	
Mastectomy	1618	*36.35*	

Table 72. Surgery, per age and stage

		Stage								Surgery	All
		I		II		III		IV			
		Surgery n	N	Surgery n	N	Surgery n	N	Surgery n	N	n	
Age											
15-49	N	400	402	472	472	182	189	24	46	1078	1109
	%	*99.50*		*100.00*		*96.30*		*52.17*		*97.20*	
50-59	N	524	524	448	449	160	165	23	56	1155	1194
	%	*100.00*		*99.78*		*96.97*		*41.07*		*96.73*	
60-69	N	451	454	348	349	124	131	22	60	945	994
	%	*99.34*		*99.71*		*94.66*		*36.67*		*95.07*	
70-79	N	235	237	308	315	128	137	29	69	700	758
	%	*99.16*		*97.78*		*93.43*		*42.03*		*92.35*	
80+	N	81	89	174	191	77	90	11	26	343	396
	%	*91.01*		*91.10*		*85.56*		*42.31*		*86.62*	
All ages	N	1691	1706	1750	1776	671	712	109	257	4221	4451
	%	*99.12*		*98.54*		*94.24*		*42.41*		*94.83*	

5.1.9 Radiotherapy per age and stage

Table 73. Radiotherapy

Radiotherapy	Frequency	Percent	Cumulative frequency
Yes	3423	*80.30*	3423
No	840	*19.70*	4263

Table 74. Radiotherapy per age and stage

		Stage								Radiotherapy	All
		I		II		III		IV			
Age		Radio. +	N	Radio. +	N	Radio. +	N	Radio. +	N	+	
15-49	N	322	383	402	453	163	176	24	48	911	1060
	%	*84.07*		*88.74*		*92.61*		*50.00*		*85.94*	
50-59	N	423	500	376	431	147	157	19	54	965	1142
	%	*84.60*		*87.24*		*93.63*		*35.19*		*84.50*	
60-69	N	381	436	298	340	118	127	15	62	812	965
	%	*87.39*		*87.65*		*92.91*		*24.19*		*84.15*	
70-79	N	179	224	229	296	111	128	22	67	541	715
	%	*79.91*		*77.36*		*86.72*		*32.84*		*75.66*	
80+	N	45	90	88	179	53	85	8	27	194	381
	%	*50.00*		*49.16*		*62.35*		*29.63*		*50.92*	
All ages	N	1350	1633	1393	1699	592	673	88	258	3423	4263
	%	*82.67*		*81.99*		*87.96*		*34.11*		*80.30*	

5.1.10 Chemotherapy

Table 75. Anthracycline Use

Anthracycline	Frequency	Percent	Cumulative Frequency
No	2526	*58.49*	2526
Yes	1793	*41.51*	4319
Doxorubicin	197	*4.56*	
Epirubicin	1377	*31.88*	
Not specified	219	*5.07*	

Table 76. Taxane Use

Taxane	Frequency	Percent	Cumulative Frequency
No	3699	*90.57*	3699
Yes	385	*9.43*	4084
Docetaxel	363	*8.89*	
Paclitaxel	22	*0.54*	

Table 77. Use of other type of chemotherapy

Any Other	Frequency	Percent	Cumulative Frequency
No	2533	*58.77*	2533
Yes	1777	*41.23*	4310
+	1	*0.02*	
+? (no detailed data forwarded)	219	*5.08*	
Cyclophosphamide	139	*3.23*	
Cyclophosphamide - Fluorouracil	1305	*30.28*	
Cyclophosphamide - Methotrexate - Fluorouracil	73	*1.69*	
Cyclophosphamide - Etoposide	1	*0.02*	
Cyclophosphamide - Methotrexate - Fluorouracil - Vinorelbine	1	*0.02*	
Capecitabine	11	*0.25*	
Capecitabine - Vinorelbine - Ci	1	*0.02*	
Carboplatinum	1	*0.02*	
Fluorouracil	21	*0.49*	
Methotrexate Fluorouracil	3	*0.07*	
Var	1	*0.02*	

Table 78. Use of combinations of chemotherapies

Combination	Frequency	Percent	Cumulative Frequency
No	2575	*59.62*	2575
Yes	1744	*40.38*	4319

Combination is defined as any combination of 2 out of the three following groups: (A, T, Other)

5.1.11 Combinations of Chemotherapies per age and stage

Table 79. Combinations of Chemotherapies per Age and Stage (all patients)

Age		stage I Combi n	I N	stage II Combi n	II N	stage III Combi n	III N	stage IV Combi n	IV N	All n	All N
15-49	N	126	382	397	462	169	184	26	48	718	1076
	%	*32.98*		*85.93*		*91.85*		*54.17*		*66.73*	
50-59	N	93	498	324	439	139	158	43	62	599	1157
	%	*18.67*		*73.80*		*87.97*		*69.35*		*51.77*	
60-69	N	38	433	157	343	98	128	26	65	319	969
	%	*8.78*		*45.77*		*76.56*		*40.00*		*32.92*	
70-79	N	4	226	39	299	43	129	16	69	102	723
	%	*1.77*		*13.04*		*33.33*		*23.19*		*14.11*	
80+	N	1	92	1	188	3	86	1	28	6	394
	%	*1.09*		*0.53*		*3.49*		*3.57*		*1.52*	
All ages	N	262	1631	918	1731	452	685	112	272	1744	4319
	%	*16.06*		*53.03*		*65.99*		*41.18*		*40.38*	

Table 80. Combinations of Chemotherapies per Age and Stage (only for patients tested for IHC)

Age		stage I combi n	I N	stage II combi n	II N	stage III combi n	III N	stage IV combi n	IV N	Combi n	All
15-49	N	121	363	382	446	161	174	23	43	687	1026
	%	*33.33*		*85.65*		*92.53*		*53.49*		*66.96*	
50-59	N	91	466	315	424	131	149	37	49	574	1088
	%	*19.53*		*74.29*		*87.92*		*75.51*		*52.76*	
60-69	N	35	406	150	329	96	121	23	55	304	911
	%	*8.62*		*45.59*		*79.34*		*41.82*		*33.37*	
70-79	N	4	212	38	285	41	119	15	65	98	681
	%	*1.89*		*13.33*		*34.45*		*23.08*		*14.39*	
80+	N	1	86	1	171	3	77	1	24	6	358
	%	*1.16*		*0.58*		*3.90*		*4.17*		*1.68*	
All ages	N	252	1533	886	1655	432	640	99	236	1669	4064
	%	*16.44*		*53.53*		*67.50*		*41.95*		*41.07*	

Table 81. Combinations of chemotherapies per age and stage (only for patients IHC 2+ and IHC 3+)

		stage								All	
		I		II		III		IV			
		combi n	N	combi n	N	combi n	N	combi n	N		
Age											
15-49	N	33	64	113	125	52	54	9	17	207	260
	%	*51.56*		*90.40*		*96.30*		*52.94*		*79.62*	
50-59	N	23	80	98	115	40	44	18	22	179	261
	%	*28.75*		*85.22*		*90.91*		*81.82*		*68.58*	
60-69	N	16	85	42	79	34	40	6	18	98	222
	%	*18.82*		*53.16*		*85.00*		*33.33*		*44.14*	
70-79	N	2	30	9	59	9	25	5	19	25	133
	%	*6.67*		*15.25*		*36.00*		*26.32*		*18.80*	
80+	N	0	11	0	37	1	17	0	8	1	73
	%	*0*		*0*		*5.88*		*0*		*1.37*	
All ages	N	74	270	262	415	136	180	38	84	510	949
	%	*27.41*		*63.13*		*75.56*		*45.24*		*53.74*	

Thirty-three out of the 64 15-49 year old patients with a stage I who were found 2+ or 3+ by IHC for neu-HER2 received a chemotherapy with at least 2 agents.

5.1.12 Subgroup analysis based on patients stage I – T1c N0

Table 82. Age distribution for patients in subgroup stage I – T1c N0

Age at diagnostic	Frequency	Percent	Cumulative frequency
15-49	244	*25.28*	244
50-59	288	*29.84*	532
60-69	238	*24.66*	770
70-79	137	*14.20*	907
80+	58	*6.01*	965

Table 83. Results of IHC test by age in subgroup stage I – T1c N0

Table of age by HER_IHC			
	HER_IHC		
Age	-, 1+	2+, 3+	Total
15-49	179 (*78.51%*)	49 (*21.49%*)	228
50-59	224 (*83.58%*)	44 (*16.42%*)	268
60-69	182 (*80.89%*)	43 (*19.11%*)	225
70-79	103 (*80.47%*)	25 (*19.53%*)	128
80+	44 (*83.02%*)	9 (*16.98%*)	53
Total	732	170	902
Frequency Missing = 63			

Table 84. Combination of chemotherapies per age in subgroup stage I – T1c N0

	Combination of Chemotherapies	
	Only Patients Tested for IHC	Only Patients Positive (2+, 3+) for IHC
Age	n/N (%)	n/N (%)
15-49	95/225 (*42.22*)	27/46 (*58.70*)
50-59	60/260 (*23.08*)	16/43 (*37.21*)
60-69	32/220 (*14.55*)	15/43 (*34.88*)
70-79	3/124 (*2.42*)	2/23 (*8.70*)
80+	1/52 (*1.92*)	0/8 (*0.00*)
Total	191/881 (*21.68*)	60/163 (*36.81*)

5.1.13 Subgroup Analysis based on Patients with T2 N0 M0/X

Table 85. Age distribution for patients in subgroup stage II – T2 N0 M0/X

Age	Frequency	Percent	Cumulative frequency
15-49	180	*25.21*	180
50-59	161	*22.55*	341
60-69	138	*19.33*	479
70-79	138	*19.33*	617
80+	97	*13.59*	714

Table 86. Results of IHC test by age in subgroup stage II – T2 N0 M0/X

Table of age by HER_IHC			
Age	HER_IHC		
	-, 1+	2+, 3+	Total
15-49	122 (*71.35%*)	49 (*28.65%*)	171
50-59	114 (*76.00%*)	36 (*24.00%*)	150
60-69	102 (*79.69%*)	26 (*20.31%*)	128
70-79	102 (*78.46%*)	28 (*21.54%*)	130
80+	68 (*79.07%*)	18 (*20.93%*)	86
Total	508	157 (*23.61%*)	665
Frequency Missing = 49			

Table 87. Combination of chemotherapies per age in subgroup stage II – T2 N0 M0/X

	Combination of chemotherapies	
	Only patients tested for IHC	Only patients positive (2+, 3+) for IHC
Age	n/N (%)	n/N (%)
15-49	137/170 (*80.59*)	42/49 (*85.71*)
50-59	83/148 (*56.08*)	26/36 (*72.22*)
60-69	41/125 (*32.80*)	9/25 (*36.00*)
70-79	5/125 (*4.00*)	1/26 (*3.85*)
80+	1/82 (*1.22*)	0/15 (*0.00*)
Total	267/650 (*41.08*)	78/151 (*51.66*)

Addendum

Stage undefined (too many missing data)

T	N	M	Count
1c	X	0	25
1c	X	X	11
1x	X	0	8
1x	X	X	3
2	X	0	33
2	X	X	15
3	X	0	4
3	X	X	5
X	0	0	23
X	0	X	2
X	1	0	8
X	1	X	6
X	2	0	5
X	X	0	82
X	X	X	68

Stage 0

T	N	M	Count
0	0	0	1
0	1	0	1
is	0	0	292
is	0	X	21
is	1	0	1
is	X	0	70
is	X	X	42

Stage I

T	N	M	Count
1a	0	0	136
1a	0	X	12
1a	X	0	11
1a	X	X	4
1b	0	0	433
1b	0	X	35
1b	X	0	13
1b	X	X	4
1c	0	0	910
1c	0	X	55
1x	0	0	92
1x	0	X	16

Stage IIa

T	N	M	Count
1a	1	0	17
1a	1	X	2
1b	1	0	67
1b	1	X	6
1c	1	0	320
1c	1	X	28
1x	1	0	13
1x	1	X	4
2	0	0	668
2	0	X	46

Stage IIb

T	N	M	Count
2	1	0	482
2	1	X	47
3	0	0	88
3	0	X	4

Stage IIIa

T	N	M	Count
1a	2	0	1
1b	2	0	12
1b	2	X	1
1c	2	0	46
1c	2	X	5
1x	2	0	2
1x	2	X	2
2	2	0	144
2	2	X	13
3	1	0	95
3	1	X	11
3	2	0	63
3	2	X	5

Stage IIIb

T	N	M	Count
4	0	0	43
4	0	X	4
4	1	0	56
4	1	X	7
4	2	0	40
4	2	X	7
4	X	0	13
4	X	X	12

Stage IIIc

T	N	M	Count
1b	3	0	2
1c	3	0	14
1c	3	X	3
2	3	0	47
2	3	X	4
3	3	0	28
3	3	X	5
4	3	0	24
4	3	X	4
X	3	0	4
X	3	X	2

Stage IV

T	N	M	Count
0	1	1	1
1a	0	1	1
1a	1	1	1
1b	0	1	5
1b	1	1	2
1b	2	1	2
1c	0	1	4
1c	1	1	6
1c	2	1	1
1c	3	1	2
1c	X	1	4
1x	0	1	1
1x	X	1	1
2	0	1	18
2	1	1	24
2	2	1	7
2	3	1	5
2	X	1	11
3	0	1	4
3	1	1	13
3	2	1	4
3	3	1	4
3	X	1	4
4	0	1	6
4	1	1	29
4	2	1	29
4	3	1	14
4	X	1	22
X	0	1	2
X	1	1	3
X	3	1	2
X	X	1	64

5.2 APPENDIX 2. CHEMOTHERAPY REGIMENS USED IN HERA TRIAL

Supplementary Appendix 1 Approved chemotherapy regimens for the HERA Trial

Regimen class	Regimens
ALL REGIMENS	Patient must have received at least four cycles of an approved (neo-) adjuvant chemotherapy regimen. In all cases, the maximum cumulative allowable dose of doxorubicin (A) is 360mg/m^2 and of epirubicin (E) is 720mg/m^2
Anthracyclines with no taxanes	Regimens in this category that are allowed for the HERA trial include the association of either A or E with cyclophosphamide (C) with or without 5-fluorouracil (F), and A or E as single agents or combined with C and followed by several cycles of CMF (where M is methotrexate). Minimum allowable starting doses of A or E associated with C with or without F: AC: 60mg/m^2 CAF/FAC: 50mg/m^2 (q21d or q28d) EC: 90mg/m^2 75mg/m^2 (day 1 q21d) if given for a minimum of 6 cycles FEC/CEF: 50mg/m^2 (days 1 and 8 q28d) 75mg/m^2 (day 1 q21d) 60mg/m^2 (day 1 q21d) if given for a minimum of 5 cycles Minimum allowable starting doses of A or E as single agents or combined with C and followed by CMF (described below): A: 75mg/m^2 E: 90mg/m^2
Anthracyclines and taxanes	Regimens in this category that are allowed for the HERA trial include sequential or combined anthracyclines (A or E) and taxanes (paclitaxel [P] and docetaxel [D]). A or E may be combined with C with or without F. Minimum allowable starting doses of A or E (with or without C and/or F) followed by P or D (sequential regimens): A: 60mg/m^2 FAC: 50mg/m^2 E: 90mg/m^2 60mg/m^2 (day 1 q21d) if followed by D 100mg/m^2 (day 1 q21d) if given for a minimum of 5 cycles FEC: 75mg/m^2 P: 175mg/m^2/3-hour 75 mg/m^2 (q7d) D: 100mg/m^2 Minimum allowable starting doses of A and E (with or without C and/or F), and P and D given concurrently (combined regimens): A: 50mg/m^2 E: 75mg/m^2 P: 135mg/m^2/3-hour D: 60mg/m^2/1-hour
Non-anthracycline regimens	Regimens in this category that are allowed for the HERA trial include C combined with methotrexate (M) and F (CMF). The minimum starting dose of C is 100mg/m^2/day days 1-14 if given orally and 600mg/m^2 per injection if given intravenously. The recommended starting dose per injection of M is 40mg/m^2 and of F is 600mg/m^2. CMF given day 1 and 8 every 28 days with oral C is the preferred schedule. Other CMF schedules are acceptable but should be used preferentially in patients who cannot tolerate oral C.
Other regimens	Any regimen that is part of a chemotherapy trial which has been approved a priori by the HERA Executive Committee[A]

[A] An updated list of these trials can be obtained from the BrEAST Data Centre. Chemotherapy trials that are initiated while recruitment to the HERA trial is ongoing can be added to this list following approval from the Executive Committee.

Legend: A=doxorubicin; C=cyclophosphamide; D=docetaxel; E=epirubicin; F=5-fluorouracil; M=methotrexate; P=paclitaxel; T=taxane

5.3 APPENDIX 3: WASTE OF TRASTUZUMAB

Table 88. Unavoidable waste measured in an academic hospital (3-weekly scheme)

Weight	8 mg/kg	Rest	%	6 mg/kg	Rest	%
58.0 kg	464.0 mg	136.0 mg	22.7%	348.0 mg	102.0 mg	22.7%
56.0 kg	448.0 mg	2.0 mg	0.4%	336.0 mg	114.0 mg	25.3%
56.0 kg	448.0 mg	2.0 mg	0.4%	336.0 mg	114.0 mg	25.3%
57.0 kg	456.0 mg	144.0 mg	24.0%	342.0 mg	108.0 mg	24.0%
57.0 kg	456.0 mg	144.0 mg	24.0%	342.0 mg	108.0 mg	24.0%
50.5 kg	404.0 mg	46.0 mg	10.2%	303.0 mg	147.0 mg	32.7%
49.5 kg	396.0 mg	54.0 mg	12.0%	297.0 mg	3.0 mg	1.0%
49.0 kg	392.0 mg	58.0 mg	12.9%	294.0 mg	6.0 mg	2.0%
92.0 kg	736.0 mg	14.0 mg	1.9%	552.0 mg	48.0 mg	8.0%
91.0 kg	728.0 mg	22.0 mg	2.9%	546.0 mg	54.0 mg	9.0%
91.0 kg	728.0 mg	22.0 mg	2.9%	546.0 mg	54.0 mg	9.0%
48.0 kg	384.0 mg	66.0 mg	14.7%	288.0 mg	12.0 mg	4.0%
50.0 kg	400.0 mg	50.0 mg	11.1%	300.0 mg	0.0 mg	0.0%
45.0 kg	360.0 mg	90.0 mg	20.0%	270.0 mg	30.0 mg	10.0%
119.1 kg	952.5 mg	97.5 mg	9.3%	714.4 mg	35.6 mg	4.7%
90.0 kg	720.0 mg	30.0 mg	4.0%	540.0 mg	60.0 mg	10.0%
59.0 kg	472.0 mg	128.0 mg	21.3%	354.0 mg	6.0 mg	21.3%
59.0 kg	472.0 mg	128.0 mg	21.3%	354.0 mg	96.0 mg	21.3%
80.0 kg	640.0 mg	110.0 mg	14.7%	480.0 mg	120.0 mg	20.0%
65.3 kg	522.7 mg	77.3 mg	12.9%	392.0 mg	58.0 mg	12.9%
49.0 kg	392.0 mg	58.0 mg	12.9%	294.0 mg	6.0 mg	2.0%
74.7 kg	597.3 mg	2.7 mg	0.4%	448.0 mg	2.0 mg	0.4%
56.0 kg	448.0 mg	2.0 mg	0.4%	336.0 mg	114.0 mg	25.3%
71.0 kg	568.0 mg	32.0 mg	5.3%	426.0 mg	24.0 mg	5.3%
73.0 kg	584.0 mg	16.0 mg	2.7%	438.0 mg	12.0 mg	2.7%
71.0 kg	568.0 mg	32.0 mg	5.3%	426.0 mg	24.0 mg	5.3%
65.0 kg	520.0 mg	80.0 mg	13.3%	390.0 mg	60.0 mg	13.3%
65.0 kg	520.0 mg	80.0 mg	13.3%	390.0 mg	60.0 mg	13.3%
67.0 kg	536.0 mg	64.0 mg	10.7%	402.0 mg	48.0 mg	10.7%
67.0 kg	536.0 mg	64.0 mg	10.7%	402.0 mg	48.0 mg	10.7%
53.0 kg	424.0 mg	26.0 mg	5.8%	318.0 mg	132.0 mg	29.3%
53.0 kg	424.0 mg	26.0 mg	5.8%	318.0 mg	132.0 mg	29.3%
53.0 kg	424.0 mg	26.0 mg	5.8%	318.0 mg	132.0 mg	29.3%
53.0 kg	424.0 mg	26.0 mg	5.8%	318.0 mg	132.0 mg	29.3%
56.0 kg	448.0 mg	2.0 mg	0.4%	336.0 mg	114.0 mg	25.3%
57.0 kg	456.0 mg	144.0 mg	24.0%	342.0 mg	108.0 mg	24.0%
57.0 kg	456.0 mg	144.0 mg	24.0%	342.0 mg	108.0 mg	24.0%
Mean = 63.9 kg	510.9 mg	60.7 mg	10.6%	383.2 mg	70.9 mg	15.6%
2.5 - 97.5%			8.1-13.1%			12.3-18.9%

Table 89. Unavoidable waste calculated for a weekly scheme (same patients as in previous table)

Weight	4 mg/kg	Rest	%	2 mg/kg	Rest	%
58.0 kg	232.0 mg	68.0 mg	22.7%	116.0 mg	34.0 mg	22.7%
56.0 kg	224.0 mg	76.0 mg	25.3%	112.0 mg	38.0 mg	25.3%
56.0 kg	224.0 mg	76.0 mg	25.3%	112.0 mg	38.0 mg	25.3%
57.0 kg	228.0 mg	72.0 mg	24.0%	114.0 mg	36.0 mg	24.0%
57.0 kg	228.0 mg	72.0 mg	24.0%	114.0 mg	36.0 mg	24.0%
50.5 kg	202.0 mg	98.0 mg	32.7%	101.0 mg	49.0 mg	32,7%
49.5 kg	198.0 mg	102.0 mg	34.0%	99.0 mg	51.0 mg	34.0%
49.0 kg	196.0 mg	104,0 mg	34.7%	98.0 mg	52.0 mg	34.7%
92.0 kg	368.0 mg	82.0 mg	18.2%	184.0 mg	116.0 mg	38.7%
91.0 kg	364.0 mg	86.0 mg	19.1%	182.0 mg	118.0 mg	39.3%
91.0 kg	364.0 mg	86.0 mg	19.1%	182.0 mg	118.0 mg	39.3%
48.0 kg	192.0 mg	108.0 mg	36.0%	96.0 mg	54.0 mg	36.0%
50.0 kg	200.0 mg	100.0 mg	33.3%	100.0 mg	50.0 mg	33.3%
45.0 kg	180.0 mg	120.0 mg	40.0%	90.0 mg	60.0 mg	40.0%
119.1 kg	476.3 mg	123.7 mg	20.6%	238.1 mg	61.9 mg	20.6%
90.0 kg	360.0 mg	90.0 mg	20.0%	180.0 mg	120.0 mg	40.0%
59.0 kg	236.0 mg	64.0 mg	21.3%	118.0 mg	32.0 mg	21.3%
59.0 kg	236.0 mg	64.0 mg	21.3%	118.0 mg	32.0 mg	21.3%
80.0 kg	320.0 mg	130.0 mg	28.9%	160.0 mg	140.0 mg	46.7%
65.3 kg	261.3 mg	38.7 mg	12.9%	130.7 mg	19.3 mg	12.9%
49.0 kg	196.0 mg	104.0 mg	34.7%	98.0 mg	52.0 mg	34.7%
74.7 kg	298.7 mg	1.3 mg	0.4%	149.3 mg	0.7 mg	0.4%
56.0 kg	224.0 mg	76.0 mg	25.3%	112.0 mg	38.0 mg	25.3%
71.0 kg	284.0 mg	16.0 mg	5.3%	142.0 mg	8.0 mg	5.3%
73.0 kg	292.0 mg	8.0 mg	2.7%	146.0 mg	4.0 mg	2.7%
71.0 kg	284.0 mg	16.0 mg	5.3%	142.0 mg	8.0 mg	5.3%
65.0 kg	260.0 mg	40,0 mg	13.3%	130.0 mg	20.0 mg	13.3%
65.0 kg	260.0 mg	40,0 mg	13.3%	130.0 mg	20.0 mg	13.3%
67.0 kg	268.0 mg	32.0 mg	10.7%	134.0 mg	16.0 mg	10.7%
67.0 kg	268.0 mg	32.0 mg	10.7%	134.0 mg	16.0 mg	10.7%
53.0 kg	212.0 mg	88.0 mg	29.3%	106.0 mg	44.0 mg	29.3%
53.0 kg	212.0 mg	88.0 mg	29.3%	106.0 mg	44.0 mg	29.3%
53.0 kg	212.0 mg	88.0 mg	29.3%	106.0 mg	44.0 mg	29.3%
53.0 kg	212.0 mg	88.0 mg	29.3%	106.0 mg	44.0 mg	29.3%
56.0 kg	224.0 mg	76.0 mg	25.3%	112.0 mg	38.0 mg	25.3%
57.0 kg	228.0 mg	72.0 mg	24.0%	114.0 mg	36.0 mg	24.0%
57.0 kg	228.0 mg	72.0 mg	24.0%	114.0 mg	36.0 mg	24.0%
Mean = 63.9 kg	255.5 mg	72.9 mg	22.2%	127.7 mg	46.6 mg	26.7%
2.5 - 97.5%			19.0-25.4%			23.0-30.5%

5.4 APPENDIX 4: ELIGIBILITY CRITERIA (LVEF)

In England, the prevalence of left-ventricular systolic dysfunction and heart failure was assessed in a large representative adult population.[42]

The prevalence of left-ventricular systolic dysfunction rose with age and was higher in men than in women. Dealing with breast cancer, we therefore used the reported age-specific data for women (n=1996). Using weighted averages, based on the number of patients in each age category, we converted the age categories of this study to those that fit our model (see table 90). The study of Davies did not collect data for people younger than 45. We suppose these young persons are not confronted with this problem. Since this group only represents a small proportion of our breast cancer population, this will not have a large influence on our estimates.

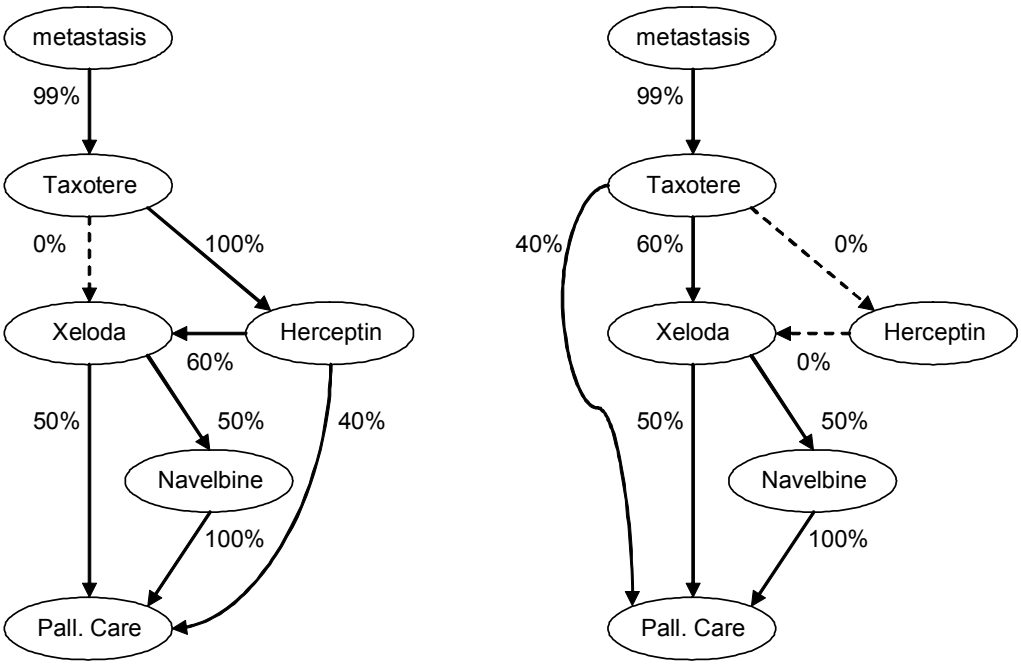
Table 90. Percentage of patients with an ejection fraction <50%

Age category	Number of patients	Ejection fraction <50%	
NCR, KCE, Belgium, 2005		Davies, 2001[42]	Estimation for several age categories
15-19	2		<50: 0.61% >50: 4.68%
20-24	5		
25-29	40		
30-34	123		
35-39	339		
40-44	674		
45-49	1030	1.3%	
50-54	1187		2.48%
55-59	1371	3.5%	
60-64	1058		3.7%
65-69	1069	3.9%	
70-74	890		6%
75-79	812	8.3%	
80-84	611		10.39%
85+	353	14%	
Total	9564		All: 3.74%

5.5 APPENDIX 5: COST METASTATIC TREATMENT

For Belgium, useful data on the cost of metastatic breast cancer treatment are lacking. Consequently, we tried to estimate these costs ourselves through modelling based on literature data and information from University Hosptial Ghent. Figure 28 presents standard treatment modalities in metastatic disease with and without trastuzumab.

Figure 28. Treatment of metastatic breast cancer with/without trastuzumab



Patients initially receive docetaxel as first-line treatment. Docetaxel (100 mg/m^2) is given for a maximum of 6 cycles and tumour response is evaluated every three cycles. Reasons for treatment discontinuation are disease progression or adverse events. Four trials with similar patient characteristics reported clinical benefit in 78% (n=94), 73.4% (n=203), 74% (n=256) and 75% (n=143) of patients.[71-74] In our model, the weighted average, i.e. 74.57%, receive six cycles. Furthermore, a study reported 5% on a total of 239 cycles received G-CSF.[75] In another trial, this was 15% on a total of 1474 cycles.[72] We incorporate the weighted average of 13.6%. These patients receive pegfilgrastim (6 mg). They usually stay in hospital for three days (305.98 euro/day) and also receive ceftazidim (3x2g/daily for three days and one extra start-up dose of 2g) and amikacine (1g/daily for three days).

Next, a distinction is made between whether or not trastuzumab is given. One might think that patients should just have a human epidermal growth factor receptor-2 (HER2) overexpressing breast cancer. However, since we are dealing with trastuzumab in adjuvant setting this depends also on whether or not patients who already received trastuzumab and progressed should receive this treatment for a second time. Furthermore, for those initially being HER2-negative and progressing to metastatic disease, HER2-status might change.[59, 58] These scenarios are dealt with in our model. If trastuzumab is given in metastatic setting, the drug is administered until disease progression (loading dose 4 mg/kg, weekly 2 mg/kg). In previous trials with the same administration schedule, the median time to disease progression was 3.1 and 3.5 months for respectively 222 and 59 patients.[76, 77] We incorporated the weighted average of 13.65 weeks.

Patients not treated with, or progressing after trastuzumab treatment could receive capecitabine (1250 mg/m^2 twice daily, days 1-14, followed by a 7-day rest period) and later on vinorelbine (30 mg/m^2, three weekly on the first and eight day). Capecitabine is

administered until disease progression or cumulative toxicity. Fumoleau and colleagues reported 126 patients who received a total of 874 cycles.[78] In another study 135 patients received a total of 700 cycles.[79] The weighted average of 6.03 cycles per patient was incorporated. Grade IV neutropenia only occurred very seldom.[79, 78] Concerning vinorelbine, in contrast to some trials who administered the drug until disease progression,[80, 81] this medication was given for a maximum of six cycles. Gasparini and colleagues reported a complete and partial response, and stable disease of respectively 4.48%, 31.34% and 29.85%.[80] In our model, these 65.67% of patients received six cycles of vinorelbine. Furthermore, 6 on 67 patients had grade IV leukopenia and granulocytopenia,[80] which we used in our model for the average of patients who received G-CSF.

Next, about 70% received hormonal treatment in metastatic disease which initially consisted of treatment with letrozole (2.5 mg/day) or anastrozole (1 mg/day). Treatment was maintained until disease progression. For letrozole, two studies reported a median time to progression of 3 and 5.6 months.[82, 83] The weighted average of 18 weeks was used in our analysis. For anastrozole, a median time to progression of 21 weeks was taken.[84] When progressing, about half of these patients were administered exemestane (25 mg/day). A median time to progression of 14.7 weeks was incorporated in our model.[85]

Finally, about 65-75% of patients had bone metastasis.[86] Bisphosphonates are an established standard of care for patients with bone metastases. As mentioned by Liberato,[87] the American Society of Clinical Oncology (ASCO) guidelines, published in 2000, recommend the use of intravenous pamidronate. 90 mg is administered every 3-4 weeks until decline of patient's performance status. The median survival from development of bone metastases is about 21 months.[88]

After 1000 Monte Carlo simulations, the costs for MBC were 31 878 euro (st.dev. 11 371) and 14 050 euro (st.dev. 2228) with and without trastuzumab. Based on a sample a 1000 patients, the resulting 95% CI for the mean was 31 878 euro (95%CI: 31 173 – 32 582) with trastuzumab and 14 050 euro (95%CI: 13 911 – 14 188) without trastuzumab.

5.6 APPENDIX 6: LIFE EXPECTANCY HEART FAILURE

The life expectancy of patients confronted with heart failure was based on data from a Dutch population. These numbers were rearranged to age categories using the number of Belgian patients with breast cancer according to age (table 91).

Table 91. Life expectancy (years) for patients with heart failure according to age

Age	life expectancy[a]	Number of patients	Age[b]	Life expectancy
25-29	7.24	40		
30-34	7.21	123		
35-39	7.12	339		
40-44	6.97	674		
45-49	6.84	1030	<50	6.95
50-54	6.59	1187	>50	5.21
55-59	6.15	1371	50-59	6.35
60-64	5.64	1058		
65-69	5.21	1069	60-69	5.42
70-74	4.73	890		
75-79	4.1	812	70-79	4.43
80-84	3.26	611		
85+	2.7	353	80+	3.05
All			All	5.61

Source: a: Hoogenveen, Dutch DisMod, RIVM report 260751 001; b: NCR, KCE, Belgium, 2005

6 REFERENCES

1. Goldhirsch A, Glick JH, Gelber RD, Coates AS, Thurlimann B, Senn HJ, et al. Meeting highlights: international expert consensus on the primary therapy of early breast cancer 2005. Ann Oncol. 2005;16(10):1569-83.
2. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, Goldhirsch A, Untch M, Smith I, et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. N Engl J Med. 2005;353(16):1659-72.
3. Romond EH, Perez EA, Bryant J, Suman VJ, Geyer CE, Jr., Davidson NE, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. N Engl J Med. 2005;353(16):1673-84.
4. Tan-Chiu E, Yothers G, Romond E, Geyer CE, Jr., Ewer M, Keefe D, et al. Assessment of cardiac dysfunction in a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel, with or without trastuzumab as adjuvant therapy in node-positive, human epidermal growth factor receptor 2-overexpressing breast cancer: NSABP B-31. J Clin Oncol. 2005;23(31):7811-9.
5. Perez EA. Further Analysis of NCCTG-N9831 (slide presentation at ASCO annual meeting). 2005. Available from: http://www.asco.org/ac/1,1003,_12-002511-00_18-0034-00_19-005815-00_21-001,00.asp
6. Romond EH. Joint analysis of NSABP-B-31 and NCCTG-N9831. Presentation at 2005 ASCO Annual Meeting. 2005. Available from: http://www.asco.org/ac/1,1003,_12-002511-00_18-0034-00_19-005817-00_21-001,00.asp
7. Joensuu H, Kellokumpu-Lehtinen P-L, Bono P, Alanko T, Kataja V, Asola R, et al. Trastuzumab in combination with docetaxel or vinorelbine as adjuvant treatment of breast cancer: the FinHer Trial. Abstract presented at the San Antonio Breast Cancer Symposium, December 8-11, 2005. 2005. Available from: http://www.abstracts2view.com/sabcs05/
8. Slamon D, Eiermann W, Robert N, Pienkowski T, Martin M, Pawlicki M, et al. Phase III randomized trial comparing doxorubicin and cyclophosphamide followed by docetaxel (ACT) with doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab (ACTH) with docetaxel, carboplatin and trastuzumab (TCH) in HER2 positive early breast cancer patients: BCIRG 006 study. Abstract presented at the San Antonio Breast Cancer Symposium, December 8-11, 2005. 2005. Available from: http://www.abstracts2view.com/sabcs05/
9. EMEA. Herceptin - European Public Assessment Report (EPAR). 2005. Available from: http://www.emea.eu.int/humandocs/Humans/EPAR/herceptin/herceptin.htm
10. FDA. Trastuzumab - Product Approval Information - Licensing Action. 1998. Available from: http://www.fda.gov/cder/biologics/products/trasgen092598.htm
11. FDA. Transcript of the 58th Meeting of the Oncologic Drug Advisory Committee, September 2, 1998. 1998. Available from: http://www.fda.gov/ohrms/dockets/ac/98/transcpt/3443t2.rtf
12. Van Eycken L, De Wever N. Cancer Incidence and Survival in Flandres, 2000-2001. Brussels: Flemish Cancer Registry Network, VLK; 2006.
13. Singletary SE, Allred C, Ashley P, Bassett LW, Berry D, Bland KI, et al. Revision of the American Joint Committee on Cancer staging system for breast cancer. J Clin Oncol. 2002;20(17):3628-36.
14. Andre S, Tomas AR, Fonseca R. [Determination of HER2 by fluorescence in situ hybridization (FISH) in breast cancer. Experience of the Reference Laboratory of Lisbon]. Acta Med Port. 2005;18(6):417-22.

15. Hudelist G, Kostler WJ, Czerwenka K, Kubista E, Attems J, Muller R, et al. Her-2/neu and EGFR tyrosine kinase activation predict the efficacy of trastuzumab-based therapy in patients with metastatic breast cancer. Int J Cancer. 2006;118(5):1126-34.

16. Arnould L, Gelly M, Penault-Llorca F, Benoit L, Bonnetain F, Migeon C, et al. Trastuzumab-based treatment of HER2-positive breast cancer: an antibody-dependent cellular cytotoxicity mechanism? Br J Cancer. 2006;94(2):259-67.

17. Imai K, Matsuyama S, Miyake S, Suga K, Nakachi K. Natural cytotoxic activity of peripheral-blood lymphocytes and cancer incidence: an 11-year follow-up study of a general population. Lancet. 2000;356(9244):1795-9.

18. Stemmler H-J, Kahlert S, Siekiera W, Untch M, Heinrich B, Heinemann V. Prolonged survival of patients receiving trastuzumab beyond disease progression for HER2 overexpressing metastatic breast cancer (MBC). Onkologie. 2005;28(11):582-6.

19. Pusztai L, Esteva FJ. Continued use of trastuzumab (herceptin) after progression on prior trastuzumab therapy in HER-2-positive metastatic breast cancer. Cancer Invest. 2006;24(2):187-91.

20. Hortobagyi G. Continuation of trastuzumab beyond disease progression. J Clin Oncol. 2005;23(12):2868-9.

21. Ellis IO, Bartlett J, Dowsett M, Humphreys S, Jasani B, Miller K, et al. Best Practice No 176: Updated recommendations for HER2 testing in the UK. J Clin Pathol. 2004;57(3):233-7.

22. Hulstaert F, Huybrechts M, Van Den Bruel A, Cleemput I, Bonneux L, Vernelen K, et al. HTA Moleculaire Diagnostiek in België. KCE reports 20 A. (D2005/10.273/23). Brussels: Federaal Kenniscentrum voor de Gezondheidszorg (KCE); 2005.

23. Joensuu H, Kellokumpu-Lehtinen P-L, Bono P, Alanko T, Kataja V, Asola R, et al. Adjuvant docetaxel or vinorelbine with or without trastuzumab for breast cancer. N Engl J Med. 2006;354(8):809-20.

24. Sledge G, O'Neill A, Thor A. Pilot trial of paclitaxel-Herceptin adjuvant therapy for early stage breast cancer (E2198). Breast Cancer Res Treat. 2001;69:209. Abstract 4. Updated based on presentation.

25. Weil RJ, Palmieri DC, Bronder JL, Stark AM, Steeg PS. Breast cancer metastasis to the central nervous system. Am J Pathol. 2005;167(4):913-20.

26. Fuchs IB, Loebbecke M, Buhler H, Stoltenburg-Didinger G, Heine B, Lichtenegger W, et al. HER2 in brain metastases: issues of concordance, survival, and treatment. J Clin Oncol. 2002;20(19):4130-3.

27. Puglisi F, Piccart M. Trastuzumab and breast cancer. Are we just beyond the prologue of a fascinating story? Onkologie. 2005;28(11):547-9.

28. Buzdar AU, Ibrahim NK, Francis D, Booser DJ, Thomas ES, Theriault RL, et al. Significantly higher pathologic complete remission rate after neoadjuvant therapy with trastuzumab, paclitaxel, and epirubicin chemotherapy: results of a randomized trial in human epidermal growth factor receptor 2-positive operable breast cancer. J Clin Oncol. 2005;23(16):3676-85.

29. Coudert B, Arnould L, Moreau L, Chollet P, Weber B, Vanlemmens L, et al. Pre-operative systemic (neo-adjuvant) therapy with trastuzumab and docetaxel for HER2-overexpressing stage II or III breast cancer: results of a multicenter phase II trial. Ann Oncol. 2005.

30. Hurley J, Doliny P, Reis I, Silva O, Gomez-Fernandez C, Velez P, et al. Docetaxel, cisplatin, and trastuzumab as primary systemic therapy for human epidermal growth factor receptor 2-positive locally advanced breast cancer. J Clin Oncol. 2006;24(12):1831-8.

31. Perez EA, Rodeheffer R. Clinical cardiac tolerability of trastuzumab. J Clin Oncol. 2004;22(2):322-9.

32. Fuchs IB, Landt S, Bueler H, Kuehl U, Coupland S, Kleine-Tebbe A, et al. Analysis of HER2 and HER4 in human myocardium to clarify the cardiotoxicity of trastuzumab (Herceptin). Breast Cancer Res Treat. 2003;82(1):23-8.

33. Minotti G, Menna P, Salvatorelli E, Cairo G, Gianni L. Anthracyclines: molecular advances and pharmacologic developments in antitumor activity and cardiotoxicity. Pharmacol Rev. 2004;56(2):185-229.

34. Ewer MS, Vooletich MT, Durand J-B, Woods ML, Davis JR, Valero V, et al. Reversibility of trastuzumab-related cardiotoxicity: new insights based on clinical course and response to medical treatment. J Clin Oncol. 2005;23(31):7820-6.

35. Behr TM, Behe M, Wormann B. Trastuzumab and breast cancer. N Engl J Med. 2001;345(13):995-6.

36. Milano G, Lescaut W, Formento J, Largillier R, Campone M, Chamorey E, et al. HER2 genetic polymorphism and pharmacodynamics of trastuzumab-based treatment in breast cancer patients. 2005. Available from: http://www.asco.org/portal/site/ASCO/menuitem.34d60f5624ba07fd506fe310ee37a01d/?vgnextoid=76f8201eb61a7010VgnVCM100000ed730ad1RCRD&vmview=abst_detail_view&confID=34&index=y&abstractID=31252

37. Page E, Assouline D, Brun O, Coeffic D, Fric D, Winckel P. Cardiac dysfunction in clinical trials of trastuzumab. J Clin Oncol. 2002;20(19):4119; author reply 20.

38. Gluck S. Adjuvant chemotherapy for early breast cancer: optimal use of epirubicin. Oncologist. 2005;10(10):780-91.

39. McConachie I, Hesketh Roberts D. Handbook of Cardiac Emergencies. 2005.

40. Bellenger NG, Burgess MI, Ray SG, Lahiri A, Coats AJ, Cleland JG, et al. Comparison of left ventricular ejection fraction and volumes in heart failure by echocardiography, radionuclide ventriculography and cardiovascular magnetic resonance; are they interchangeable? Eur Heart J. 2000;21(16):1387-96.

41. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr. 2005;18(12):1440-63.

42. Davies M, Hobbs F, Davis R, Kenkre J, Roalfe AK, Hare R, et al. Prevalence of left-ventricular systolic dysfunction and heart failure in the Echocardiographic Heart of England Screening study: a population based study. Lancet. 2001;358(9280):439-44.

43. Genentech. Herceptin - Important Drug Warning Letter. 2005. Available from: http://www.fda.gov/medwatch/safety/2005/HerceptinDDL_0805.FINAL.pdf

44. Cleemput I, Crott R, Vrijens F, Huybrechts M, Van Wilder P, Ramaekers D. Voorlopige richtlijnen voor farmaco-economisch onderzoek in België. Brussel : Federaal Kenniscentrum voor de gezondheidszorg (KCE) ; Mei 2006. KCE Reports vol. 28A. Ref. D/2006/10.273/10. 2006.

45. Johannesson M. Economic evaluation of drugs and its potential uses in policy making. Pharmacoeconomics. 1995;8(3):190-8.

46. Gold MR. Cost-effectiveness in health and medicine. New York: Oxford University Press; 1996.

47. Drummond MF. Methods for the economic evaluation of health care programmes. 3rd ed. Oxford ; New York: Oxford University Press; 2005.

48. Raftery J. NICE: faster access to modern treatments? Analysis of guidance on health technologies. BMJ. 2001;323(7324):1300-3.

49. Russell LB. Modelling for cost-effectiveness analysis. Stat Med. 1999;18(23):3235-44.

50. Berkowitz N, Gupta S, Silberman G. Estimates of the lifetime direct costs of treatment for metastatic breast cancer. Value Health. 2000;3(1):23-30.

51. Clemons M, Danson S, Hamilton T, Goss P. Locoregionally recurrent breast cancer: incidence, risk factors and survival. Cancer Treat Rev. 2001;27(2):67-82.

52. Ernst MF, Voogd AC, Coebergh JWW, Poortmans PM, Roukema JA. Using loco-regional recurrence as an indicator of the quality of breast cancer treatment. Eur J Cancer. 2004;40(4):487-93.

53. Pendlebury SC, Ivanov O, Renwick S, Stevens GN. Long-term review of a breast conservation series and patterns of care over 18 years. ANZ J Surg. 2003;73(8):577-83.

54. Benchalal M, Le Prise E, de Lafontan B, Berton-Rigaud D, Belkacemi Y, Romestaing P, et al. Influence of the time between surgery and radiotherapy on local recurrence in patients with lymph node-positive, early-stage, invasive breast carcinoma undergoing breast-conserving surgery: results of the French Adjuvant Study Group. Cancer. 2005;104(2):240-50.

55. Clarke M, Collins R, Darby S, Davies C, Elphinstone P, Evans E, et al. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. Lancet. 2005;366(9503):2087-106.

56. Huang EH, Tucker SL, Strom EA, McNeese MD, Kuerer HM, Hortobagyi GN, et al. Predictors of locoregional recurrence in patients with locally advanced breast cancer treated with neoadjuvant chemotherapy, mastectomy, and radiotherapy. Int J Radiat Oncol Biol Phys. 2005;62(2):351-7.

57. Heys SD, Chaturvedi S, Hutcheon AW, Sarkar TK. Guidelines, guidelines and more guidelines: and we still do not know how to follow-up patients with breast cancer. World J Surg Oncol. 2005;3:54.

58. Zidan J, Dashkovsky I, Stayerman C, Basher W, Cozacov C, Hadary A. Comparison of HER-2 overexpression in primary breast cancer and metastatic sites and its effect on biological targeting therapy of metastatic disease. Br J Cancer. 2005;93(5):552-6.

59. Regitnig P, Schippinger W, Lindbauer M, Samonigg H, Lax SF. Change of HER-2/neu status in a subset of distant metastases from breast carcinomas. J Pathol. 2004;203(4):918-26.

60. Will BP, Berthelot JM, Le Petit C, Tomiak EM, Verma S, Evans WK. Estimates of the lifetime costs of breast cancer treatment in Canada. Eur J Cancer. 2000;36(6):724-35.

61. Wai ES, Trevisan CH, Mates D, Jackson JS, Olivotto IA. Health system costs of metastatic breast cancer. Breast Cancer Res Treat. 2001;65(3):233-40.

62. Rao S, Kubisiak J, Gilden D. Cost of illness associated with metastatic breast cancer. Breast Cancer Res Treat. 2004;83(1):25-32.

63. Remak E, Brazil L. Cost of managing women presenting with stage IV breast cancer in the United Kingdom. Br J Cancer. 2004;91(1):77-83.

64. Duchnowska R, Czartoryska-Arlukowicz B, Radecka B, Szostakiewicz B, Karpinska A, Dziadziuszko R, et al. Brain metastases in HER2 positive metastatic breast cancer (MBC) patients. European Journal of Cancer Supplements. 2006;4(2):165.

65. Briggs A. Probabilistic analysis of cost-effectiveness models: statistical representation of parameter uncertainty. Value Health. 2005;8(1):1-2.

66. Briggs AH, Goeree R, Blackhouse G, O'Brien BJ. Probabilistic analysis of cost-effectiveness models: choosing between treatment strategies for gastroesophageal reflux disease. Med Decis Making. 2002;22(4):290-308.

67. Claxton K, Sculpher M, Drummond M. A rational framework for decision making by the National Institute For Clinical Excellence (NICE). Lancet. 2002;360(9334):711-5.

68. Parmigiani G. Uncertainty and the value of diagnostic information, with application to axillary lymph node dissection in breast cancer. Stat Med. 2004;23(5):843-55.

69. Mellemkjaer L, Friis S, Olsen J, Scelo G, Hemminki K, Tracey E, et al. Risk of second cancer among women with breast cancer. Int J Cancer. 2006;118(9):2285-92.

70. Ades AE, Claxton K, Sculpher M. Evidence synthesis, parameter correlation and probabilistic sensitivity analysis. Health Econ. 2006;15(4):373-81.

71. Nabholtz JM, Senn HJ, Bezwoda WR, Melnychuk D, Deschenes L, Douma J, et al. Prospective randomized trial of docetaxel versus mitomycin plus vinblastine in patients with metastatic

breast cancer progressing despite previous anthracycline-containing chemotherapy. 304 Study Group. J Clin Oncol. 1999;17(5):1413-24.

72. Sjostrom J, Blomqvist C, Mouridsen H, Pluzanska A, Ottosson-Lonn S, Bengtsson NO, et al. Docetaxel compared with sequential methotrexate and 5-fluorouracil in patients with advanced breast cancer after anthracycline failure: a randomised phase III study with crossover on progression by the Scandinavian Breast Group. Eur J Cancer. 1999;35(8):1194-201.

73. O'Shaughnessy J, Miles D, Vukelja S, Moiseyenko V, Ayoub J-P, Cervantes G, et al. Superior survival with capecitabine plus docetaxel combination therapy in anthracycline-pretreated patients with advanced breast cancer: phase III trial results. J Clin Oncol. 2002;20(12):2812-23.

74. Marty M, Cognetti F, Maraninchi D, Snyder R, Mauriac L, Tubiana-Hulin M, et al. Randomized phase II trial of the efficacy and safety of trastuzumab combined with docetaxel in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer administered as first-line treatment: the M77001 study group. J Clin Oncol. 2005;23(19):4265-74.

75. Alba E, Martin M, Ramos M, Adrover E, Balil A, Jara C, et al. Multicenter randomized trial comparing sequential with concomitant administration of doxorubicin and docetaxel as first-line treatment of metastatic breast cancer: a Spanish Breast Cancer Research Group (GEICAM-9903) phase III study. J Clin Oncol. 2004;22(13):2587-93.

76. Cobleigh MA, Vogel CL, Tripathy D, Robert NJ, Scholl S, Fehrenbacher L, et al. Multinational study of the efficacy and safety of humanized anti-HER2 monoclonal antibody in women who have HER2-overexpressing metastatic breast cancer that has progressed after chemotherapy for metastatic disease. J Clin Oncol. 1999;17(9):2639-48.

77. Vogel CL, Cobleigh MA, Tripathy D, Gutheil JC, Harris LN, Fehrenbacher L, et al. Efficacy and safety of trastuzumab as a single agent in first-line treatment of HER2-overexpressing metastatic breast cancer. J Clin Oncol. 2002;20(3):719-26.

78. Fumoleau P, Largillier R, Clippe C, Dieras V, Orfeuvre H, Lesimple T, et al. Multicentre, phase II study evaluating capecitabine monotherapy in patients with anthracycline- and taxane-pretreated metastatic breast cancer. Eur J Cancer. 2004;40(4):536-42.

79. Reichardt P, Von Minckwitz G, Thuss-Patience PC, Jonat W, Kolbl H, Janicke F, et al. Multicenter phase II study of oral capecitabine (Xeloda(")) in patients with metastatic breast cancer relapsing after treatment with a taxane-containing therapy. Ann Oncol. 2003;14(8):1227-33.

80. Gasparini G, Caffo O, Barni S, Frontini L, Testolin A, Guglielmi RB, et al. Vinorelbine is an active antiproliferative agent in pretreated advanced breast cancer patients: a phase II study. J Clin Oncol. 1994;12(10):2094-101.

81. Keller AM, Mennel RG, Georgoulias VA, Nabholtz J-M, Erazo A, Lluch A, et al. Randomized phase III trial of pegylated liposomal doxorubicin versus vinorelbine or mitomycin C plus vinblastine in women with taxane-refractory advanced breast cancer. J Clin Oncol. 2004;22(19):3893-901.

82. Dombernowsky P, Smith I, Falkson G, Leonard R, Panasci L, Bellmunt J, et al. Letrozole, a new oral aromatase inhibitor for advanced breast cancer: double-blind randomized trial showing a dose effect and improved efficacy and tolerability compared with megestrol acetate. J Clin Oncol. 1998;16(2):453-61.

83. Buzdar A, Douma J, Davidson N, Elledge R, Morgan M, Smith R, et al. Phase III, multicenter, double-blind, randomized study of letrozole, an aromatase inhibitor, for advanced breast cancer versus megestrol acetate. J Clin Oncol. 2001;19(14):3357-66.

84. Buzdar A, Jonat W, Howell A, Jones SE, Blomqvist C, Vogel CL, et al. Anastrozole, a potent and selective aromatase inhibitor, versus megestrol acetate in postmenopausal women with advanced breast cancer: results of overview analysis of two phase III trials. Arimidex Study Group. J Clin Oncol. 1996;14(7):2000-11.

85. Lonning PE, Bajetta E, Murray R, Tubiana-Hulin M, Eisenberg PD, Mickiewicz E, et al. Activity of exemestane in metastatic breast cancer after failure of nonsteroidal aromatase inhibitors: a phase II trial. J Clin Oncol. 2000;18(11):2234-44.

86. Gainford MC, Dranitsaris G, Clemons M. Recent developments in bisphosphonates for patients with metastatic breast cancer. BMJ. 2005;330(7494):769-73.

87. Liberato NL, Marchetti M, Barosi G. Clinical and economic issues in the treatment of advanced breast cancer with bisphosphonates. Drugs Aging. 2003;20(9):631-42.

88. McCloskey EV, Guest JF, Kanis JA. The clinical and cost considerations of bisphosphonates in preventing bone complications in patients with metastatic breast cancer or multiple myeloma. Drugs. 2001;61(9):1253-74.

This page is left intentionally blank.

Dépôt légal : D/2006/10.273/24

KCE reports

1. Efficacité et rentabilité des thérapies de sevrage tabagique. D/2004/10.273/2.
2. Etude relative aux coûts potentiels liés à une éventuelle modification des règles du droit de la responsabilité médicale (Phase 1). D/2004/10.273/4.
3. Utilisation des antibiotiques en milieu hospitalier dans le cas de la pyélonéphrite aiguë. D/2004/10.273/6.
4. Leucoréduction. Une mesure envisageable dans le cadre de la politique nationale de sécurité des transfusions sanguines. D/2004/10.273/8.
5. Evaluation des risques préopératoires. D/2004/10.273/10.
6. Validation du rapport de la Commission d'examen du sous financement des hôpitaux. D/2004/10.273/12.
7. Recommandation nationale relative aux soins prénatals: Une base pour un itinéraire clinique de suivi de grossesses. D/2004/10.273/14.
8. Systèmes de financement des médicaments hospitaliers: étude descriptive de certains pays européens et du Canada. D/2004/10.273/16.
9. Feedback: évaluation de l'impact et des barrières à l'implémentation – Rapport de recherche: partie 1. D/2005/10.273/02.
10. Le coût des prothèses dentaires. D/2005/10.273/04.
11. Dépistage du cancer du sein. D/2005/10.273/06.
12. Etude d'une méthode de financement alternative pour le sang et les dérivés sanguins labiles dans les hôpitaux. D/2005/10.273/08.
13. Traitement endovasculaire de la sténose carotidienne. D/2005/10.273/10.
14. Variations des pratiques médicales hospitalières en cas d'infarctus aigu du myocarde en Belgique. D/2005/10.273/12
15. Evolution des dépenses de santé. D/2005/10.273/14.
16. Etude relative aux coûts potentiels liés à une éventuelle modification des règles du droit de la responsabilité médicale. Phase II : développement d'un modèle actuariel et premières estimations. D/2005/10.273/16.
17. Evaluation des montants de référence. D/2005/10.273/18.
18. Utilisation des itinéraires cliniques et guides de bonne pratique afin de déterminer de manière prospective les honoraires des médecins hospitaliers: plus facile à dire qu'à faire.. D/2005/10.273/20
19. Evaluation de l'impact d'une contribution personnelle forfaitaire sur le recours au service d'urgences. D/2005/10.273/22.
20. HTA Diagnostic Moléculaire en Belgique. D/2005/10.273/24, D/2005/10.273/26.
21. HTA Matériel de Stomie en Belgique. D/2005/10.273.28.
22. HTA Tomographie par Emission de Positrons en Belgique. D/2005/10.273/30.
23. HTA Le traitement électif endovasculaire de l'anévrysme de l'aorte abdominale (AAA). D/2005/10.273.33.
24. L'emploi des peptides natriurétiques dans l'approche diagnostique des patients présentant une suspicion de décompensation cardiaque. D/2005/10.273.35
25. Endoscopie par capsule. D2006/10.273.02.
26. Aspects médico-légaux des recommandations de bonne pratique médicale. D2006/10.273/06.
27. Qualité et organisation des soins du diabète de type 2. D2006/10.273/08.
28. Recommandations provisoires pour les évaluations pharmacoéconomiques en Belgique. D2006/10.273/11.
29. Recommandations nationales Collège d'oncologie : A. cadre général pour un manuel d'oncologie B. base scientifique pour itinéraires cliniques de diagnostic et traitement, cancer colorectal et cancer du testicule. D2006/10.273/13.
30. Inventaire des bases de données de soins de santé. D2006/10.273/15.
31. Health Technology Assessment : l'antigène prostatique spécifique (PSA) dans le dépistage du cancer de la prostate. D2006/10.273/18.
32. Feedback: évaluation de l'impact et des barrières à l'implémentation - Rapport de recherche: partie II. D2006/10.273/20.
33. Effets et coûts de la vaccination des enfants Belges au moyen du vaccin conjugué antipneumococcique. D2006/10.273/22.
34. Trastuzumab pour les stades précoces du cancer du sein. D2006/10.273/24.