



# Trastuzumab bij vroegtijdige stadia van borstkanker

*KCE reports vol. 34A*

Federaal Kenniscentrum voor de gezondheidszorg  
Centre fédéral d'expertise des soins de santé  
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# Trastuzumab bij vroegtijdige stadia van borstkanker

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## Voorwoord

Trastuzumab (Herceptin, Roche) is een bestaand geneesmiddel dat tot nu toe enkel werd gebruikt bij vrouwen met gemetastaseerde borstkanker. Trastuzumab is een uitgelezen voorbeeld van hoe geavanceerd moleculair biologisch onderzoek kan leiden tot baanbrekende klinische toepassingen.

Gunstige resultaten werden in de loop van 2005 bekend voor studies met trastuzumab en chemotherapie in vroegtijdige stadia van borstcarcinoom zonder dat in parallel een dossier was neergelegd voor uitbreiding van de indicatie. Uitgebreide mediabelangstelling startte onmiddellijk. Onder druk van patiëntenorganisaties werd dit product in een aantal landen ter beschikking gesteld en gefinancierd nog voor de verplichte evaluatie door de bevoegde overheid kon plaatsvinden. Zulke praktijken zijn niet zonder risico. In deze context werd door de Minister van Sociale Zaken en Volksgezondheid aan het KCE gevraagd een farmaco-economische studie uit te voeren.

Een jaar behandeling met trastuzumab, zoals uitgetest in de ondertussen alom geprezen HERA-studie waarin Belgische onderzoekers een vooraanstaande rol spelen, kost de ziekteverzekerling ongeveer 40 000 euro. In België komen jaarlijks momenteel een 500-tal vrouwen met borstkanker in aanmerking voor behandeling. Of dat nu als ‘kosten-effectief’ kan beschouwd worden, kunt u in dit KCE rapport lezen.

Eén majeure nevenwerking is hartfalen, waardoor een deel van de vrouwen met hartziekte niet in aanmerking komt voor trastuzumab. Maar de wetenschap staat niet stil en ook daar bieden er zich interessante perspectieven aan. Recent werd de FinHER studie gepubliceerd in het prestigieuze *New England Journal of Medicine*. In die kleinere studie wordt trastuzumab toegediend vóór i.p.v. na de chemotherapie en over een kortere duur van 9 weken. Zelfs met 3 jaar follow-up werden er geen cardiale nevenwerkingen vastgesteld, terwijl de ziektevrije overleving significant verbeterde.

In de onderliggende farmaco-economische studie spreken we ons niet uit voor of tegen de één of andere toedieningsvorm of duur. Anderzijds hadden we ook onvoldoende rationele argumenten om ons (zoals bij de EMEA evaluatie) te beperken tot louter de gegevens van de HERA trial.

Als aandachtig lezer verwacht u dan een vergelijkende klinische studie om de beste volgorde van toediening en de bij elke volgorde horende optimale duur van toediening te weten. Of die vergelijking er komt zal de geschiedenis uitwijzen.

Jean-Pierre CLOSON

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## Samenvatting

Lijst met afkortingen volgt na deze samenvatting.

## INLEIDING

Trastuzumab (Herceptin, Roche) is een recombinant, gehumaniseerd monoklonaal antilichaam gericht tegen het neu-HER2 eiwit. HER2, human epidermal growth factor receptor 2, kan voorkomen op het celoppervlak van borstkankercellen en maakt die cellen meer gevoelig voor groeifactoren. HER2 positieve (HER2+) tumoren kunnen daardoor vlugger groeien. De proportie HER2+ borstcarcinomen daalt met de leeftijd. Bijkomend kan de HER2 status van een primaire borstkanker negatief zijn terwijl de corresponderende metastases HER2 positief zijn. Directe detectie van HER2 overexpressie bij borstkanker gebeurt klassiek met immunochemische analyse (IHC). Bij de mens ligt amplificatie van het HER2 gen op chromosoom 17 nauwelijks altijd aan de basis van de HER2 overexpressie. Daarom kan HER2 testing ook indirect via bepaling van amplificatie van dit chromosoom met FISH (Fluorescence in situ hybridisation) of CISH (Chromogenic in situ hybridisation). FISH en CISH HER2 resultaten zijn beter reproduceerbaar dan IHC resultaten.

Trastuzumab wordt in de praktijk al gebruikt voor de behandeling van HER2+ borstcarcinoom in een gevorderd stadium (gemetastaseerd). Vier grote gerandomiseerde studies zijn gestart om de werkzaamheid en veiligheid te testen van trastuzumab in vroege stadia van HER2+ borstkanker (niet gemetastaseerd). Veelbelovende gedeeltelijke resultaten van deze trastuzumab studies zijn publiek gemaakt vanaf mei 2005 via presentaties op conferenties en als wetenschappelijke publicaties. Deze studies vormen de basis voor het dossier voor mogelijke uitbreiding van de indicaties voor trastuzumab. Dit dossier werd pas recent (in februari 2006) ingediend bij het Europees agentschap voor geneesmiddelen (EMEA) door het farmaceutisch bedrijf Roche. In deze relatief lange tussentijd hebben in een aantal landen patiëntenverenigingen, soms met succes, geprotesteerd voor het voortijdig ter beschikking stellen en vergoeden van trastuzumab in HER2+ vroege vormen van borstkanker. Dit alles gebeurde nog voor de noodzakelijke kritische evaluatie van werkzaamheid en nevenwerkingen door de bevoegde autoriteiten plaats kon vinden. Deze praktijk is niet zonder risico. Na een versnelde evaluatieprocedure keurde EMEA in mei 2006 de extensie van indicatie goed voor trastuzumab in vroege stadia van borstkanker.

In dit kader en op vraag van de Belgische Minister van Sociale Zaken en Volksgezondheid werd een project gestart binnen het KCE. Dit project betreft een schatting van het aantal patiënten, een kosten-effectiviteit evaluatie en budget impact analyse vanuit het perspectief van de betaler (payer) van de terugbetaling van trastuzumab in deze nieuwe indicatie. Dossiers voor goedkeuring van farmaceutische producten zijn niet toegankelijk voor het publiek noch voor de meeste instellingen belast met "Health Technology Assessment", zoals het KCE. Daarom kan dit rapport ook geen exhaustive evaluatie van werkzaamheid en nevenwerkingen claimen. Contact werd opgenomen met Roche België als bron van publieke gegevens. De resultaten in dit rapport zijn dus gebaseerd op publiek beschikbare informatie voor efficaciteit en veiligheid, alsook epidemiologische en kostgegevens, waarvan een deel specifiek zijn voor België.

## BORSTKANKER IN BELGIË

Het aantal invasieve borstcarcinomen per leeftijds categorie gediagnosticeerd in België werd berekend op basis van de 5337 nieuw gediagnosticeerde borstkancers in Vlaanderen, geregistreerd door het Vlaams Kankerregistratiennetwerk voor het jaar 2001, en representatief voor ongeveer 60% van de Belgische bevolking. De incidentie per 5-jaars leeftijds klasse toegepast op de volledige vrouwelijke Belgische populatie op 1 januari 2005 leverde een totaal van 9564 nieuwe gevallen van borstkanker per jaar.

Het KCE startte een bevraging van de 80 oncologie centra in februari 2006. Tweeëndertig ziekenhuizen waren akkoord om hun gegevens door te geven betreffende het laatste volledige registratiejaar en in totaal 4528 gevallen van invasief borstcarcinoom met bepaling van het stadium. Overexpressie van neu-HER2 was meer frequent bij borstcarcinoom op jongere leeftijd. De frequentie van HER2 positiviteit was ongeveer twee maal hoger in gemetastaseerde

borstkanker dan bij borstcarcinoom kleiner dan 2 cm met negatieve lymfeklieren. De frequentie van HER2 FISH positiviteit voor alle invasieve borstkancers in België werd geschat op 13,55%.

De behandeling met een invasief borstcarcinoom stadium I, II en III bij vrouwen tot de leeftijd van 70 jaar omvatte chirurgie en radiotherapie in 99% en 88% van de gevallen. De grote meerderheid (79%) van de patiënten met een oestrogeen receptor positieve borstkanker startten ook hormonale therapie, vooral tamoxifen. Chemotherapie was de vierde hoeksteen van de behandeling in patiënten tot 70 jaar met een tumor stadium II (71%) of stadium III (86%). De voornaamste component was een anthracycline (in 97%), gecombineerd met ofwel een taxaan of andere chemotherapie. Het meest frequent voorkomende regime bestond uit 5-fluorouracil, epirubicin en cyclophosphamide (FEC), eventueel gevolgd door docetaxel cycli. Borstcarcinomen met HER2 overexpressie werden relatief meer frequent behandeld met chemotherapie.

## KLINISCHE GEGEVENS

### WERKZAAMHEID

In Europa is Herceptin momenteel op de markt als single dose vial met een inhoud van 150 mg trastuzumab. In de US worden multidose vials van 440 mg gebruikt. De goedgekeurde dosis voor de indicatie gemetastaseerd borstcarcinoom is 2 mg trastuzumab per kg lichaamsgewicht, wekelijks intraveneus toegediend. De eerste ladingsdosis bedraagt 4 mg/kg. Het juiste werkingsmechanisme van trastuzumab is niet goed gekend. Meer bepaald is nog onduidelijk of trastuzumab op HER2+ tumorcellen een cytostatisch dan wel een cytotoxisch effect heeft. De rationale voor een continue toediening tot ziekteprogressie optreedt bij vrouwen met gemetastaseerd borstcarcinoom is enkel gebaseerd op resultaten van dierproeven.

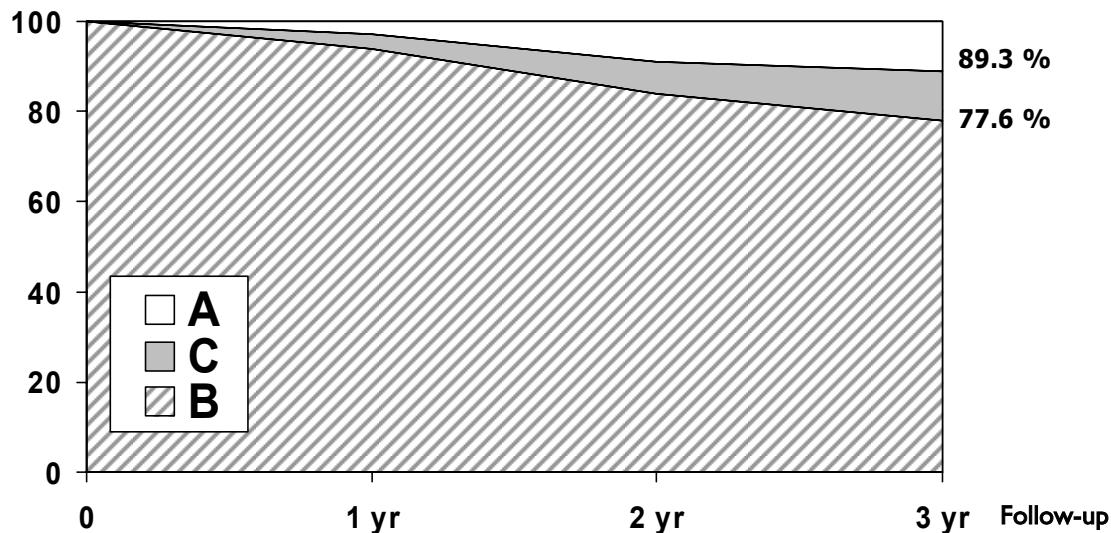
Vier grote en twee kleinere open-label gerandomiseerde studies zijn opgestart om het effect van trastuzumab te evalueren in vroegtijdige vormen van HER2+ borstkanker (Tabel 1). HER2 positiviteit was gedefinieerd als IHC 3+ of FISH+. De meeste patiënten geïncludeerd in deze studies hadden borstkanker met positieve lymfeklieren (N+). Een minderheid had borstkanker met verhoogd risico maar zonder invasie van de lymfeklieren (N0). De standaard trastuzumab intraveneuze dosis, namelijk 2 mg/kg per week (na een éénmalige ladingsdosis van 4 mg/kg), werd in alle studies gebruikt behalve in de HERA studie waar 6 mg/kg werd toegediend om de drie weken (na een éénmalige ladingsdosis van 8 mg/kg). Ook dit doseringsregime blijkt voldoende om een minimumspiegel aan trastuzumab te onderhouden. Drie van de 4 grote studies hadden elk drie armen. Alle vrouwen in de studies kregen anthracyclines toegediend vooraleer trastuzumab werd gestart, behalve 6% van de vrouwen in de HERA studie en de patiënten in één arm van de BCIRG006 studie. In de FinHer studie werden HER2 CISH+ patiënten gerandomiseerd naar 9 weken trastuzumab of geen trastuzumab (samen met docetaxel of vinorelbine), gevolgd door epirubicin-bevattende chemotherapie (FEC). Zulk een omgekeerde behandelingsvolgorde werd ook gebruikt in de E2198 fase 2 studie, waar het vergeleken werd met hetzelfde schema plus een extra jaar trastuzumab. Een vijfde grote trial, PACS04, loopt nog en bestudeert ook 52 weken trastuzumab na anthracycline chemotherapie. Er gebeurde nog geen analyse naar efficaciteit voor deze studie.

Tabel I. Ontwerp van de studies met trastuzumab in vroegtijdige vormen van borstcarcinoom

| Studiecode, regio, patiënten (pat.) en inclusiecriteria        | Anthracycline vooraf (of nadien in FinHer/E2198)   | Trastuzumab start in combinatie | Trastuzumab sequentieel na    | Trastuzumab regime                    |
|--|--|---------------------------------|-------------------------------|---------------------------------------|
| B31, US,<br>2 armen: 1960? pat,<br>N+ of N0 high-risk          | doxorubicine<br>+cyclophosphamide (AC)   | Paclitaxel                      |                               | 2 mg/kg/wk<br>1 jaar                  |
| N9831, US,<br>3 armen: 3046 pat,<br>N+ of N0 high-risk         | doxorubicine<br>+cyclophosphamide  |                                 | paclitaxel (arm B)            | 2 mg/kg/wk<br>1 jaar                  |
|  |  | paclitaxel (arm C)              |                               |                                       |
| HERA, ex-US,<br>3 armen: 5090 pat,<br>N+ of N0 with T1c        | geen anthracycline (6%),<br>doxorubicine zonder<br>taxane (23%), epirubicine<br>zonder taxane (45%),<br>anthracycline + taxanes<br>(26%) |                                 | alle chemotherapie            | 6 mg/kg/3wk<br>1 jaar                 |
|  |  |                                 |                               | 6 mg/kg/3wk<br>2 jaar                 |
| BCIRG006, globaal,<br>3 armen: 3222 pat,<br>N+ of N0 high-risk | doxorubicine<br>+cyclophosphamide  | docetaxel arm                   |                               | 2 mg/kg/wk<br>1 jaar                  |
|  | geen anthracycline voor<br>of na   | docetaxel +<br>carboplatin      |                               |                                       |
| FinHer, Finland,<br>2 armen: 232 pat,<br>N+ of N0 >2cm         | na: 5FU+epirubicin<br>+cyclophosphamide (FEC)  | docetaxel or<br>vinorelbine     |                               | 2 mg/kg/wk<br>9 weken                 |
| E2198, US,<br>2 armen: 200 pat,<br>N+, stadium II of IIIa      | na: doxorubicin<br>+cyclophosphamide   | Paclitaxel                      |                               | 2 mg/kg/wk<br>10 weken                |
|  |  |                                 | deels ook na<br>chemotherapie | 2 mg/kg/wk<br>10 w voor +<br>1y na AC |

Het primaire eindpunt in de studies was ziektevrije overleving (disease-free survival, DFS). De resultaten kunnen weergegeven worden als percentage overleving per studie arm. Patiënten kunnen aldus ingedeeld worden in drie groepen (Figuur I). Groep A bestaat uit de patiënten die hervallen of overlijden gedurende de follow-up periode (omdat ze refractair of resistent zijn aan de nieuwe behandeling). Groep B bestaat uit patiënten die niet zouden hervallen of overlijden, ook al krijgen ze de nieuwe behandeling niet. Dit stelt in feite de controle arm voor, namelijk observatie of de standaard behandeling aanbevolen op het ogenblik dat de studie start voor de patiënten in het betreffende ziekte stadium. Groep C bestaat uit patiënten die hervallen zouden zijn of overleden mochten ze de experimentele behandeling niet gekregen hebben. Patiënten in groep A en B halen dus geen voordeel uit de experimentele behandeling terwijl ze wel blootstaan aan de toxiciteit, nevenwerkingen, psychosociale impact van de nieuwe behandeling. Dit wordt geïllustreerd met de resultaten voor ziektevrije overleving in de FinHer studie (Figuur I). Het gebied C komt overeen met de 11% van de patiënten die dankzij trastuzumab niet hervallen. De overige 89% van de patiënten (A+B) haalden geen voordeel uit de trastuzumab behandeling, omdat ze niet antwoordden op trastuzumab (gebied A, 11%) of omdat ze niet zouden hervallen (gebied B, 78%), zelfs al hadden ze geen trastuzumab gekregen. Overlevingsresultaten kunnen ook weergegeven worden als de verhouding tussen de voorspelde ‘hazard’ (vergelijkbaar met risico) voor iemand in de behandelingsgroep en iemand in de controlegroep (hazard ratio, HR), zoals gegeven voor ziektevrije overleving in Tabel II and Figuur II.

Figuur I. Grafiek voor ziektevrije overleving in een gecontroleerde studie



Resultaten voor trastuzumab gestart in combinatie met taxanes na AC (doxorubicin plus cyclophosphamide) werden als gezamenlijke analyse van B31 samen met arm C van N9831 publiek gemaakt. Resultaten voor trastuzumab sequentieel gestart na alle chemotherapie werden apart publiek gemaakt (1 jaar arm van HERA studie en arm B van N9831). Voor een analyse van de 2 jaar trastuzumab arm van de HERA studie is het nog te vroeg. Voor een vierde trial, de BCIRG006, zijn voorlopig enkel resultaten voor DFS voorgesteld op een congres. Noteer dat de resultaten voor overleving (overall survival, OS) ook de effecten omvatten van trastuzumab gestart nadat ziekteprogressie werd vastgesteld bij patiënten in de controlegroep.

Trastuzumab gestart in combinatie met taxanes na AC verbetert significant de DFS met HR 0,49 (0,41-0,57), gebaseerd op een gepoolde analyse van de gepubliceerde gegevens. Deze bestaan uit de B31/N9831 resultaten, HR 0,48 (0,39-0,59), alsook in de preliminaire analyse van de BCIRG006 studie, HR 0,49 (0,37-0,65) in de AC arm. In de gezamenlijke analyse B31/N9831 verbeterde ook de overall survival (OS) significant na trastuzumab, HR 0,67 (0,48-0,93), bij een mediane opvolgingsduur van 2 jaar (Tabel II).

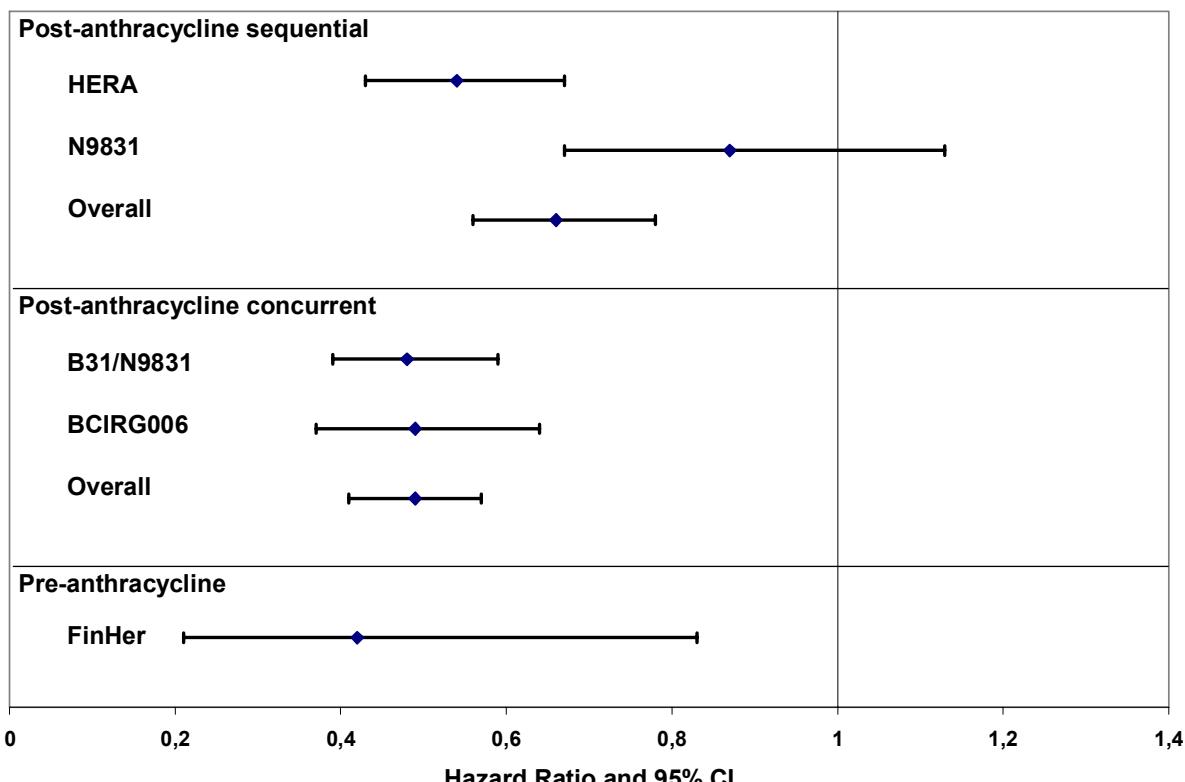
De verbetering in DFS voor trastuzumab sequentieel gestart na alle chemotherapie varieert meer per studie dan voor trastuzumab combinatietherapie. DFS in de sequentiële behandelingsarm B van N9831 is niet significant beter t.o.v. de controle arm A, HR 0,87 (0,67-1,13). Dit contrasteert met de HR 0,54 (0,43-0,67) voor de 1 jaar trastuzumab arm van HERA. Bij gezamenlijke analyse van DFS met een fixed effects model is de HR 0,66 (0,56-0,78). In beide studies, na respectievelijk slechts 1,5 en 1 jaar mediane opvolgingsduur, blijft de analyse voor overall survival negatief. Bij gezamenlijk analyse is voor overall survival de HR 0,81 (0,58-1,12).

De verbetering in DFS na trastuzumab in FinHer is significant met HR 0,42 (0,21-0,83) bij een mediane follow-up van 3 jaar. Anthracycline toediening (matige dosis epirubicin in FEC combinatie) werd hierbij gestart na een totaal van slechts 9 weken trastuzumab in combinatie met docetaxel of vinorelbine. Voor de E2198 studie zijn geen resultaten voor efficaciteit publiek gemaakt.

**Table II. Ziektevrije overleving na trastuzumab in adjuvante setting voor borstkanker.**

| Studie (mediaan follow-up)    | Control DFS (j)       | DFS (% and HR)<br>Ij seq. (na alle chemo)          | DFS (% and HR)<br>Ij comb. (na AC)                        | DFS (% and HR)<br>9w comb (voor FEC) |
|-------------------------------|-----------------------|--|---|--------------------------------------|
| <b>HERA (1j)</b>              | <b>77,4%*</b><br>(2j) | <b>85,8%</b><br>HR 0,54 (0,43-0,67)                | Niet bestudeerd   |                                      |
| <b>B3I (2,4j)</b>             | <b>74%</b><br>(3y)    | Niet bestudeerd                                    | <b>87%</b><br>HR 0,45                                     |                                      |
| <b>N983I (1,5j)</b>           | <b>78%</b>            | HR 0,87 (0,67-1,13)                                | <b>87%</b><br>HR 0,55                                     |                                      |
| <b>B3I/N983I</b>              | <b>75,4%</b><br>(3j)  |  | <b>87,1%</b><br>HR 0,48 (0,39-0,59)                       |                                      |
| <b>BCIRG006 (2j)</b><br>AC→TH | <b>77,0%</b><br>(3j)  | Niet bestudeerd                                    | <b>86,0%</b><br>HR 0,49 (0,37-0,65)                       |                                      |
| TCH                           |                       | Niet bestudeerd                                    | <b>80,0%**</b><br>HR 0,61 (0,47-0,79)**                   |                                      |
| <b>Overall</b>                |                       | <i>HR 0,66 (0,56-0,78)</i><br><i>(HERA, N983I)</i> | <i>HR 0,49 (0,41-0,57)</i><br><i>(B3I,N983I,BCIRG006)</i> |                                      |
| <b>FinHer (3j)</b>            | <b>77,6%</b><br>(3j)  |  |   | <b>89,3%</b><br>HR 0,42 (0,21-0,83)  |

\* 2-jaar DFS is 78,2% in de EMEA summary of product characteristics; \*\*Chemotherapie zonder anthracycline, niet opgenomen in overall analyse; DFS: disease-free survival; HR: hazard ratio

**Figuur II. Ziektevrije overleving (DFS) na trastuzumab per type regime en studie**

In de gerapporteerde analyses was de incidentie van hersenmetastase als eerste event hoger in de trastuzumab studie arm dan in de controle groep (21 gevallen vs. 15 in HERA, 21 vs. 11 in B3I en 12 vs. 4 in N983I). Dit verschil kan verklaard worden doordat in de controle groep vroegere metastasering gezien wordt naar andere plaatsen. De relatieve onwerkzaamheid van trastuzumab voor het verhinderen van de ontwikkeling van hersenmeta's, ook gerapporteerd in andere publicaties, kan mede te wijten zijn aan de lage penetratie van trastuzumab door de bloed-hersenbarrière. Het is nog onduidelijk hoe sterk dit gegeven op lange termijn de ziekte progressie en overleving na trastuzumab beïnvloedt.

## NEVENWERKINGEN

Trastuzumab bindt specifiek met HER2. HER2 komt niet voor op het oppervlak van de meeste cellen, maar soms wel in kleine hoeveelheden op hartspiercellen. Patiënten met een specifieke genetische variant van HER2 zijn mogelijks gevoeliger voor cardiotoxiciteit na trastuzumab. Hartfalen wordt vooral gezien na voorbehandeling of gelijktijdige behandeling met anthracyclines (doxorubicin en epirubicin). Anthracyclines zijn op zich al cardiotoxisch, epirubicin mogelijks wat minder dan doxorubicin. In de vier grote trastuzumab studies in vroege stadia van borstkanker werden anthracyclines toegediend voor de start van trastuzumab (behalve in de arm zonder anthracycline in BCIRG006). Nadat bekend werd dat het halfleven van trastuzumab langer was dan eerst beschreven, waarschuwde EMEA de artsen voor het gebruik van anthracyclines na het stoppen van trastuzumab. Nochtans, in de FinHer studie werd het anthracycline (epirubicin in matige dosis) toegediend na 9 weken trastuzumab behandeling, zonder cardiotoxiciteit als gevolg. In de E2198 studie werd één enkel geval van hartfalen geobserveerd na trastuzumab behandeling en vier gevallen na de daaropvolgende AC behandeling. Daarnaast dient ook vermeld dat interstiële pneumonitis werd gezien bij 0,6% van de met trastuzumab behandelde patiënten in de B3I/N983I analyse (fataal in 2 patiënten).

In tegenstelling tot de eerste klinische studies uitgevoerd in het kader van gemitastaseerd borstcarcinoom werd de hartfunctie prospectief opgevolgd tijdens de studies met trastuzumab in vroege stadia van borstkanker. De linkerventrikel-ejectiefractie (LVEF) werd elke drie maand gemeten met echocardiografie of met multi-gated acquisition (MUGA) scan. In studie B3I werd enkel MUGA gebruikt. De MUGA techniek maakt gebruik van radioactief materiaal. MUGA is duurder maar beter reproduceerbaar dan echocardiografie. Met MUGA wordt 50% aangenomen als ondergrens voor een normale LVEF. Met echocardiografie geven verschillende berekeningsmethodes van de LVEF verschillende resultaten. Methode standaardisatie voor LVEF meting met echocardiografie is dus noodzakelijk. De 'modified Simpson's rule' is recent aanbevolen als 2D echocardiografische methode voor LVEF, met een ondergrens voor normaalwaarden van 55%. Alvorens met trastuzumab te starten (dus na AC in de meeste gevallen) diende de LVEF >50% te zijn in alle studies behalve de HERA studie waar een hogere cut-off van 55% werd gehanteerd. Het gebruik van een normaal EKG voor het uitsluiten van hartfalen werd niet vermeld in de studie publicaties.

In trials B3I en N983I werd een significante stijging in cardiotoxiciteit gezien na trastuzumab. Dit feit werd als 'warning letter' door Genentech gecommuniceerd naar de artsen in de US. In beide studies misten 30,5% van de patiënten minstens 4 weken trastuzumab behandeling na een daling van de LVEF (24% in B3I) of na cardiale symptomen (8% in B3I). In totaal hadden 34% van de patiënten in de trastuzumab arm een significante LVEF daling versus 17% in de controlegroep van studie B3I. Er dient ook opgemerkt dat in B3I/N983I er 233 van de 3497 patiënten (6,7%) vooraf waren uitgesloten van trastuzumab behandeling wegens een daling in LVEF of cardiale symptomen na doxorubicin. Dit illustreert de belangrijke onmiddellijke en vertraagde cardiotoxiciteit van doxorubicin. In trials B3I en N983I (combinatie arm C) was de 3 jaar cumulatieve incidentie van NYHA (New York Heart Association) klasse 3 of 4 hartfalen of cardiale dood 0,8% en 0% in de controle groep en 4,1% en 2,9% in de trastuzumab arm. In studie B3I waren zowel de post-AC LVEF alsook de leeftijd onafhankelijke voorspellende parameters voor ernstig hartfalen na trastuzumab. De gecumuleerde 3-jarige incidentie van ernstig hartfalen bij de 48 patiënten  $\geq 50$  jaar met een post-AC LVEF van 50%-54% was 20%. Merk op dat deze vrouwen niet toegelaten werden tot de HERA studie waar een LVEF cut-off van 55% gebruikt werd. Het hartfalen geassocieerd met trastuzumab verbeterde deels door stoppen met trastuzumab en instellen van behandeling.

Voor de HERA studie werd niet gerapporteerd hoeveel patiënten niet konden deelnemen door cardiale problemen of een LVEF <55% na chemotherapie. Een vergelijking van de cardiotoxiciteit

gezien in de HERA met de B3I studie wordt bemoeilijkt door het verschil in gebruikte methode voor LVEF bepaling (echo en MUGA), de hogere LVEF cut-off van 55% gebruikt in HERA i.p.v. 50% voor het starten van trastuzumab, en de meer restrictieve definitie gebruikt voor een significante daling in LVEF (daling van minstens 10% tot een LVEF onder de 50% in HERA versus 55% in B3I en FinHer). Deze verschillen alleen al kunnen verklaren waarom een significante LVEF daling meer frequent werd gezien in B3I (+17%) dan in HERA (+4,9%). In HERA ontwikkelden 1,7% van de patiënten symptomatisch hartfalen in associatie met een significante daling in LVEF. 0,5% van de patiënten ontwikkelden ernstig hartfalen (NYHA klasse 3 of 4) in combinatie met een significante daling in LVEF. De enige studie die een directe vergelijking toelaat tussen een sequentiële of combinatie post-AC therapie met trastuzumab is N983I, waarin een ietwat lagere frequentie van ernstig hartfalen gezien werd in het sequentiële regime, maar geassocieerd met een lagere efficaciteit. In BCIRG006 vertoonden relatief weinig patiënten een daling in LVEF maar opnieuw werd een andere definitie gehanteerd: een daling van minstens 15% (i.p.v. 10%) tot onder de normale limiet.

## BENEFIT-RISK ANALYSE

Trastuzumab verbetert significant de ziektevrije overleving (DFS, primair studie eindpunt) bij patiënten met een HER2+ vroegtijdige vorm van borstkanker in 6 van de 7 trastuzumab behandelingsarmen waarvoor tot nu toe resultaten publiek werden gemaakt. Een significante toename van de overleving van 2,5% is enkel gerapporteerd voor de gezamenlijke analyse van twee behandelingsarmen (combinatiearm N983I en B3I). Absolute winst in DFS na trastuzumab varieert tussen behandelingsarmen van 3,0% (niet-anthracycline arm in BCIRG006) tot 11,7% (B3I en FinHer) terwijl de hazard ratio voor DFS varieert van 0,42 (FinHer) tot 0,87 (sequentiële arm N983I). Dit betekent dat de grote meerderheid van de behandelde patiënten geen voordeel halen uit de trastuzumab behandeling, maar wel de psychosociale last ondervinden van een verlengde behandeling en blootgesteld zijn aan de mogelijke ernstige nevenwerkingen. In studies N983I en B3I ontwikkelden 2,9% en 4,1% van de patiënten ernstig congestief hartfalen of overleden door cardiale oorzaken binnen de drie jaar. In studie B3I hadden 11% uit van de vrouwen die startten met trastuzumab een LVEF van 50-54%. De incidentie van ernstig hartfalen na trastuzumab was 20% bij patiënten boven de 50 jaar in deze risicogroep. Het voordeel van trastuzumab bij deze en mogelijk andere cardiovasculaire risicopopulaties is zeer waarschijnlijk klein vergeleken met het risico. Het gevolg is dat patiënten boven de 50 jaar met een LVEF 50-54% na anthracycline best niet behandeld worden met trastuzumab. Oudere patiënten hebben dikwijls een verminderde hartfunctie, een verhoogde bloeddruk of coronairlijden. De benefit-risk verhouding van trastuzumab bij patiënten boven de 70 jaar is niet voldoende bestudeerd.

De curven van DFS van de controlegroep in de studies zijn eerder gelijk, wat suggereert dat er geen majeure verschillen waren in de patiëntpopulaties en de standaard behandeling. De relatieve efficaciteit, veiligheid en robuustheid van de ondersteunende data voor de drie behandelingsconcepten gebruikt in de trastuzumab studies zijn in Tabel III samengevat. De doeltreffendheid van een jaar trastuzumab behandeling op ziektevrije overleving (DFS) bij vroegtijdige vormen van borstkanker lijkt beter wanneer na anthracycline voorbehandeling trastuzumab gestart wordt samen met een taxaan in plaats van na het taxaan. Zulk een sequentiële behandelingsschema is wat minder doeltreffend maar ook wat minder cardiotoxisch dan het combinatieschema. In deze context kan epirubicin, dikwijls gebruikt in Europa, wat minder cardiotoxisch zijn dan doxorubicin, wat meer in de US gebruikt wordt. Voor de post-anthracycline toediening van trastuzumab is het probleem van de optimale toedieningduur nog niet opgelost. De resultaten van de 2-jaar behandelingsarm in de HERA studie zullen spoedig bekend zijn. Het Frans Nationaal Kankerinstituut start een vergelijkende studie tussen 6 maand en 12 maand trastuzumab post-chemotherapie. Gebaseerd op reeds bestaande gegevens, zou men de DFS met de nodige voorzichtigheid kunnen analyseren in deze patiënten die minder trastuzumab toegediend kregen wegens cardiale nevenwerkingen (31% van de met trastuzumab behandelde patiënten in de B3I studie).

**Tabel III. Efficaciteit, nevenwerkingen, and robuustheid van de data gerangschikt voor de drie regime types van trastuzumab behandeling**

|                         | Post-anthracycline<br>Sequentieel, 1 jaar<br>(HERA, N9831) | Post-anthracycline<br>Combinatie, 1 jaar<br>(B31, N9831, BCIRG006) | Pre-anthracycline<br>Combinatie, 9 weken<br>(FinHer) |
|-------------------------|--|--|--|
| Efficaciteit            | +  | ++   | ++   |
| Cardiale veiligheid     | +  | +/-  | ++   |
| Robuustheid van de data | + (grote trials, variabele efficaciteit tussen trials)     | ++ (grote trials, efficaciteit gelijkaardig tussen de trials)      | + (matige sample size, trial in één land)            |

Het omkeren van de behandelingsvolgorde en vroegtijdig starten met een korte behandeling met trastuzumab van 9 weken zoals in de FinHer studie is een veelbelovende aanpak vanuit het standpunt van efficaciteit en veiligheid, die dringend vraagt om bevestiging. Gezien de gevoeligheid van het hart voor trastuzumab waarschijnlijk verband houdt met de voorbehandeling met anthracyclines lijkt een omkering van de behandelingsvolgorde zeker zinvol. Op korte termijn zou verdere ondersteuning voor deze aanpak kunnen komen uit de analyse naar efficaciteit van de E2198 studie. Het concept van 52 weken behandeling met trastuzumab na anthracyclines zoals in HERA is nog niet direct vergeleken met het 9 weken regime met omgekeerde volgorde zoals in FinHer. Gebaseerd op de puntestimmaties, weliswaar verkregen in aparte studies, heeft het FinHer regime een aantal voordelen t.o.v. een 52 weken trastuzumab behandeling post-anthracycline. Bovendien is de behandeling minder zwaar en minder lang voor de patiënt.

Tenslotte, wil men de resultaten van de klinische studies herhalen in de routine praktijk, dringt standaardisatie en kwaliteitsborging van de HER2 en LVEF testen zich op, en dit onafhankelijk van de medische specialiteit die deze testen uitvoert. Voor HER2 testing blijven FISH of CISH te verkiezen. For LVEF bepalingen is MUGA te verkiezen bij grensgevallen, wachtend op de standaardisatie van echocardiografie voor dit doel.

### *Key points (klinisch)*

- Trastuzumab leidt tot een indrukwekkende daling van metastases en een verbetering van het ziektevrij overleven op 2 à 3 jaar van 75-78% tot 86-89% bij vrouwen met een vroege vorm van borstkanker. Dit geldt zowel voor een behandeling van 9 weken vóór anthracyclines als voor een behandeling van 52 weken na anthracyclines. Het 'number needed to treat' voor ziektevrij overleven gebaseerd op de studieresultaten na 2 à 3 jaar is 9-12.
- Jammer genoeg veroorzaakt post-anthracycline behandeling met trastuzumab ook ernstig hartfalen, in het bijzonder bij vrouwen ouder dan 50 met een verlaagde linker ventrikel ejectiefractie.
- Indien trastuzumab gedurende 52 weken wordt toegediend na anthracyclines, wijzen de gepoolde resultaten voor ziektevrije overleving op een minder gunstig resultaat voor het sequentiële toedienen van trastuzumab in vergelijking met een start in combinatie met een taxaan. De post-anthracycline sequentiële behandeling met trastuzumab is wel wat minder cardiotoxisch in vergelijking met de gelijktijdige behandeling.
- Pre-anthracycline (FEC aan matige dosis) behandeling met trastuzumab gedurende 9 weken was werkzaam in een recente kleinere studie. In deze studie waarin ook patiënten met een wat verzwakte hartfunctie waren opgenomen werd geen congestief hartfalen vastgesteld.
- Trastuzumab kan waarschijnlijk de ontwikkeling van hersenmetastases niet vermijden.
- Trastuzumab behandeling is nog niet voldoende bestudeerd bij patiënten ouder dan 70 jaar.

## GEZONDHEIDSECONOMISCHE EVALUATIE

De gezondheidseconomische evaluatie van trastuzumab is gebaseerd op een kosten-effectiviteits analyse en budget impact analyse, beide vanuit het standpunt van de betaler.

### KOSTEN-EFFECTIVITEITS ANALYSE

Een volwaardige economische evaluatie vergelijkt zowel de kosten als gevolgen van bepaalde alternatieven. De resultaten worden uitgedrukt in een incrementale kosten-effectiviteitsratio (ICER). Deze ratio vergelijkt de additionele kosten (euro) ten opzichte van de gewonnen levensjaren in een bepaald scenario. Een scenario wordt bepaald door het behandelingsregime, de patiënten populatie (leeftijd, stadium van borstkanker, hartfunctie) en een aantal specifieke veronderstellingen. De analyse werd uitgevoerd vanuit het perspectief van de betaler. Verschillen in gezondheidsuitkomsten en kosten voor trastuzumab behandeling in adjuvante setting werden vergeleken met het alternatief waarbij dit monoklonale antilichaam niet wordt toegediend. Een lange termijn perspectief, namelijk de volledige levensduur, werd aangenomen voor deze kosten-effectiviteits analyse.

Gepubliceerde trastuzumab trials bij vroegtijdig borstkanker (HERA, B3I/N9831, en FinHer) werden gemodelleerd rekening houdende met het specifieke behandelingsregime, de veiligheids- en werkzaamheidsresultaten. Voor deze studies zijn geen overlevingsdata op lange termijn beschikbaar gezien de mediane opvolgingsduur voor deze trials varieert tussen 1 (HERA) en 3 jaar (FinHer). De korte termijn resultaten werden in ons model omgezet naar lange termijn gevolgen door gebruik te maken van de hazard ratio van patiënten die gespaard blijven van metastase. Voor patiënten die niet naar metastase evolueren werd de levensverwachting op basis van de Belgische sterftetafels gebruikt, minimaal aangepast gezien patiënten behandeld voor borstkanker iets meer kans maken op het ontwikkelen van een secundaire kanker. Voor patiënten die wel progressie maken naar metastase kon de levensverwachting berekend worden door het sommeren van de duur tot progressie, afhankelijk van leeftijd en borstkanker stadium, en de bijhorende overlevingsduur van metastase, zoals gepubliceerd door Berkowitz in 2000. De gewonnen levensjaren kunnen zodoende geschat worden door gebruik te maken van de levensverwachtingen in beide groepen en deze in verband te brengen met de gepubliceerde hazard ratios en het basisrisico (zonder trastuzumab behandeling) op progressie.

Incrementale kosten omvatten de kosten voor diagnose, behandeling en opvolgingsprocedures die in verband staan met de behandeling van borstkanker op zich of de neveneffecten van trastuzumab (congestief hartfalen) tijdens het verdere leven van de patiënt. Zowel het (grootste) deel gedekt door de Belgische ziekteverzeker (RIZIV/INAMI) als de directe medische bijdrage die door de patiënt wordt betaald werden in rekening gebracht. Een eerste incrementale kost wordt veroorzaakt door de IHC 2+ en 3+ borstkanker patiënten ter bevestiging te testen op HER2 met FISH. Het onderzoek van het KCE onder de Belgische oncologische centra (2005 data) bepaalde de proportie van IHC 2+ en 3+ borstkanker patiënten, per leeftijd en stadium, en diegene die bevestigd werden op HER2+ door FISH. Incrementale kosten geassocieerd met trastuzumab behandeling variëren naargelang het behandelingsscenario (HERA, B3I/N9831, en FinHer). Deze extra kosten bevatten de kosten voor het medicijn op zich (deel toegediend en ook het deel niet toegediend) en voor de toediening in het ziekenhuis als er een extra bezoek nodig is naast diegene voor de chemotherapie. De duur van de behandeling varieert van 9 weken tot één jaar en heeft een invloed op zowel het volume aan medicijnen die wordt toegediend als op het aantal extra bezoeken aan het ziekenhuis. Daarnaast is het ook van belang te weten dat het toedieningsschema (wekelijks versus 3-wekelijks) bepalend is voor de berekening van het deel dat niet toegediend maar wel aangerekend wordt. Ook de extra kost voor het MUGA onderzoek (echo nog niet gestandaardiseerd) werd aangerekend bij patiënten die kandidaat zijn voor dergelijke behandeling en elke drie maand tijdens behandeling met trastuzumab.

Trastuzumab behandeling leidt niet noodzakelijk tot extra kosten. Indien men bij een hoger aantal patiënten kan vermijden dat ze naar metastase gaan, dan worden er ook op langere termijn kosten bespaard. Kosten voor de behandeling van metastase omvatten deze voor chemotherapie, hormonale therapie, bisfosfonaten, groefactoren, enz. Kosten voor verzorging bij het levenseinde zijn niet opgenomen. Vervolgens heeft men ook de kosten tijdens het ziektevrije overleven waarbij de patiënt wordt opgevolgd en er diagnostische onderzoeken worden uitgevoerd. Deze kosten wijzigen indien de levensverwachting wordt beïnvloed. Daarnaast werd de gerapporteerde

relatieve verbetering in ziektevrije overleving na behandeling met trastuzumab ook gebruikt voor lokaal herval. De kosten ter behandeling van lokaal herval (mastectomie, mogelijks radiotherapie) werden derhalve ook opgenomen. Vervolgens werd de incrementele frequentie, kost en reductie in levensverwachting geassocieerd met hartfalen in rekening gebracht. Nederlandse overlevingsdata per leeftijd en geslacht werden hierbij gebruikt. Ook de kosten ter behandeling van hartfalen zijn gebaseerd op Nederlandse data.

Voor de HERA en FinHer trial werden de incrementele kosten en gezondheidsopbrengsten berekend voor verschillende subgroepen naargelang leeftijd (allemaal, <50, 50-59, 60-69, 70-79, 80+) en borstkanker stadium (I, II en III). Voor het combinatieregime met 1 jaar toediening van trastuzumab (B31/N9831) werden afzonderlijke ICERs berekend volgens leeftijd (allemaal, <50, >=50) en LVEF bij het begin van trastuzumab behandeling (50-54% of >=55%) aangezien deze variabelen belangrijke determinanten waren voor hartfalen na behandeling met trastuzumab. Voor deze analyse werden gegevens betreffende de werkzaamheid gebaseerd op de B31/N9831 studie en gecombineerd met de frequentie van hartfalen die enkel in detail werd besproken voor de B31 trial.

### **Scenario analyse, modelleren van onzekerheid betreffende de input variabelen en het uitvoeren van probabilistische sensitiviteitsanalyse**

De mogelijkheid dat trastuzumab niet in staat is om de ontwikkeling van hersenmetastases te vermijden vormt een specifiek probleem voor het modelleren van de gezondheidsopbrengsten. Daarom werden twee scenario's gemodelleerd. Enerzijds wordt verondersteld dat trastuzumab werkzaam is zoals bij andere metastases, en anderzijds, het referentie scenario, waarbij trastuzumab de ontwikkeling van metastases niet kan vermijden maar wel kan uitstellen met ongeveer één jaar bij een deel van de patiënten die uiteindelijk hersenmetastases ontwikkelen. De overlevingsduur voor patiënten met hersenmetastase werd gelijk verondersteld als voor andere metastases. Andere scenarios die werden gemodelleerd zijn de volgende: het al dan niet opnemen van het percentage ongebruikt trastuzumab (referentie: wel opnemen), het al dan niet opnieuw behandelen met trastuzumab indien de patiënt progresseert naar metastase (referentie: niet opnieuw toedienen), het al dan niet verhogen van de kost van metastase behandeling met 5000 euro (referentie: niet verhogen), het toepassen van verschillende discontovoeten (3% voor kosten en 1,5% voor gezondheidswinst (referentie), 3% voor beide, 5% voor beide, 5% enkel voor kosten, 3% enkel voor kosten, en tot slot geen discontovoet voor beide). Al deze scenario's werden gemodelleerd voor de verschillende behandelingsregimes en subpopulaties.

Vele van de inputvariabelen in het model zijn schattingen waar een bepaalde onzekerheid op rust, zoals bijvoorbeeld gedocumenteerd in de publicaties. Bij die variabelen waarvoor geen schattingen van onzekerheid vorhanden was werd arbitrair een variatie toegevoegd. Voor de data die gebaseerd zijn op de zeer uitgebreide studie bij Belgische oncologische centra werd de puntschatting gebruikt. De onderliggende verdeling voor input variabelen is meestal een normale verdeling. Om te vermijden dat onrealistische waarden gebruikt worden bij het simuleren werden dergelijke delingen afgeknot op het 99% betrouwbaarheidsinterval. Voor variabelen die als een proportie worden uitgedrukt werd een beta distributie toegepast. Probabilistische sensitiviteitsanalyse geeft de implicaties weer van het tezelfdertijd combineren van de onzekerheden op alle variabelen. Na het toepassen van 1000 Monte Carlo simulaties werd de onzekerheid op de input variabelen vertaald naar de onzekerheid op het resultaat. Uiteindelijk werd een rang correlatie coëfficiënt berekend tussen de output waarden en de opgelegde input waarden om een indicatie op te leveren betreffende de relatieve belangrijkheid van de variabelen.

### **Kosten-effectiviteits resultaten**

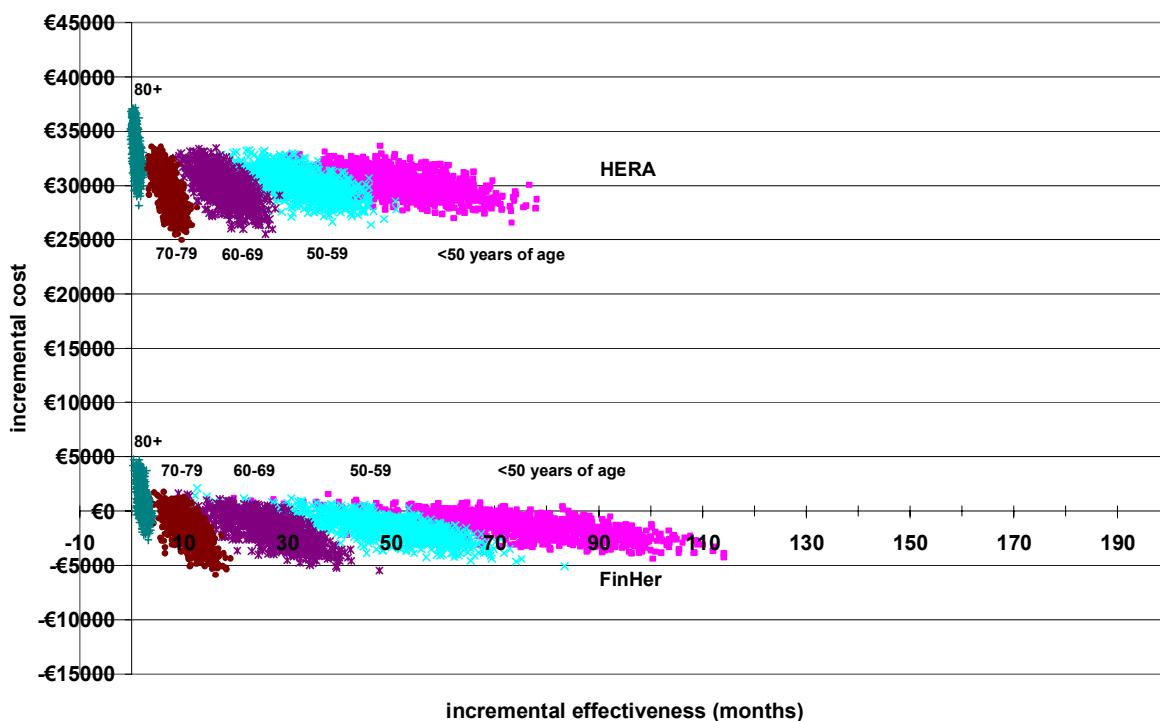
Gebruik makende van het referentie scenario voor discontovoeten was trastuzumab effectief voor patiënten met een LVEF >=55% (HERA) of LVEF >=50% (FinHer) bij de start van trastuzumab behandeling. Dit was het geval voor de meeste subgroepen gedefinieerd per leeftijd en stadium van borstkanker (I, II en III). De enige uitzondering waren patiënten in het HERA regime met een stage I borstkanker in de 80+ leeftijdscategorie. Als voorbeeld, voor in aanmerking komende patiënten met stage II borstkanker in de leeftijdscategorie 50-59, leverde het HERA regime een geschatte levenswinst op van 32,81 maanden (21,54 – 44,36). Bij het FinHer regime was dit gemiddeld 48,65 maanden (26,29 – 65,69) voor een grotere populatie van patiënten die in aanmerking komen aangezien er minder vrouwen uitgesloten worden wegens verzwakte hartfunctie. De gezondheidswinst is overlappend maar hoger voor het FinHer regime

ten opzichte van HERA. Dit is het meest zichtbaar bij de jongere patiënten populaties (Figuur III). Het bredere betrouwbaarheidsinterval voor de hazard ratio van de FinHer trial weerspiegelt zich in een bredere puntenwolk. Bij het vergelijken van de resultaten tussen de verschillende subgroepen was het aantal gewonnen levensjaren hoger bij jongere patiënten en bij vrouwen met een verder stadium van borstkanker.

De incrementale kost per patiënt behandeld volgens het kortere FinHer regime is slechts een fractie van de kosten voor het HERA regime van één jaar. Deze waren zelfs negatief bij FinHer voor stadium II en III borstkanker, wat wijst op netto besparingen. Bijvoorbeeld, in dezelfde subgroep van stadium II borstkanker patiënten tussen 50 en 59 jaar, waren de incrementale kosten gemiddeld 30 101 euro (27 647 – 32 508) in de HERA trial ten opzichte van -1559 euro (-3783 – 527) voor FinHer (Figuur III). In het laatste geval overstijgen de verdisconteerde toekomstige besparingen de initiële ‘investering’.

Het combineren van de lagere incrementale kost met de hogere schattingen voor gezondheidswinst resulteert in een over het algemeen betere ICER voor de FinHer in vergelijking met HERA, en dit voor alle borstkankerstadia en leeftijdsgroepen. Binnen elk regime is de ICER beter voor jongere patiënten (een groter absoluut percentage patiënten kan voordeel halen uit de behandeling en een groter aantal levensjaren kunnen gewonnen worden) en voor patiënten met een verder borstkankerstadium (een groter absoluut percentage aan patiënten haalt voordeel uit de behandeling). Vroegtijdige behandeling van borstkanker met trastuzumab is niet kosten-effectief voor zes van de 15 subgroepen bij het HERA scenario, namelijk voor stadium I: 60-69, 70-79, 80+; stadium II: 70-79, 80+; en stadium III: 80+. Bij het FinHer regime is dit enkel het geval voor stadium I borstkanker patiënten ouder dan 80.

**Figure III. Incrementale kosten-effectiviteit voor het HERA en FinHer behandelingsregime (volgens leeftijd bij stadium II borstkanker)**



Het modeleren van de B3I studie resultaten was interessant wegens de verhoogde incidentie aan trastuzumab gerelateerd hartfalen bij patiënten met een LVEF 50-54% na anthracycline behandeling en vóór het toedienen van trastuzumab. Gebruik makende van het B3I behandelingsregime werd trastuzumab effectief bevonden voor patiënten jonger dan 50, maar niet voor stadium I en II borstkankerpatiënten die ouder waren dan 50 met een LVEF 50-54%. Bijvoorbeeld, bij stadium II borstkankerpatiënten, was de incrementale effectiviteit gemiddeld 38 maanden (7,15 – 61,54) voor patiënten jonger dan 50. Bij patiënten ouder dan 50 was er een

verlies aan levensjaren van gemiddeld 8,15 maanden (-28,64 – 5,95). Dit contrasteert met het FinHer regime waar trastuzumab minder of geen hartproblemen veroorzaakte in alle populaties en waarbij patiënten met een LVEF 50-54% ook opgenomen waren.

## BUDGET IMPACT ANALYSE

De totale jaarlijkse incidentie van invasieve borstkanker in België werd afgeleid uit de leeftijdsgelateerde incidentie geobserveerd in Vlaanderen (2001) en Belgische demografische data. We hebben verondersteld dat de verdeling van tumoren volgens stadium op basis van ons omvangrijk onderzoek representatief was voor de Belgische situatie. Deze distributie werd toegepast op de Belgische leeftijdsgelateerde incidentie om een schatting te krijgen van het aantal nieuwe borstkancers per leeftijd en per stadium voor het jaar 2005.

Voor elk stadium van borstkanker en leeftijdsklasse hebben we geschat hoeveel patiënten aan twee voorwaarden voldoen, namelijk: expressie van neu-HER2 door FISH en behandeling met chemotherapie. Daarna werden de patiënten met een te lage LVEF voor of na anthracycline behandeling uitgesloten. Aangezien de resultaten van behandeling met chemotherapie en trastuzumab positief zijn hebben we uiteindelijk een hypothese gemaakt waarbij 50% van de neu-HER2 positieve patiënten die in het verleden niet met chemotherapie werden behandeld uiteindelijk zouden kiezen voor een meer agressieve behandeling om hun geneeskans te verhogen (= meer chemotherapie).

De kosten voor trastuzumab en zijn toediening zijn verschillend naargelang de drie trials en bedragen 8667, 40 657 en 48 172 euro voor respectievelijk de FinHer, HERA, en B31/N9831. Indien de populatie die uiteindelijk met chemotherapie wordt behandeld uitgebreid zou worden, dan zou de kost voor trastuzumab en deze voor een klassieke chemotherapie voor iedere nieuwe patiënt een additionele kost van 14 727, 45 537 en 59 223 euro bedragen.

De keuze om trastuzumab toe te dienen gedurende 9 weken voor anthracycline of 52 weken na chemotherapie heeft grote gevolgen voor het aantal vrouwen die trastuzumab kunnen krijgen en het budget (Tabel IV). De kost voor trastuzumab behandeling voor stage I, II en III borstkanker samen zou 5,17 miljoen euro bedragen in een 9-weken schema waarbij 597 vrouwen worden behandeld. Dit is 19,96 miljoen euro in een 52-weken schema waarbij ‘slechts’ 491 vrouwen worden behandeld (doordat meer vrouwen een risico op hartfalen lopen en worden uitgesloten).

In geval een meer agressieve behandeling wordt verkozen door 50% van de patiënten die tegenwoordig geen behandeling krijgen met cytostatica, dan zou de totale kost voor stadium I, II en III borstkanker stijgen tot 9,08 miljoen euro in het 9-weken schema en 29,84 miljoen met 52 weken. Naast het feit dat een grotere populatie van vrouwen behandeld kan worden in het 9-weken schema mag men ook niet vergeten dat het 52-weken regime een totale behandelingsduur heeft van 616 dagen versus 189 dagen en tweemaal zoveel hospitalisaties met zich meebrengt. Dit vergt de inzet van meer oncologen, meer verpleegkundigen en meer bedinnames voor ambulante zorg. Tot slot, de lagere kost van het 9-weken regime voor het sociale zekerheidssysteem kan meer ruimte creëren voor de terugbetaling van andere innovatieve behandelingen.

**Tabel IV. Totale kost voor het behandelen van patiënten die in aanmerking komen in 2005**

|                               | Chemo & LVEF ≥50%    | Chemo & LVEF ≥55%    | Meer chemotherapie   | Meer chemotherapie   |
|-------------------------------|----------------------|----------------------|----------------------|----------------------|
|                               | T 9 weken            | T 52 weken           | T 9 weken            | T 52 weken           |
| <b>Stage I</b>                | 0,85 M€              | 3,25 M€              | 2,82 M€              | 8,26 M€              |
| <b>Stage II</b>               | 2,81 M€              | 10,86 M€             | 4,30 M€              | 14,59 M€             |
| <b>Stage III</b>              | 1,52 M€              | 5,85 M€              | 1,96 M€              | 6,99 M€              |
| <b>Stages I, II &amp; III</b> | <b>5,17 M€</b>       | <b>19,96 M€</b>      | <b>9,08 M€</b>       | <b>29,84 M€</b>      |
|                               | <b>597 patiënten</b> | <b>491 patiënten</b> | <b>862 patiënten</b> | <b>708 patiënten</b> |

Chemo & LVEF ≥50% (of LVEF ≥55%): patiënten die neu-HER2 FISH positief zijn, behandeld met adjuvante therapie en LVEF ≥50% (of LVEF ≥55%) bij het aanvangen van trastuzumab behandeling; kost door de additionele behandeling met trastuzumab.

Meer chemotherapie: huidig aantal chemo + 50% van de chemotherapie-naïeve FISH positieve patiënten met LVEF ≥50% (of LVEF ≥55%) bij het aanvangen van trastuzumab behandeling; de kost van de toegevoegde trastuzumab behandeling en de nieuwe chemotherapie bij naïeve patiënten.

T 9 weeks: trastuzumab 9-wekelijks schema (FinHer studie).

T 52 weeks: trastuzumab 52-wekelijks schema (HERA studie).

*Key points (gezondheid-economisch)*

- Volgens het lange termijn gezondheideconomisch model blijkt post-anthracycline trastuzumab behandeling gemiddeld gezien werkzaam bij de meeste patiëntenpopulaties gedefinieerd volgens leeftijd en borstkankerstadium terwijl het pre-anthracycline regime effectief was bij alle bestudeerde subgroepen volgens leeftijd en ziektestadium. Binnen elk gemodelleerd regime was trastuzumab behandeling meer effectief voor jongere patiënten en bij diegenen met borstkanker in een verder stadium.
- Bij het modelleren van het post-anthracycline regime bij patiënten met een wat verzwakte hartfunctie (LVEF 50-54%) resulteert trastuzumab behandeling gemiddeld in een daling van de levensverwachting bij stadium I en II borstkanker patiënten ouder dan 50.
- In ons model is de pre-anthracycline trastuzumab behandelingsoptie meer kosten-effectief dan de post-anthracycline behandeling. Het pre-anthracycline regime kan zelfs leiden tot besparingen en laat 20% meer vrouwen voor een behandeling in aanmerking komen. Behandeling met trastuzumab volgens de HERA trial is niet kosten-effectief bij 6 van de 15 subgroepen waar dit bij FinHer slechts voor één van de 15 subgroepen het geval is.
- Ongeveer 14% van de geschatte jaarlijkse 9564 gediagnosticeerde borstkancers testen positief op HER2. Enkel een deel van deze patiënten worden de dag van vandaag behandeld met chemotherapie en hebben een hartfunctie die toelaat met trastuzumab een behandeling te starten. Een totaal van 597 en 491 patiënten komen aldus in aanmerking voor respectievelijk pre-en post-anthracycline behandeling met trastuzumab. Deze trastuzumab behandeling kost de gezondheidsbetaler jaarlijks dus theoretisch 5,17 miljoen en 19,96 miljoen euro respectievelijk .
- Deze aantallen zijn een conservatieve schatting. Door de verbeterde behandelingsresultaten kunnen we veronderstellen dat meer vrouwen zich zullen laten behandelen met cytotoxische chemotherapie en trastuzumab, wat zal resulteren in hogere uitgaven.

## CONCLUSIES EN AANBEVELINGEN

Veelbelovende gedeeltelijke resultaten van de studies met het monoklonale antilichaam trastuzumab (Herceptin) in vroege stadia van HER2+ borstkanker (niet gemetastaseerd) zijn publiek gemaakt vanaf mei 2005. Het dossier werd pas recent (in februari 2006) ingediend bij het Europees agentschap voor geneesmiddelen (EMEA) door het farmaceutische bedrijf Roche voor evaluatie van efficaciteit en veiligheid. Na een versnelde evaluatieprocedure gaf EMEA in mei 2006 de goedkeuring voor extensie van indicatie van trastuzumab in vroege stadia van borstkanker. Details van deze evaluatie werden slechts publiek bij de finalisatie van dit rapport. (<http://www.emea.eu.int/humandocs/Humans/EPAR/herceptin/herceptin.htm>)

Sinds mei 2005 is er een uitgebreide mediabelangstelling en hebben in een aantal landen patiëntenverenigingen, soms met succes, gepleit voor het voortijdig ter beschikking stellen en vergoeden van trastuzumab in HER2+ vroege vormen van borstkanker. Dit alles gebeurde nog voor de noodzakelijke kritische evaluatie van werkzaamheid en nevenwerkingen door de bevoegde autoriteiten plaats kon vinden. Deze praktijk vond plaats in meerdere landen en is niet zonder risico.

Trastuzumab reduceert zeer significant het aantal patiënten dat naar metastase evolueert en leidt tot een verbetering in de 2-3 jaar ziektevrije overleving. De lopende evaluaties lijken zich vooral te baseren op het behandelingsregime en de duur zoals uitgetest in de HERA studie. Meerdere vragen blijven open i.v.m. het optimale behandelingsregime (pre- of post-anthracycline) en de trastuzumab behandelingsduur bij elk van die opties.

Trastuzumab is zeer duur. Conservatieve schattingen voor België geven een totaal van 597 en 491 patiënten per jaar die in aanmerking komen voor pre- en post-anthracycline trastuzumab, respectievelijk. Deze behandelingen met trastuzumab kosten de betaler van de gezondheidszorg theoretisch 5,17 en 19,96 miljoen euro, respectievelijk. In geval 50% meer HER2+ patiënten een chemotherapie plus trastuzumab zouden aanvaarden zou de kost voor de betaler oplopen tot 9,08 en 29,4 miljoen euro, respectievelijk.

Volgens ons lange termijn farmaco-economisch model is 1 jaar trastuzumab post-anthracycline kosteneffectief voor 9 van de 15 patiëntengroepen terwijl het pre-anthracycline regime gedurende 9 weken kosteneffectief blijkt voor op één na alle bestudeerde patiëntengroepen. In bepaalde gevallen blijkt het een dominante strategie te zijn, i.e. gezondheidswinst in combinatie met kostenbesparingen. De meest kosteneffectieve estimaties zijn gebaseerd op een weliswaar kleinere studie uitgevoerd in één land gesponsord door de Finse overheid.

Dit plaatst de beleidsmakers voor een moeilijk dilemma. Momenteel is trastuzumab door EMEA uitsluitend goedgekeurd in een post-chemotherapie schema gedurende 1 jaar, hetgeen lokale overheden in landen die trastuzumab overwegen te financieren weinig keuze laat. Bij terugbetaling van het 52-weken HERA behandelingsschema zoals goedgekeurd door EMEA zullen publieke middelen voor een deel niet kosten-effectief besteed worden. Ofwel kijkt men naar alle klinische en economische wetenschappelijke gegevens en wordt men geconfronteerd met de provocatieve resultaten van de kleinere FinHer studie die recent in de NEJM werd gepubliceerd. Een kortere behandelingsduur van 9 weken trastuzumab, pre-anthracycline (matige dosis FEC), blijkt ook effectief en vrij van cardiotoxiciteit. Bovendien kunnen 20% meer vrouwen (ook deze met een wat verminderde hartfunctie) behandeld worden en zijn er positieve implicaties voor levenskwaliteit en kosten voor de gemeenschap.

In de geconsulteerde literatuur wordt geen rationale gegeven voor de minimum duur van 52 weken trastuzumab toediening zoals gebruikt in de vier grote fase 3 studies. Het is ook niet duidelijk waarom het kortere pre-anthracycline behandelingsconcept zoals gebruikt in de E2198 en FinHer studies niet werd weerhouden in een fase 3 studie. Slechts een vergelijkende klinische studie, vermoedelijk gesponsord door overheden, kan uitmaken welk behandelingsregime, pre- of post-anthracycline, meer effectief is. Ideaal zou zulk een studie in een internationale setting dienen plaats te vinden.

Deze gezondheidseconomische evaluatie geeft duidelijke cijfers en ramingen voor klinische en kosten effectiviteit van trastuzumab gebaseerd op de beschikbare gegevens. Het levert nuttige evidence voor toekomstige discussies bij de bevoegde organen van het RIZIV i.v.m. de terugbetaling van trastuzumab na de registratie. Gebaseerd op de huidige conclusies kunnen al een aantal aanbevelingen geformuleerd worden.

*Key points (conclusies en aanbevelingen)*

- Het percentage ongebruikt trastuzumab kan gereduceerd worden door het op de markt brengen van kleinere vials. Dit dient met de producent te worden besproken.
- Indien men de resultaten van de klinische studies wil reproduceren in de dagdagelijkse praktijk, is kwaliteitsborging en standaardisatie van de testen voor HER2 en LVEF noodzakelijk. Voor HER2 testing blijven FISH of CISH te verkiezen. For LVEF bepalingen is MUGA te verkiezen, zeker bij grens gevallen en in situaties waarbij echografische bepaling van LVEF minder accuraat is. Op te merken valt dat MUGA een duurdere techniek is dan echocardiografie.
- De terugbetaling dient voorwaardelijk te zijn aan strikte criteria voor inclusie en exclusie en ingebed in de kwaliteitsprocedures van de oncologische zorgprogramma's in de Belgische ziekenhuizen. Met de criteria gebaseerd op de HERA studie, is 52 weken trastuzumab meestal een effectieve maar niet altijd een kosten-effectieve behandeling voor vrouwen met een linker ventrikel ejectiefractions van minstens 55% en zonder cardiovasculaire exclusiecriteria. Tijdens de behandeling dient de hartfunctie te worden gevolgd.
- Een performante kankerregistratie aangevuld met een aantal prognostische en outcome variabelen bij patiënten met borstkanker is essentieel voor de follow-up van de behandeling met trastuzumab in België. Een dergelijk register is ook nodig om accuraat het aantal patiënten in te schatten dat in aanmerking komt voor toekomstige behandelingen. Dit rapport geeft een aantal van de variabelen die daarvoor gebruikt kunnen worden.
- Een vergelijkende klinische studie tussen 9-weken trastuzumab pre-anthracycline en het 52-weken post-chemotherapie regime moet zonder uitstel opgestart worden.

## Scientific summary

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## 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 <i>in situ</i> 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 <i>in situ</i> 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   |

# I INTRODUCTION

## I.I 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<sup>1</sup>).

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.

## I.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)<sup>2</sup>, or given concurrently with adjuvant chemotherapy for operable breast cancer (trials B31 and N9831).<sup>3, 4</sup> These and other studies had also been presented at the 2005 ASCO<sup>5, 6</sup> and San Antonio<sup>7, 8</sup> 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](http://www.controlled-trials.com), [www.clinicaltrials.gov](http://www.clinicaltrials.gov) and [www.roche-trials.com](http://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)<sup>9</sup> 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,<sup>10</sup> 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,<sup>11</sup> which includes the discussion of the trastuzumab BLA. Where other sources were used the reference is given.

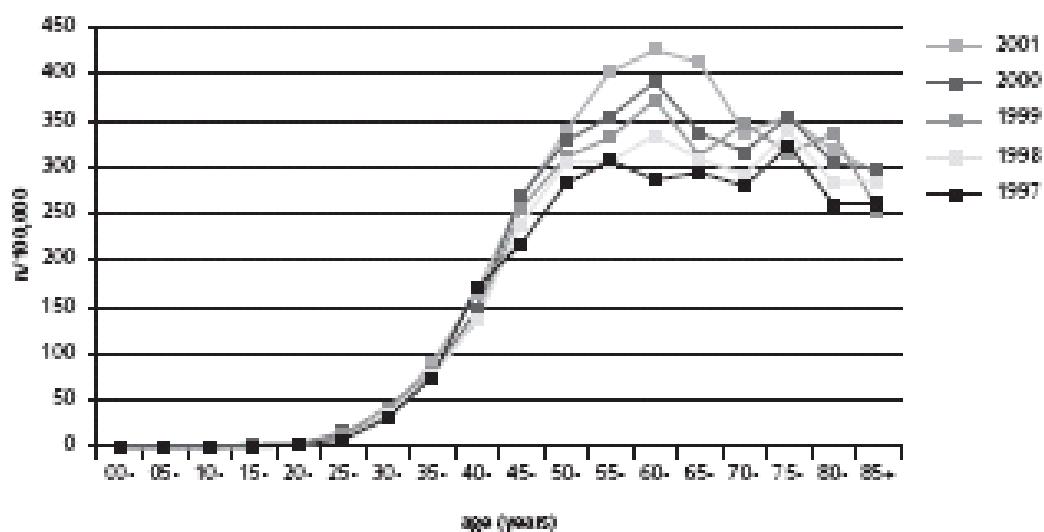
After an accelerated assessment the EMEA Committee for Medicinal Products for Human Use adopted in May 2006 the indication extension of trastuzumab for early breast cancer ([www.emea.eu.int](http://www.emea.eu.int)).

### 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.<sup>12</sup> 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.<sup>12</sup> 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 1<sup>st</sup> 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 1<sup>st</sup> 2005 (5 334 527, NIS). The calculated figures in table I do not incorporate any trend to an increase in the incidence of breast cancer since the year 2001.

**Table I. 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 I.

The TNM (Tumour, Nodal status, Metastasis) classification system, revised in 2002 by the American Joint Committee on Cancer<sup>13</sup> 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 6<sup>th</sup> 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            |
|------------------------|---------------|---------------|---------------|--------------|----------------|
| <b>15-49 years old</b> | 405           | 474           | 192           | 55           | 1126           |
|                        | <i>8.94%</i>  | <i>10.47%</i> | <i>4.24%</i>  | <i>1.21%</i> | <i>24.87%</i>  |
| <b>50-59 years old</b> | 527           | 452           | 166           | 64           | 1209           |
|                        | <i>11.64%</i> | <i>9.98%</i>  | <i>3.67%</i>  | <i>1.41%</i> | <i>26.70%</i>  |
| <b>60-69 years old</b> | 456           | 353           | 132           | 68           | 1009           |
|                        | <i>10.07%</i> | <i>7.80%</i>  | <i>2.92%</i>  | <i>1.50%</i> | <i>22.28%</i>  |
| <b>70-79 years old</b> | 237           | 315           | 138           | 77           | 767            |
|                        | <i>5.23%</i>  | <i>6.96%</i>  | <i>3.05%</i>  | <i>1.70%</i> | <i>16.94%</i>  |
| <b>80+ years old</b>   | 96            | 198           | 91            | 32           | 417            |
|                        | <i>2.12%</i>  | <i>4.37%</i>  | <i>2.01%</i>  | <i>0.71%</i> | <i>9.21%</i>   |
| <b>All ages</b>        | 1721          | 1792          | 719           | 296          | 4528           |
|                        | <i>38.01%</i> | <i>39.58%</i> | <i>15.88%</i> | <i>6.54%</i> | <i>100.00%</i> |

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 <sup>+</sup> in | FISH <sup>+</sup> 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.<sup>14</sup>

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

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

#### *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 4<sup>th</sup> 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          |              |
|-------|--------------|--------------|--------------|--------------|--------------|--------------|
|       | 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+ <i>estimated</i>                | 325   | 84    | 150   | 67    | 24  |
| FISH+ <i>estimated</i> & chemotherapy | 256   | 43    | 136   | 64    | 13  |
| Age 50-59 years                       | 2 557 | 1 115 | 956   | 351   | 135 |
| FISH+ <i>estimated</i>                | 354   | 112   | 149   | 59    | 34  |
| FISH+ <i>estimated</i> & chemotherapy | 241   | 32    | 127   | 54    | 28  |
| Age 60-69 years                       | 2 128 | 962   | 745   | 278   | 143 |
| FISH+ <i>estimated</i>                | 299   | 116   | 103   | 53    | 27  |
| FISH+ <i>estimated</i> & chemotherapy | 131   | 22    | 55    | 45    | 9   |
| Age 70-79 years                       | 1 702 | 526   | 699   | 306   | 171 |
| FISH+ <i>estimated</i>                | 199   | 47    | 85    | 40    | 27  |
| FISH+ <i>estimated</i> & chemotherapy | 37    | 3     | 13    | 14    | 7   |
| Age 80+                               | 964   | 222   | 458   | 210   | 74  |
| FISH+ <i>estimated</i>                | 118   | 19    | 59    | 26    | 14  |
| FISH+ <i>estimated</i> & chemotherapy | 2     | 0     | 0     | 2     | 0   |
| All breast cancers                    | 9 564 | 3 621 | 3 790 | 1 522 | 631 |
| FISH+ <i>estimated</i>                | 1 295 | 378   | 546   | 245   | 126 |
| FISH+ <i>estimated</i> & 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 tyrosine residues, has been suggested as a condition for cytoidal effects of trastuzumab.<sup>15</sup> 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.<sup>16</sup> An increased NK cell activity has been reported to be associated with a lower incidence of cancer.<sup>17</sup>

## 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,<sup>18</sup> but there is very little evidence for decision making.<sup>19</sup> Practice pattern surveys suggest that about half of oncologists continue trastuzumab treatment beyond disease progression.<sup>20</sup> 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,<sup>9</sup> 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.<sup>21</sup> 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.<sup>22</sup>

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  $\geq 2.0$  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  $\geq 2.0$  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<sup>2</sup> and the joint analysis of the B3I/N9831 trials<sup>3</sup> 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 B3I/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.<sup>5</sup> 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 B3I/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.<sup>23</sup> 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/NCT0003992>).<sup>24</sup> 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 Week | 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 |             |  |
|------------|------|---|---|---|--------------|----|----|----|----|----|----|----|------|------|------|------|-----|-----|-----|-----|------|------|------|------------|----|----|----|----|-------------|--|
|            |      |   |   |   | Mast or Lump | H4 | H2 | H2 | H2 | H2 | H2 | H2 | F600 | F600 | F600 | F600 | E60 | E60 | E60 | E60 | C600 | C600 | C600 | Rx therapy |    |    |    |    | E<br>N<br>D |  |

Herceptin is administered immediately before anthracyclines.

D100-80 = Docetaxel 100-80 mg/m<sup>2</sup> every 3 weeks

H4 = Herceptin 4 mg/kg

H2 = Herceptin 2 mg/kg weekly

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

F60 = 5-fluorouracil 600 mg/m<sup>2</sup> every 3 weeks

E60 = Epirubicin 60 mg/m<sup>2</sup> every 3 weeks

C600 = Cyclophosphamide 600 mg/m<sup>2</sup> every 3 weeks

**The HERA study**

| Cycle Week | Diag | 1    | 2    | 3    | 4            | 5  | 6  | 7  | 8  | 9  | 10 | 11 | 12   | 13   | 14   | 15   | 2    | 16          | 17          | 18          | 3           | 19   | 20   | 21   | 4    | 22   | 23   | 24   | 1    | 25 | 26 | 27 | 2 | 28 | 29 | 30 |  |
|------------|------|------|------|------|--------------|----|----|----|----|----|----|----|------|------|------|------|------|-------------|-------------|-------------|-------------|------|------|------|------|------|------|------|------|----|----|----|---|----|----|----|--|
|            |      |      |      |      | Mast or Lump |    |    |    |    |    |    |    | F500 | F500 | F500 | F500 | C500 | E100 or A60 | E100 or A60 | E100 or A60 | E100 or A60 | C500 | C500 | C500 | C500 | C600 | D100 | C600 | D100 |    |    |    |   |    |    |    |  |
| Cycle Week | 3    | 31   | 32   | 33   | 4            | 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 |   |    |    |    |  |
|            |      | D100 | C600 | D100 |              | H8 |    | H6 |    | H6 |    | H6 |      | H6   |      | H6   |      | H6          |             | H6          |             | H6   |      | H6   |      | H6   |      | H6   |      | H6 |    |    |   |    |    |    |  |

| Cycle Week | 9 | 61 | 62 | 63 | 10 | 64 | 65 | 66 | 11 | 67 | 68 | 69 | 12 | 70 | 71 | 72 | 13 | 73 | 74 | 75 | 14 | 76 | 77 | 78 | 15 | 79 | 80 | 81 | 16 | 82 | 83          | 84 | 17 | 85 | 86 | 87 | 18 | 88 |  |
|------------|---|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|-------------|----|----|----|----|----|----|----|--|
|            |   | H6 |    |    | H6 |    | E<br>N<br>D |    |    |    |    |    |    |    |  |

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

Herceptin was administered after anthracyclines.

F500 = 5-fluorouracil 500 mg/m<sup>2</sup> every 3 weeks

C500 = Cyclophosphamide 500 mg/m<sup>2</sup> every 3 weeks

P175 = Paclitaxel 175 mg/m<sup>2</sup> every 3 weeks

M40 = Methotrexate 40 mg/m<sup>2</sup> twice every 4 weeks

H8 = Herceptin 8 mg/kg

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

E100 = Epirubicin 100 mg/m<sup>2</sup> every 3 weeks

D100 = Docetaxel 100 mg/m<sup>2</sup> every 3 weeks

C600 = Cyclophosphamide 600 mg/m<sup>2</sup> twice every 4 weeks

F600 = 5-fluorouracil 600 mg/m<sup>2</sup> twice every 4 weeks

H6 = Herceptin 6 mg/kg every 3 weeks

**The N9831- B31 studies**

| Cycle Week | Diag | 1  | 2  | 3  | 4            | 5   | 6   | 7   | 8   | 9   | 10  | 11  | 12 | 13 | 14 | 15 | 16 | 1  | 2  | 3  | 4  | 5  | 6  | 7  | 8  | 9  | 10 | 11 | 12 | 13 | 14 |  |
|------------|------|----|----|----|--------------|-----|-----|-----|-----|-----|-----|-----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|--|
|            |      |    |    |    | Mast or Lump | A60 | H4 | H2 |    |  |
| Cycle Week | 15   | 31 | 16 | 32 | 17           | 33  | 18  | 34  | 19  | 35  | 20  | 36  | 21 | 37 | 22 | 38 | 23 | 39 | 24 | 40 | 25 | 41 | 26 | 42 | 27 | 43 | 28 | 44 |    |    |    |  |
|            |      | 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 |    |  |

| Cycle Week | 45 | 61 | 46 | 62 | 47 | 63 | 48 | 64 | 49 | 65 | 50 | 66 | 51 | 67 | 52 | 68 |  | E | N | D |
|------------|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|--|---|---|---|
|            |    | H2 |  |   |   |   |

Herceptin is administered immediately after anthracyclines.

A60 = Doxorubicin 60 mg/m<sup>2</sup> every 3 weeks

P80 = Paclitaxel 80 mg/m<sup>2</sup> weekly

Rx = Radiotherapy

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

C600 = Cyclophosphamide 600 mg/m<sup>2</sup> every 3 weeks

H4 = Herceptin 4 mg/kg

H2 = Herceptin 2 mg/kg weekly

In the HERA trial and in trials B31/N9831 the incidence of isolated brain metastases 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.<sup>25</sup> 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.<sup>26</sup>

## 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.<sup>27</sup>

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.<sup>7, 23</sup> 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 inverted 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.<sup>28, 29</sup> 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.<sup>28, 30</sup> 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](http://www.controlled-trials.com), , [www.clinicaltrials.gov](http://www.clinicaltrials.gov) and [www.roche-trials.com](http://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)<br>Dec 2001 – Mar 2005<br>Piccart-Gebhart, 2005 <sup>2</sup> | 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.<br>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.<br>Tamoxifen or aromatase inhibitor if receptor+. Trastuzumab stopped early in 8.5% (non relapse). | Age 49 y<br>>= 60y: 16%<br><br>N0: 32%<br>Anthracycli: 94%<br><br>FU: 1 y | Arm<br><br>Pts rand with FU<br><br>DFS events<br>HR (1y H)<br>TDR events<br>HR (1y H)<br>Mortality<br>HR (1y H)<br>CNS meta<br>LVEF decr<br>(to < 50%)<br>CHF any<br>CHF3/4 | P<0.0001<br>0.54 (0.43-0.67)<br>P<0.0001<br>0.49 (0.38-0.63)<br>P=0.26<br>0.76 (0.47-1.23)<br>15 (0.9%)<br>34 (2.2%)<br>1 (0.06%)<br>P=0.002 | Observe<br><br>1693<br>nearly all<br>220<br>171<br>37<br>95.1% (2y)<br>15 (0.9%)<br>34 (2.2%)<br>1 (0.06%)<br>0 (0%) | 1 y H<br><br>1694<br>nearly all<br>127<br>89<br>77.4% (2y)<br>85.8% (2y)<br>90.6% (2y)<br>21 (1.2%)<br>113 (7.1%)<br>29 (1.7%)<br>9 (0.5%) | 2 y H<br><br>1694<br>nearly all<br>128 |

| Joint analysis<br>(B3I+N9831)   | Romond,<br>2005 <sup>3</sup>                               | Surgically removed HER2+ breast cancer N+ or N0 high-risk. Analysis of groups I+A versus groups 2+C (n=3387). Group B (N9831) not reported.<br><br>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<br>≥ 60y: 16%<br><br>N0: 6%<br>AC: 100%<br><br>FU: 2.0 y | Arm<br><br>Pts rand with FU<br>DFS events<br>HR<br><br>TDR events<br>HR<br>Mortality<br>HR<br>CNS meta<br>LVEF decr.<br>CHF3/4 | I + A<br><br>P<0.0001<br>0.48 (0.39-0.59)<br>75.4% (3y)<br>261<br>193<br>81.5% (3y)<br>92<br>91.7% (3y)<br>15<br>5 (0.4%)? | 1843<br>1679<br>261<br>75.4% (3y)<br>134<br>1672<br>96<br>90.4% (3y)<br>62<br>94.3% (3y)<br>33<br>30.5%?<br>51 (3.5%)? | 2 + C   |  |
|---------------------------------|--|---|---|--|--|--|--|---|--|
| B3I (US)<br>FEB 2000 – FEB 2005 | Romond,<br>2005 <sup>6</sup> , Tan-Chiu, 2005 <sup>4</sup> | Randomization (1960?, 2 arms) of surgically removed HER2+ breast cancer (N+)<br><br>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<br>≥ 60y: 15%<br><br>N0: 0%<br>AC: 100%<br><br>FU: 2.4 y | Arm<br><br>Pts rand with FU<br>DFS events<br>HR<br><br>LVEF decr<br><br>CHF3/4 or cardiac death                                | AC→P (group I)<br><br>P<0.0001<br>0.45<br>(3y cumul., to < 55%)<br><br>(3y cumul.)   | 1024<br>872<br>171<br>17%<br>0.8%  | AC→PH (group 2)<br><br>1019<br>864<br>83<br>34%<br>4.1% |  |

| N9831 (US)<br>MAY 2000 – NOV 2004<br><br>Perez, 2005 <sup>5</sup> | Randomization (3046 patients, 3 arms) of surgically removed HER2+ breast cancer (N+ or N0 and >2cm, or N0 and >1cm and ER- and PR-.<br><br>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.<br><br>Radiotherapy continued. Tamoxifen or aromatase inhibitor if receptor+.                   | Age: 49 y<br>>= 60y: 17%<br>N0: 12%<br>AC: 100%<br>Follow-up: 1.5 y | Arm<br>Pts rand with FU<br>DFS events<br>HR C vs A<br>DFS events<br>HR B vs A<br>DFS events<br>HR C vs B<br>Mortality<br>HR B vs A<br>HR C vs B<br>CHF3/4 | 2p=0.0005<br>0.55<br>2p=0.29<br>0.87 (0.67-1.13)<br>2p=0.011<br>0.64 (0.46-0.91)<br>0.85 (0.55-1.33)<br>0.74 (0.43- 1.26) | AC→P (group A)<br>979/971?<br>807<br>90<br>117<br>51                                 | AC→P+H→H (group C)<br>840/814?<br>808<br>53   | AC→P→H (group B)<br>985/981?<br>?<br>103<br>84                           |
|---|--|--|---|---|---|--|---|--|
| BCIRG006 (global)<br><br>Slamon, ASCO, 2005 <sup>8</sup>          | Randomization (3222 patients, 3 arms) of surgically removed HER2+ early breast cancer N+ or high risk N0.<br><br>Normal LVEF at start.                               | AC→D: AC q3w x 4 → docetaxel (D) q3w x 4<br>AC→DH: H (4mg/kg start, then 2mg/kg for 1 year) started with D<br>DCarboH: D+carboplatin q3w x 6, started with H (1 year).<br><br>LVEF decrease if >15% decrease to below LLN. | 2 y (23 months)   | Arm<br>Pts rand with FU<br>DFS events<br>HR AC→DH<br>HR DCarboH<br>TDR<br>Mortality<br>LVEF decr.<br>Card. AEs<br>CHF3/4                                  | 0.49 (0.37-0.65)<br>0.61 (0.47-0.79)  | AC→D<br>1043/1050?<br>77.0% (3y)<br>77.0% (3y)<br>NA<br>NA<br>0.7%<br>12 (1.2%)<br>I | AC→DH<br>1072/1068<br>86.0% (3y)<br>77.0% (3y)<br>NA<br>NA<br>2.7%<br>25 (2.3%)<br>I8 | DCarboH<br>1056/1056<br>80.0% (3y)<br>NA<br>NA<br>0.4%<br>13 (1.2%)<br>I |

|   |   |  |                      |  |  |  |   |  |
|---|---|--|----------------------|--|--|--|---|--|
| FinHer<br>Joensuu,<br>2005 <sup>7, 23</sup> | Randomization (1010 patients) of EBC pN+ or pN0 (tumour >2cm, PR-) to docetaxel 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<br><br>Pts rand<br>DFS events<br>HR<br>TDR events<br>HR<br>Mortality<br>HR<br>LVEF decr.<br>CHF3/4 | P=0.008<br><br>0.42 (0.21-0.83)<br>P=0.002<br><br>0.29 (0.13-0.64)<br>p=0.07<br><br>0.41 (0.16-1.08) | No H   | Herceptin   |  |
|   |   |  |                      |  |  | 58+58<br>27<br>77.6% (3y)<br>26<br>76.0 (3y)<br>14<br>89.7% (3y)<br>7 (6%)<br>1 (1%) | 57+58<br>12<br>89.3% (3y)<br>8<br>92.0% (3y)<br>6<br>96.3% (3y)<br>4 (3%)<br>0 (1%)                     |  |
| E2198<br>Sledge, 2001 <sup>24</sup>         | Randomization (200 planned) of EBC N+ stage II/Ila to receive H for 1 additional 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 additional year   | 1.3 y<br>(15 months) | DFS<br>TDR<br>Mortality<br>LVEF decr.<br>CHF any   |  | No control arm   | NA<br>NA<br>NA<br>9.3% after 10 weeks of H<br>13.2% post-AC<br>0.4% after 10 weeks of H<br>1.7% post-AC |  |

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

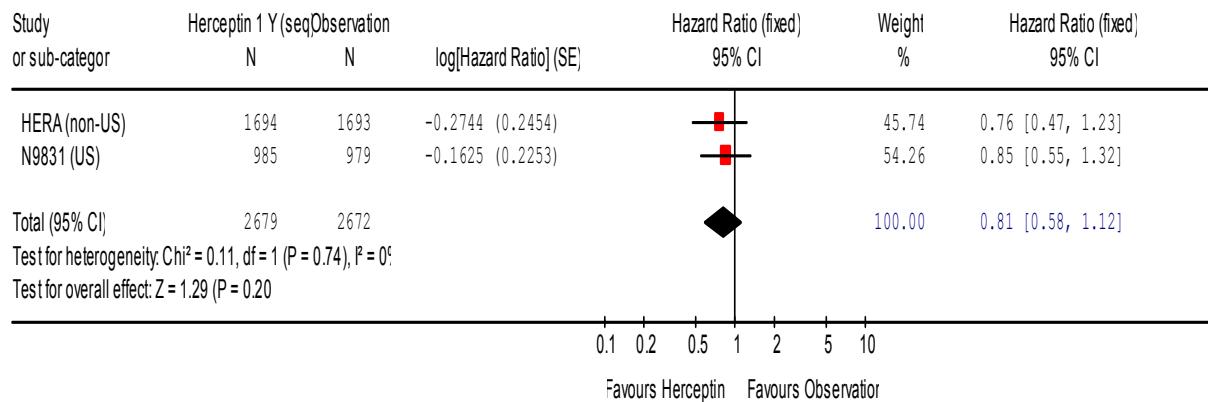
**Table 8. Trastuzumab in neoadjuvant setting, clinical trials identified in public trial registries.**

| 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) <sup>28</sup>  | 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 Trastuzumab (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                  |

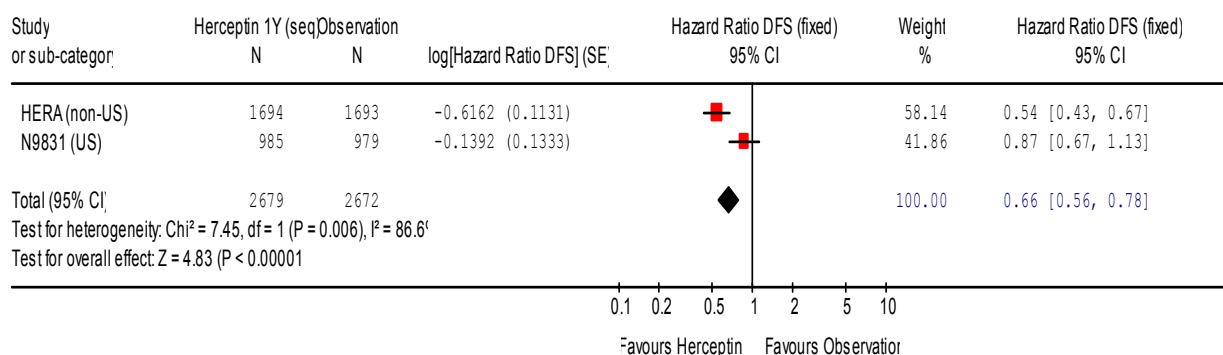
**Figure 3. Pooled Analysis of Overall Survival for 1 year of Trastuzumab Sequential Regimen (Fixed Effects)**

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



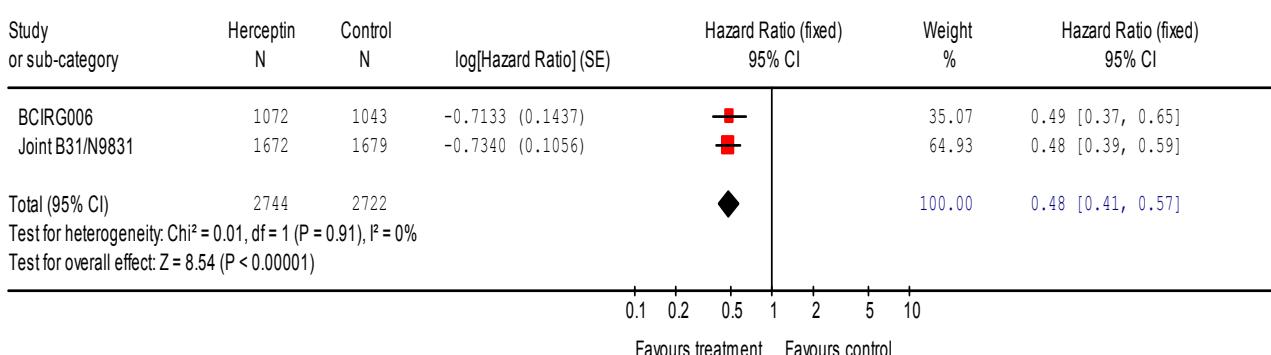
**Figure 4. Pooled Analysis of Disease Free Survival for 1 year of Trastuzumab Sequential Regimen (Fixed Effects)**

Review: Herceptin  
 Comparator: 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 trastuzumab 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.<sup>31</sup> Despite the undetectable or low level expression of HER2 on IHC (not assessed with the trastuzumab antibody),<sup>32</sup> 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.<sup>32</sup> Localization of HER2 may be in the transverse tubules of ventricular myocytes, also a target of anthracyclines.<sup>33</sup> 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.<sup>34</sup> 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.<sup>35</sup> 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).<sup>36</sup> 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.<sup>37</sup> However, the FinHer study results suggest that trastuzumab given for only 9 weeks does not result in a LVEF decrease.<sup>23</sup> 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.<sup>38</sup> 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 fraction (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.<sup>39</sup> Different methods of LVEF measurement provide different results.<sup>40</sup> 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.<sup>41</sup> 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.<sup>42</sup> 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 B3I 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                              |                               |
| B3I (MUGA) | ≥50% post-AC      | ≥10% to <55%              | Not studied           | + 17% (3y cumul)                         |                               |
| N983I      | ≥50% post-AC      |                           | ?                     | ?  |                               |
| BCIRG006   | ≥50% post-surgery | >15% to <50%              |                       | + 2.0% (n=21, AC)<br>- 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<br>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)<br>LVEF>=55%<br>epi > doxorubicin | NA   |                                     |
| B3I      | NA  | +3.3% (n=27)<br>2.6% if LVEF>=55%<br>12.8% if LVEF 50-54%<br>20% if LVEF 50-54% and age >50y |                                     |
| N983I    | +2.2% (n=15)                                  | +2.9% (n=20)   |                                     |
| BCIRG006 |   | +1.6% (n=17), AC<br>0% (n=0), no AC  |                                     |
| FinHer   |   |  | - 1% (n=1), FEC later               |
| E2198    |   |  | + 0.4% (n=1), + 1.7% (n=4) after AC |

In trials B3I and N983I 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.<sup>43</sup> Cardiac monitoring in trial B3I was performed after AC and at month 6, 9 and 18 using MUGA scans.<sup>4</sup> In trial N983I 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 B3I.<sup>4</sup> In both trials trastuzumab was

withheld (repeat assessment after 4 weeks) if an absolute decrease from baseline in LVEF of  $\geq 16\%$  was found or a decrease  $\geq 10\%$  together with a LVEF  $< \text{LLN}$ . 30.5% of the patients required at least one dose delay because of a decrease in LVEF (24% in B3I) or cardiac symptoms (8% in B3I). 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 B3I and N983I 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 B3I both the post-AC LVEF as well as age were found to be independent predictors of trastuzumab-associated CHF.<sup>6, 4</sup> 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  $\geq 50$  years in this group 9 (20%) experienced severe CHF.<sup>4</sup> Note that patients with a LVEF 50-54% were excluded from the HERA trial where a post-chemotherapy LVEF of  $\geq 55\%$  was required. Also important to note is that in trials B3I and N983I 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 B3I, 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%).<sup>4</sup> 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 (B3I), 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.<sup>4</sup> The reintroduction of trastuzumab under CHF medical treatment may be appropriate for some individuals.<sup>34</sup>.

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 B3I/N983I). 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 N983I, 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 180 mg/m<sup>2</sup> epirubicin while the maximum tolerated cumulative dose of epirubicin is of 720mg/m<sup>2</sup>. In the B31/N9831 studies doxorubicin was administered at a cumulative dose of 240 mg/m<sup>2</sup> while its maximum tolerated cumulative dose is only 500 mg/m<sup>2</sup>. Epirubicin is generally presented as a less cardiotoxic agent.

Indeed as stated in the FinHer paper<sup>23</sup>, 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 tachyarrhythmia, 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<sup>2</sup> 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.<sup>2</sup> 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.<sup>44</sup>

##### 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.<sup>45</sup> 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.<sup>46</sup> 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.<sup>44</sup>

##### 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.<sup>44</sup> 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.<sup>47</sup>

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.<sup>48</sup> 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.<sup>44</sup> 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.<sup>49</sup> 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.<sup>44</sup>

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.<sup>42</sup> 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<sup>42</sup>, 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 B3I, 96 out of 841 patients (11.4%) who started trastuzumab had a LVEF 50%-54%.<sup>4</sup> This percentage is used as a proxy for our exclusion criterion of the HERA trial. Furthermore, in trials B3I 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.<sup>4</sup> 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 (2<sup>nd</sup> group) or positive. In the group with positive study results, patients might (3<sup>rd</sup>) or might not (4<sup>th</sup> 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,<sup>47</sup> 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.<sup>47</sup>

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,<sup>50</sup> 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.<sup>44</sup> In the HERA trial, randomisation to no trastuzumab or one- or two-year treatment is performed after primary treatment.<sup>2</sup> 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 B3I/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.<sup>46</sup> 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...<sup>44</sup> 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.<sup>44</sup> 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.<sup>44</sup> 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.<sup>7, 2, 3</sup> 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, B3I/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 B3I/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, B3I/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<br>(start up: 8mg/kg) | 52 weeks | mean: 15.6%<br>(95%CI: 12.3% - 18.9%) | 18 x €245.98        | €40 657                |
| B3I-<br>N9831 | 2 mg/kg weekly<br>(start up: 4mg/kg)   | 52 weeks | mean: 26.7%<br>(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.<sup>2</sup> 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.<sup>7</sup> 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.<sup>3</sup> In trial B3I, 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 B3I/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/kostenverzorgingen/site\\_nl/index1.htm](http://www.rivm.nl/kostenverzorgingen/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](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<sup>2, 3, 23</sup>, 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.<sup>51</sup> A decrease in the 8-year loco-regional recurrence rate from 20.1% to 5.4% was reported in the Netherlands.<sup>52</sup> 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.<sup>51, 53-56</sup> 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.<sup>55</sup> 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.<sup>2, 3, 23</sup> 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.<sup>57</sup> 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".<sup>44</sup>

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<sup>50</sup>, 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](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.<sup>2, 3, 23</sup> Furthermore, cost-effectiveness is not driven by relative benefit but by absolute benefit.<sup>47</sup> 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.<sup>58</sup> 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.<sup>59</sup> 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.<sup>60</sup> Similar results were reported by Wai and colleagues, i.e. a mean cost of CAD36 474.<sup>61</sup> 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.<sup>50</sup> 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.<sup>62</sup> 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.<sup>63</sup> 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](http://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.<sup>47</sup> 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.<sup>25</sup> A possible explanation could be the low penetration through the blood-brain barrier of trastuzumab.<sup>26</sup> 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).<sup>64</sup> 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).<sup>44</sup> 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.<sup>44</sup> 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 I). 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,<sup>44</sup> 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.<sup>65</sup> Probabilities are constrained on the interval zero to one. Due to the relationship with binomial data, beta distributions can be applied on probability parameters.<sup>66-68, 65</sup>

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**

| <b>Endpoint</b>  | <b>Input Variable</b>                          | <b>Source</b>  | <b>Estimate</b> | <b>Uncertainty</b>  |
|--|--|--|-----------------|---|
| Survival free of distant recurrence                            | Hazard Ratio                                   | Piccart, 2005 <sup>2</sup> ; Romond, 2005 <sup>3</sup> ; Joensuu, 2006 <sup>23</sup>   | Published       | Based on published 95% CI   |
| Survival free of disease                                       | Hazard Ratio                                   | Piccart, 2005 <sup>2</sup> ; Romond, 2005 <sup>3</sup> ; Joensuu, 2006 <sup>23</sup>   | Published       | Based on published 95% CI   |
| Probability brain metastasis                                   | Percentage                                     | Duchnowska, 2006 <sup>64</sup>   | Published       | Beta distribution: based on 95% CI  |
| Mean time brain relapse  | Mean Time to brain relapse                     | Duchnowska, 2006 <sup>64</sup>   | Estimation      | Computed based on gamma distribution  |
| Progression to MBC   | Risk per subgroup (according to age and stage) | Berkowitz, 2000 <sup>50</sup>  | Published       | Beta distribution: range of +/- 10 ppt  |
| Progression to MBC   | Mean Time (according to age and stage)         | Berkowitz, 2000 <sup>50</sup>  | Published       | Normal distribution: 95% CI +/- 10% above and under mean                              |
| Survival of MBC  | Mean Time (according to age and stage)         | Berkowitz, 2000 <sup>50</sup>  | 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 <sup>69</sup>  | 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 <sup>2</sup> ; Joensuu, 2006 <sup>23</sup> ; Tan-Chiu, 2005 <sup>4</sup> | 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 <sup>42</sup> ; Tan-Chiu, 2005 <sup>4</sup>                               | Published       | Beta distribution: range of +/- 2.5 ppt   |
| Retesting HER2   | Percentage                                     | Expert opinion   | Estimation      | Beta distribution: range of +/- 5 ppt   |

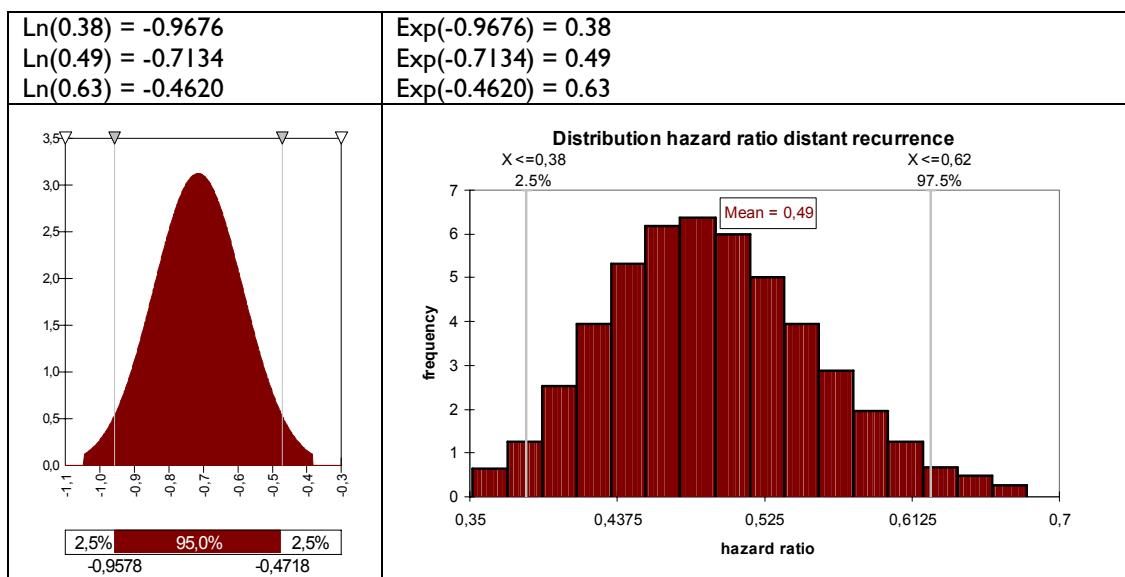
| Endpoint                          | Input Variable                          | Source             | Estimate      | Uncertainty  |
|-----------------------------------|---|--------------------|---------------|--|
| IHC positive                      | Percentage (according to age and stage) | Belgian 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.

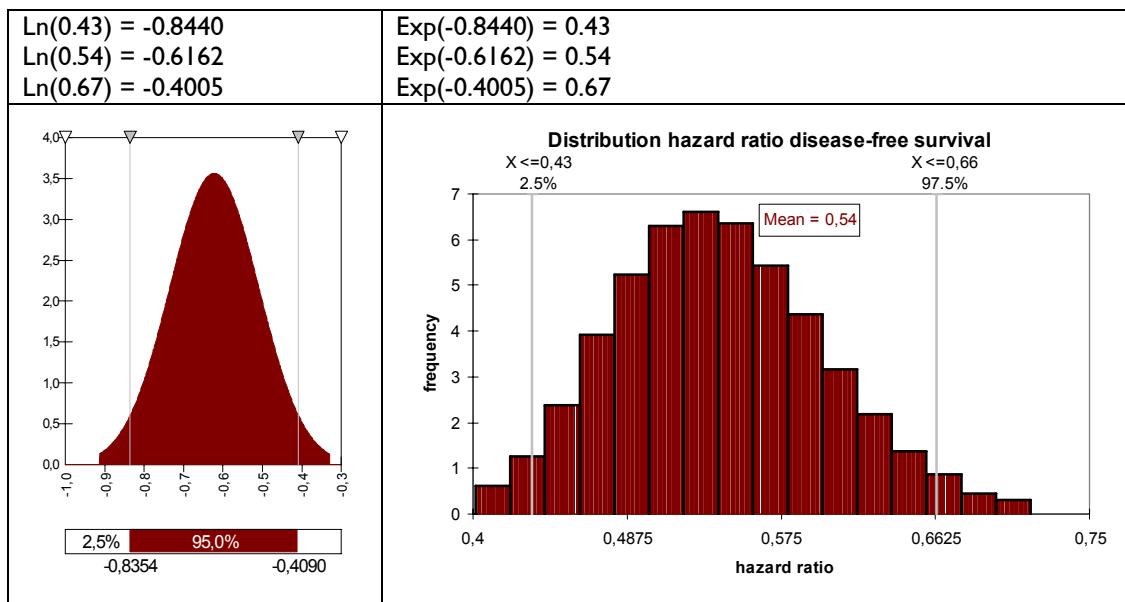
### Survival free of distant recurrence and Survival free of disease

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.<sup>2, 3, 23</sup> 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)**



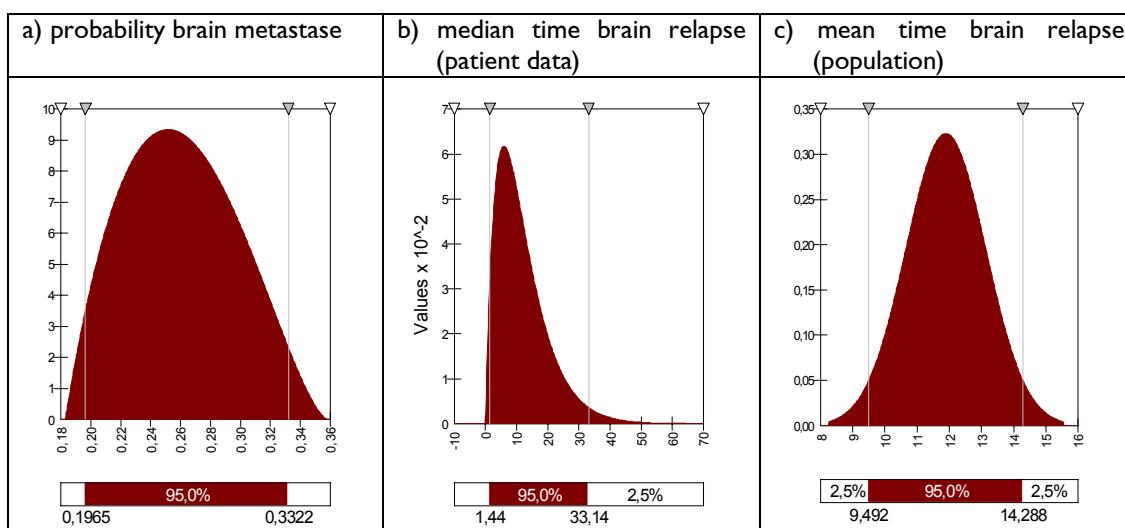
Remark: truncation of the distribution function results in slightly different 95% CI.

**Table 24. Hazard ratio free of disease (HERA)**

### 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.<sup>64</sup> 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).<sup>64</sup> 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).

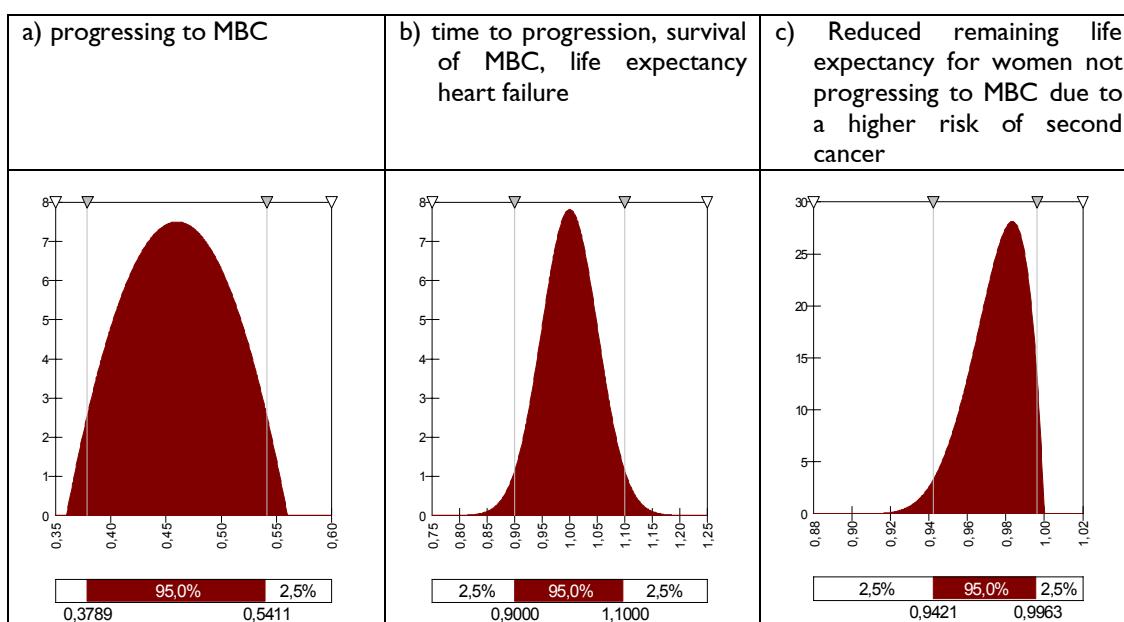
**Table 25. Brain metastasis**

### 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.<sup>66-68, 65</sup> 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**



### TTP, survival of MBC, and life expectancy heart failure

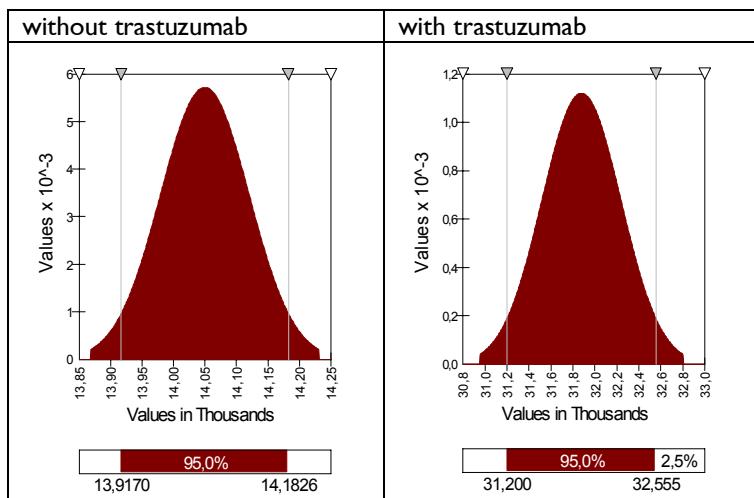
We applied a normal distribution on the following variables: mean time of progressing to metastatic disease (table 17), mean survival of metastasis (table 18), and life expectancy for patients with heart failure (table 20). The distribution was set up so that 95% of the data would be comprised within 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

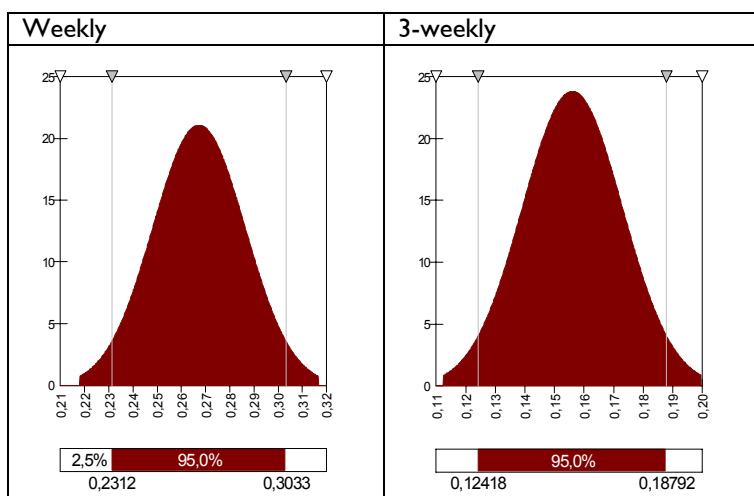
Next, the excess of cancer after a breast cancer diagnosis is likely to be explained by treatment for breast cancer, by shared genetic or environmental risk factors, or additional explanations such as increased surveillance and general cancer susceptibility.<sup>69</sup> In other words, the mean life 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 of 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****Percentage of unused trastuzumab**

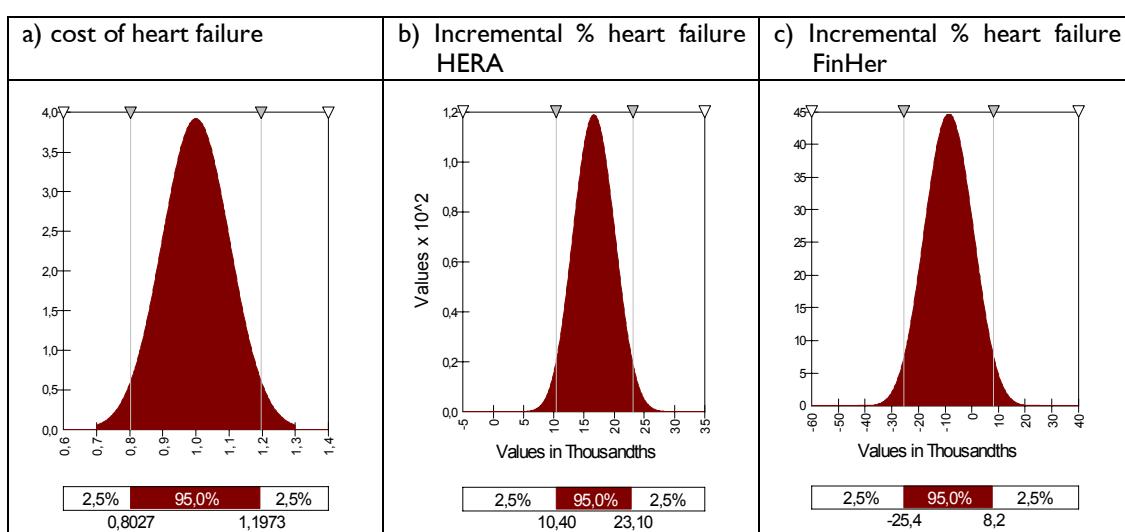
Trastuzumab is currently marketed as single use vial of 150 mg. Patients receive 2 mg/kg weekly or 6 mg/kg 3-weekly. If a vial is opened and not completely used, the unused part is discarded. This cost should also be taken into account. Instead of working with the percentage of women weighing more than 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**

## 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**



## 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,<sup>2</sup> 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,<sup>23</sup> 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%).<sup>4</sup>

The frequency of severe CHF after trastuzumab was lower in patients with a LVEF of  $\geq 55\%$ . 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 (B3I study)**

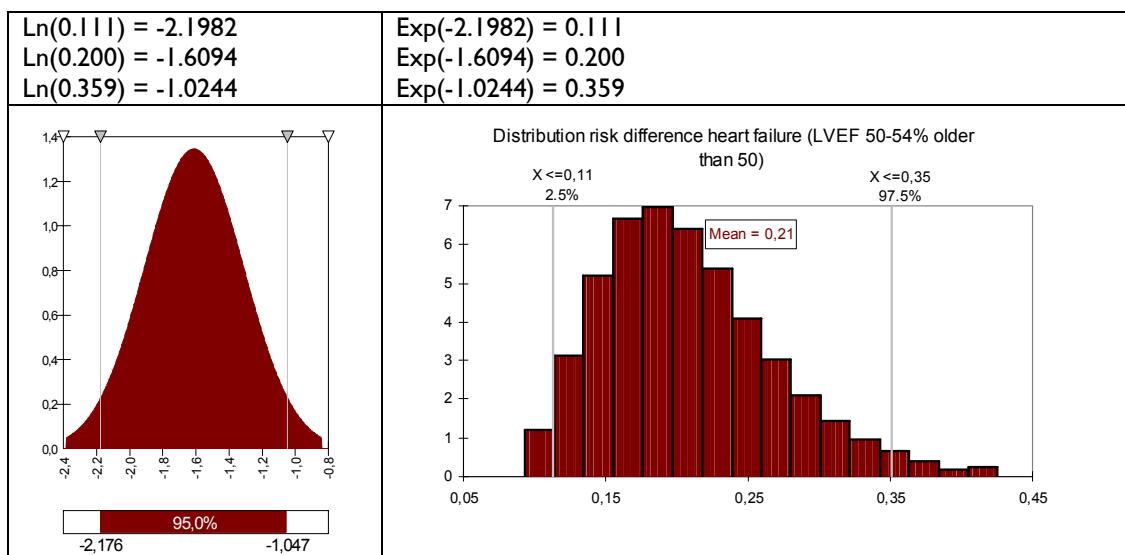
|             | Younger than 50   | Older than 50  | All  |
|-------------|---|--|--|
| LVEF 50-54% | 6.8% <sup>a</sup><br>95% CI: 2.3% - 20.5%               | 20.0% <sup>a</sup><br>95% CI: 11.1% - 35.9%              | 12/96, i.e. 12.5% <sup>b</sup><br>95% CI: 6.63% - 20.82% |
| LVEF >55%   | 6/389,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

Source: a: 3-year cumulative incidence <sup>4</sup>; b: <sup>4</sup> 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.<sup>4</sup> 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%**



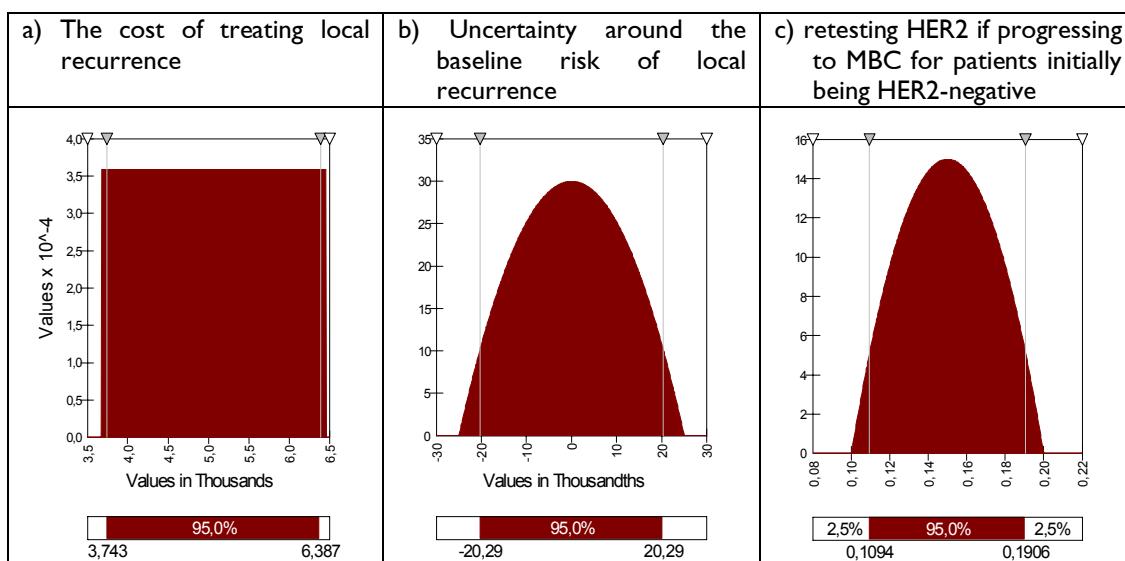
### Local recurrence

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**



### Variation on eligibility criteria

First of all, based on a study in the UK,<sup>42</sup> 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.<sup>4</sup> 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%.<sup>4</sup> 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<br>>=50% LVEF    | 3.74%               | 0.61%  | 4.68%  | 2.48%  | 3.70%  | 6.00%  | 10.39% |
| B31<br>>=50% LVEF       | 10.44% <sup>a</sup> | 7.31%  | 11.38% | 9.18%  | 10.40% | 12.70% | 17.09% |
| HERA, B31<br>>=55% LVEF | 21.08% <sup>b</sup> | 17.94% | 22.02% | 19.82% | 21.04% | 23.34% | 27.72% |

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

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

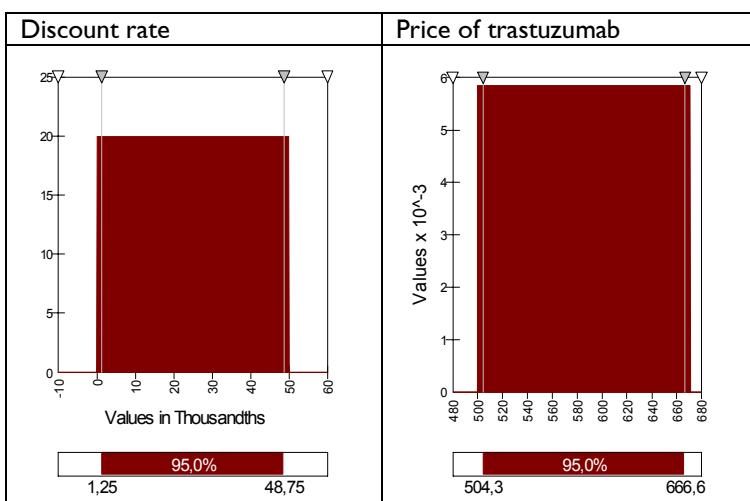
Several studies have shown that HER2 status might differ between primary breast cancers and corresponding metastases.<sup>59, 58</sup> According to expert opinion, about 15% of patients initially diagnosed with HER2-negative breast cancer and progressing to MBC would be retested. In about one third of 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**

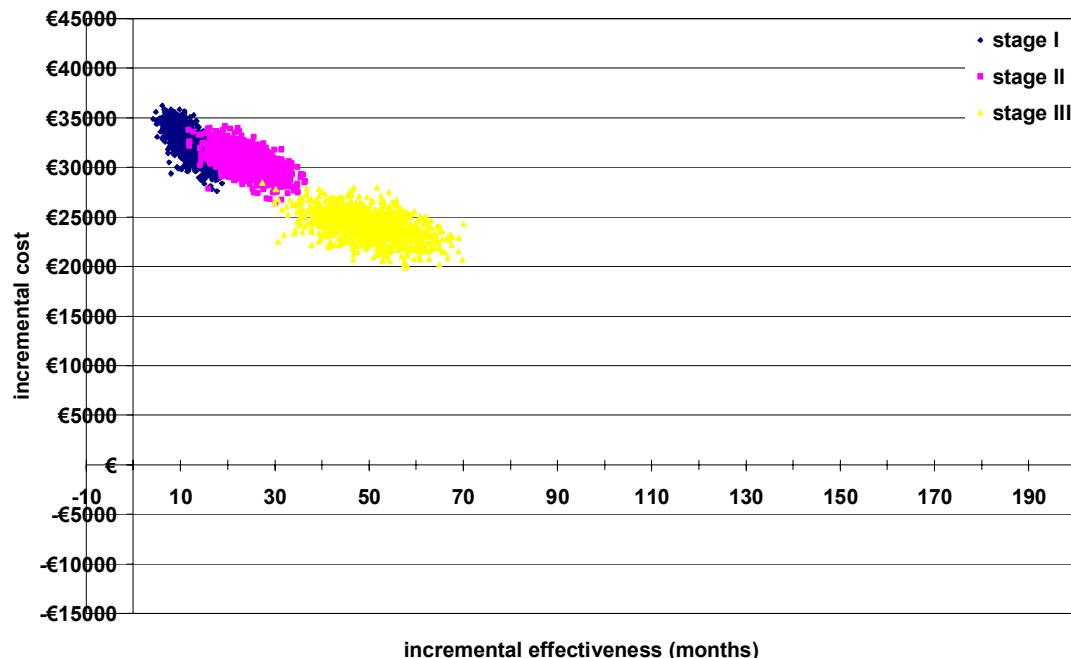
## 4.1.2 Results

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 B3I/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 |
|-----------------------|---------|----------|-----------|
| <b>IE (months)</b>    | 11.99   | 23.88    | 49.74     |
| 2.5%                  | 6.48    | 15.91    | 35.48     |
| 97.5%                 | 18.06   | 32.85    | 63.98     |
| <b>IC (euro)</b>      | 32 320  | 30 608   | 24 202    |
| 2.5%                  | 29 244  | 28 152   | 21 301    |
| 97.5%                 | 35 103  | 33 093   | 26 813    |
| <b>ICER (euro/LY)</b> | 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.

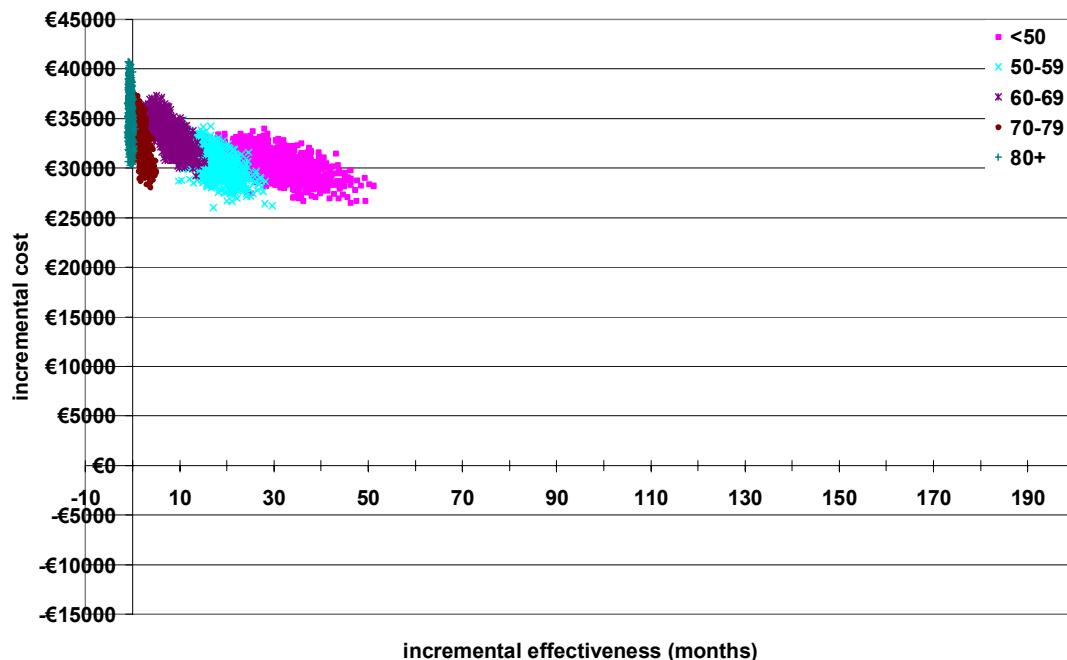
**Figure 7. Cost-effectiveness plane HERA trial (stage I; according to age)**

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 patient 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

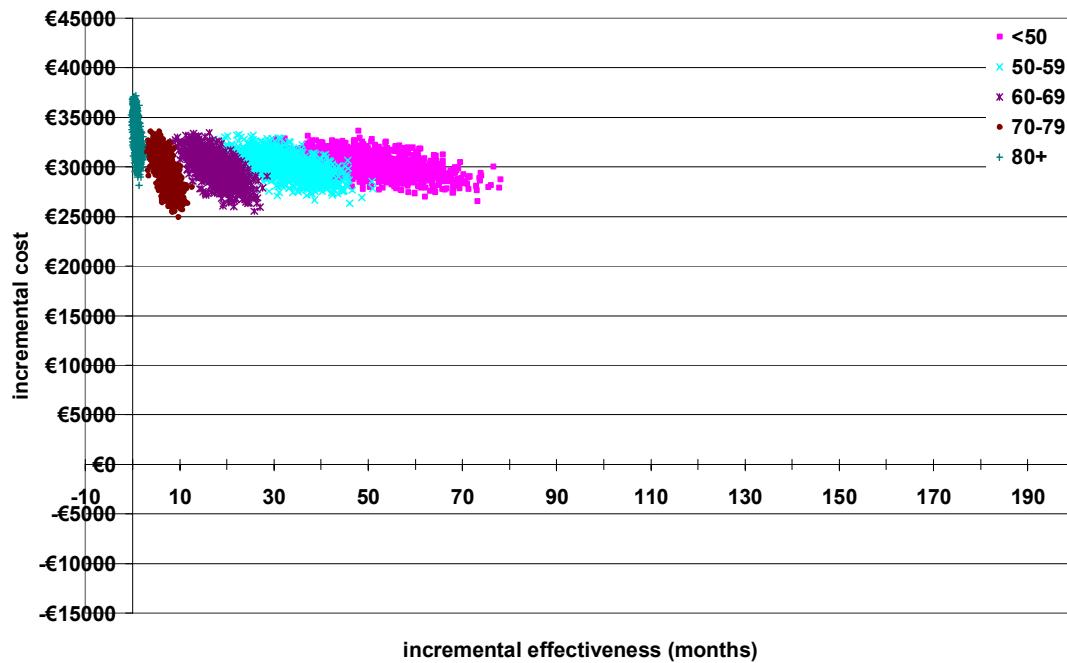
simulations provided an ICER of 55 502 euro with a degree of uncertainty as characterized by the 95% confidence interval, which ranged from 28 960 euro to 107 728 euro (table 36). For the age categories 70-79 and older than 80, some dots were even situated in the fourth quadrant, i.e. negative IC with 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+    |
|-----------------------|--------|--------|--------|---------|----------------|--------|
| <b>IE (months)</b>    | 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   |
| <b>IC (euro)</b>      | 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 |
| <b>ICER (euro/LY)</b> | 34 999 | 12 289 | 23 510 | 55 502  | / <sup>a</sup> | /      |
| 2.5%                  | 19 493 | 7 739  | 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+    |
|-----------------------|--------|--------|--------|--------|--------|--------|
| <b>IE (months)</b>    | 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   |
| <b>IC (euro)</b>      | 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 |
| <b>ICER (euro/LY)</b> | 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 | /      |

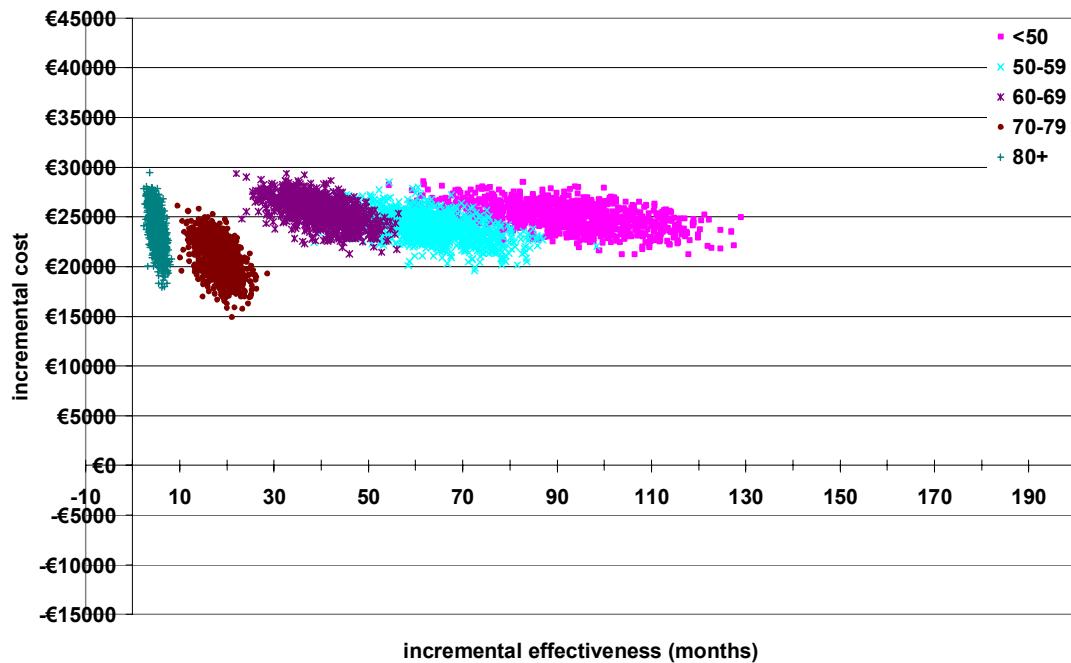
**Figure 9. Cost-effectiveness plane HERA trial (stage III; according to age)**

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+    |
|-----------------------|--------|--------|--------|--------|--------|--------|
| <b>IE (months)</b>    | 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   |
| <b>IC (euro)</b>      | 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 |
| <b>ICER (euro/LY)</b> | 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)**

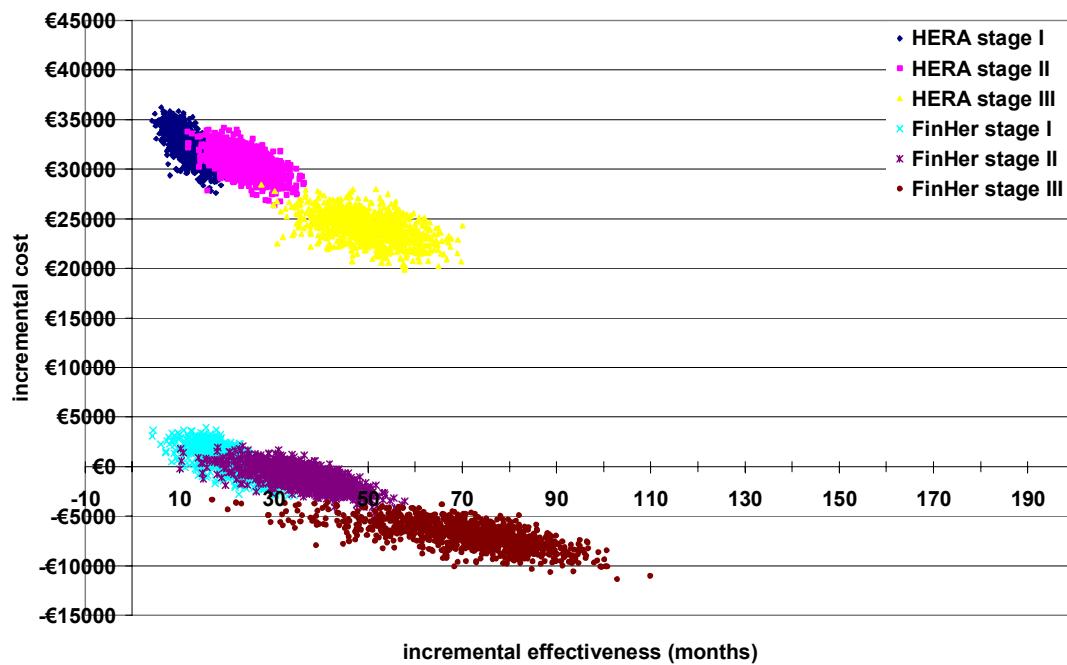
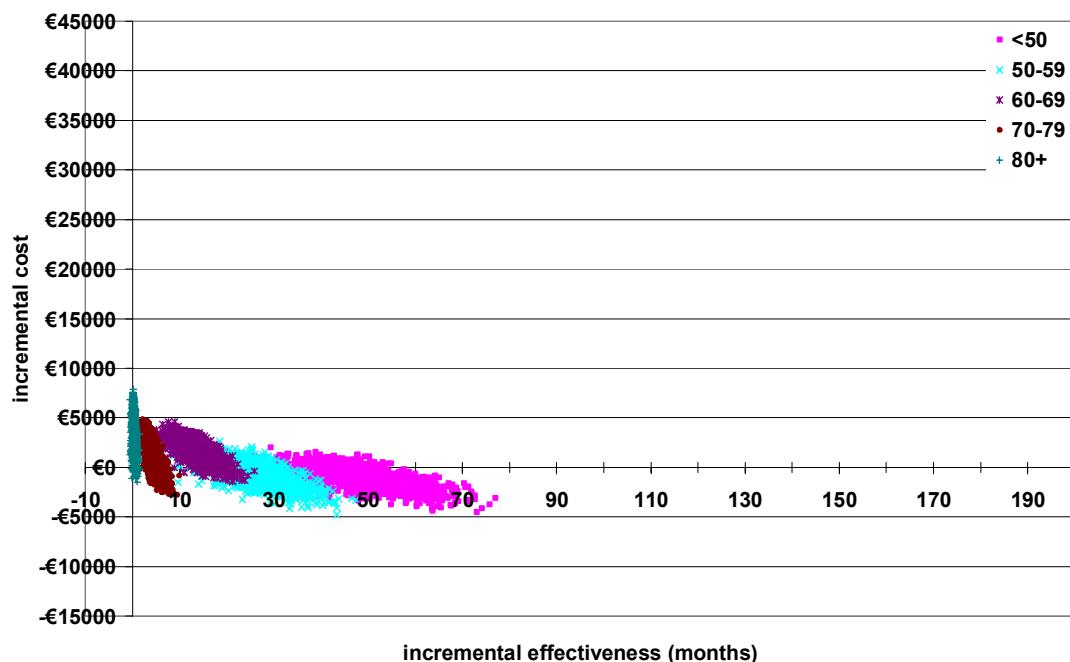


Figure 10 shows the results of our simulations for both the HERA and FinHer trials for stage I, II, and III breast cancer patients. The modelled FinHer trial results provide better cost-effectiveness results in comparison with the HERA trial. First of all, the incremental effectiveness is situated more 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 |
|-----------------------|---------|----------|-----------|
| <b>IE (months)</b>    | 20.35   | 36.09    | 70.33     |
| 2.5%                  | 10.21   | 19.12    | 38.63     |
| 97.5%                 | 30.13   | 50.15    | 94.54     |
| <b>IC (euro)</b>      | 668     | -1045    | -6869     |
| 2.5%                  | -2033   | -3244    | -9522     |
| 97.5%                 | 3040    | 1100     | -4327     |
| <b>ICER (euro/LY)</b> | /       | /        | -1195     |
| 2.5%                  | /       | /        | -1764     |
| 97.5%                 | /       | /        | -868      |

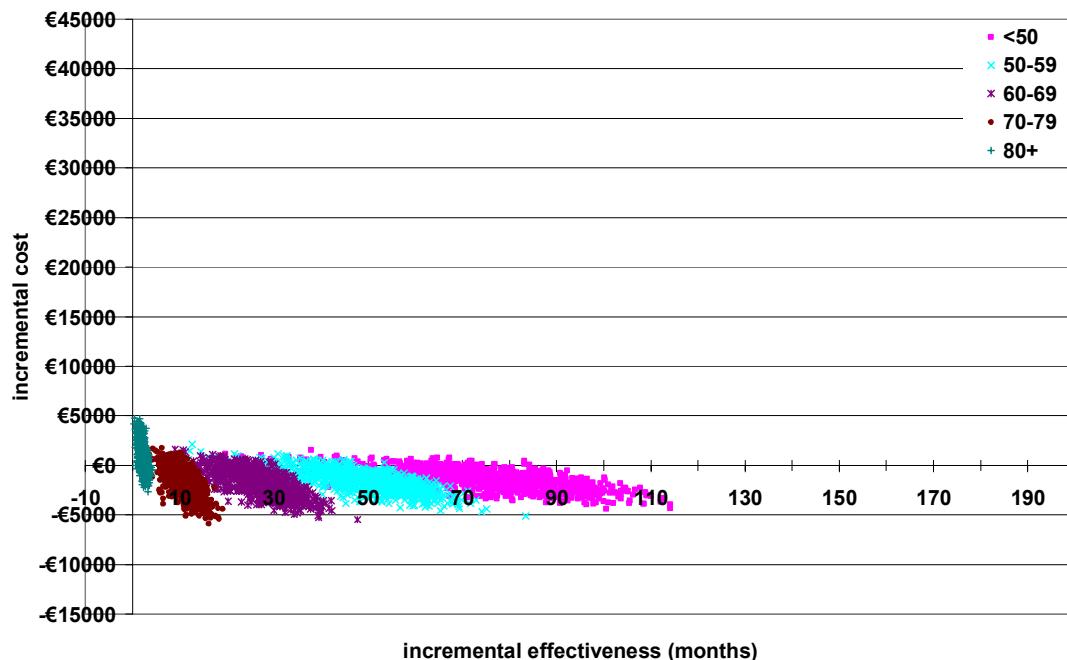
**Figure 11. Cost-effectiveness plane FinHer trial (stage I; according to age)**

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+   |
|--------------------|-------|-------|-------|-------|-------|-------|
| <b>IE (months)</b> | 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  |
| <b>IC (euro)</b>   | 668   | -1057 | -724  | 1570  | 1198  | 3513  |
| 2.5%               | -2033 | -3364 | -3262 | -718  | -1841 | 56    |
| 97.5%              | 3040  | 1000  | 1649  | 3696  | 4147  | 7001  |

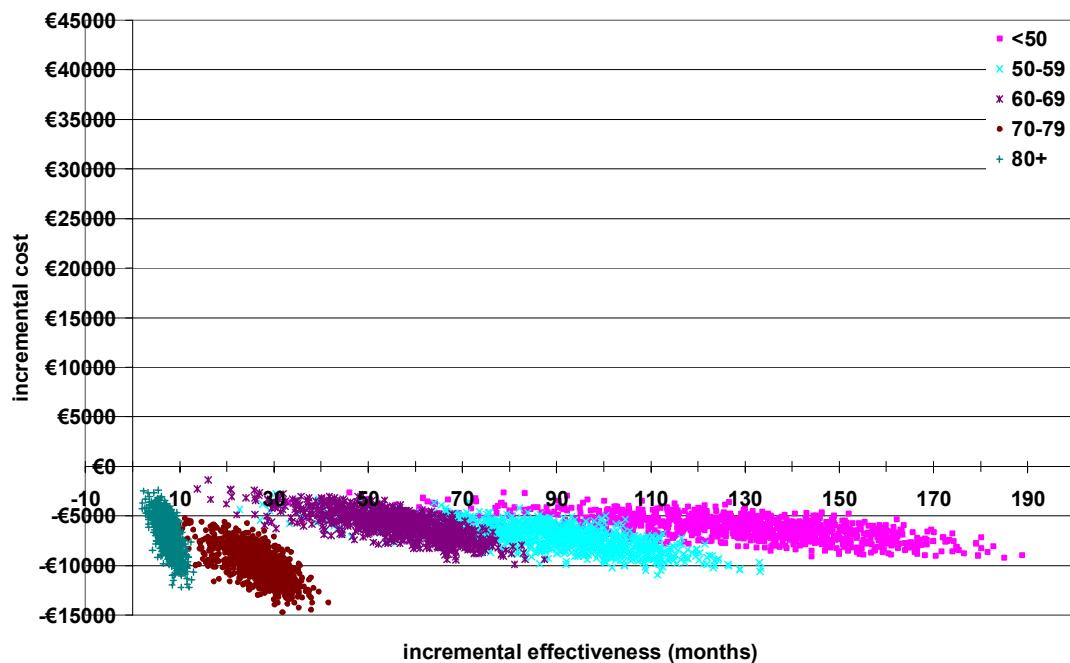
Remark: since simulation results are in different quadrants of the cost-effectiveness plane no ICERs are provided.

**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)**

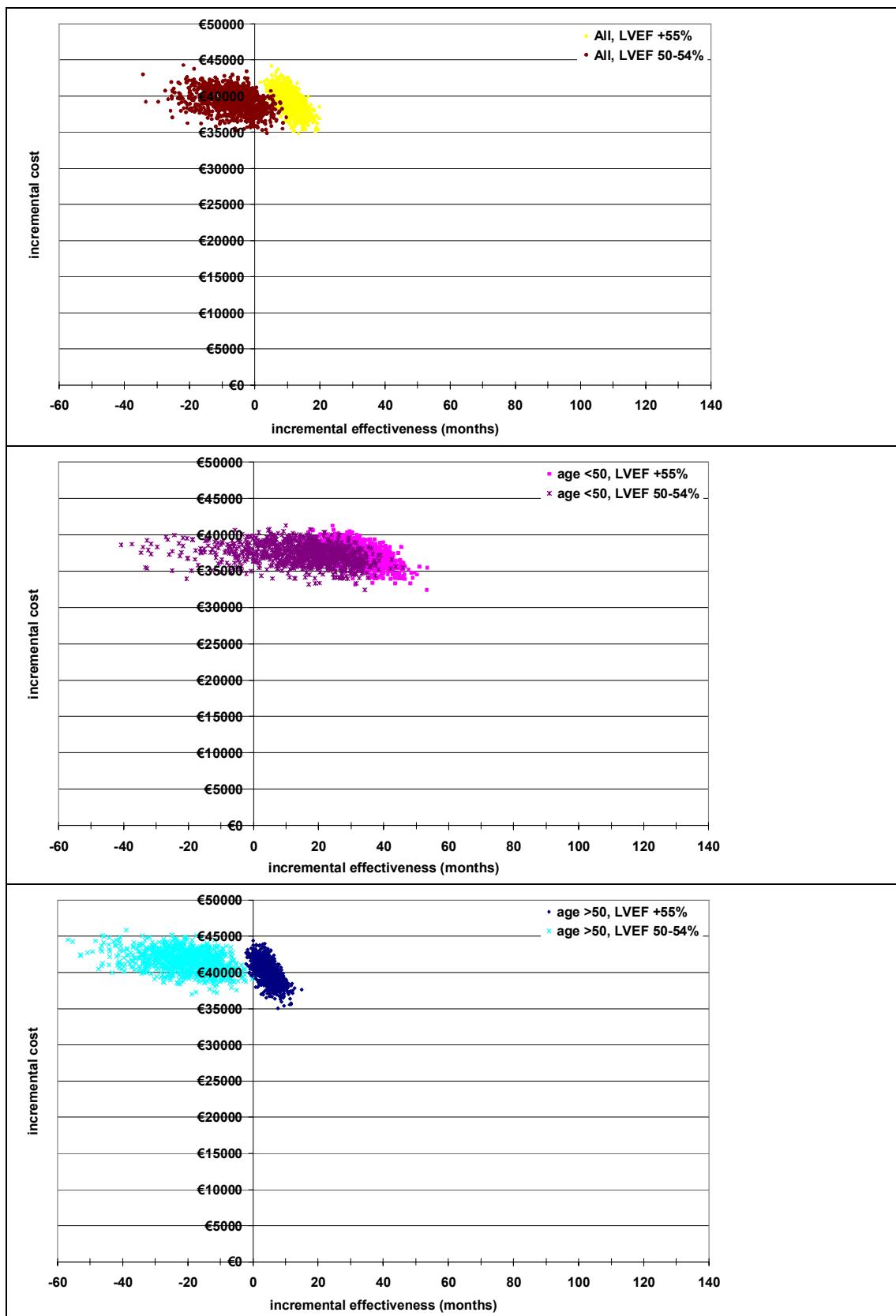
For stage III breast cancer patients, treatment with trastuzumab for 9 weeks is a dominant strategy in 100% of our simulations for all age categories. All dots are distributed over the second quadrant (figure 13). For all age categories of stage III breast cancer patients, positive health gains are generated 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 from 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+     |
|--------------------|-------|--------|--------|-------|---------|---------|
| <b>IE (months)</b> | 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   |
| <b>IC (euro)</b>   | -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 B3I 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 B3I/N983I 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 B3I trial applies a weekly schedule, instead of a 3-weekly schedule, resulting in higher incremental administration costs (table 43 versus 35).

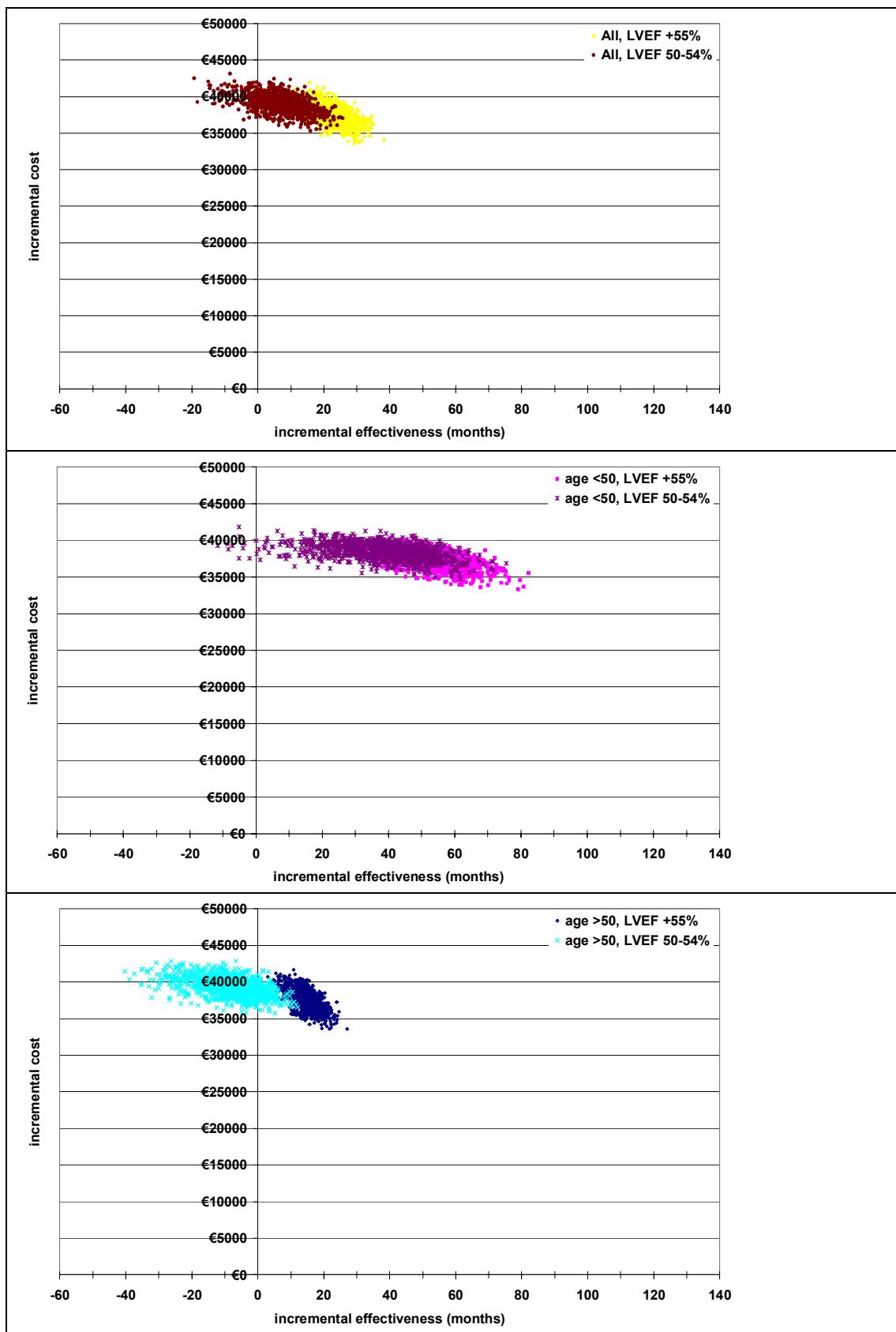
When looking at the impact of a lower LVEF on incremental costs, the influence is rather minimal. In contrast, the influence on the incremental effectiveness is of greater importance. In the first graph of figure 14, all patients are regarded, i.e. no distinction is made according to age. Whereas the 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 B3I-N983I trial and stage I breast cancers**

|                       | LVEF +55% |        |        | LVEF 50-54% |        |        |
|-----------------------|-----------|--------|--------|-------------|--------|--------|
|                       | All       | <50    | >50    | All         | <50    | >50    |
| <b>IE (months)</b>    | 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  |
| <b>IC (euro)</b>      | 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 |
| <b>ICER (euro/LY)</b> | 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 B3I-N983I trial and stage II breast cancers

|                       | LVEF +55% |        |        | LVEF 50-54% |        |        |
|-----------------------|-----------|--------|--------|-------------|--------|--------|
|                       | All       | <50    | >50    | All         | <50    | >50    |
| <b>IE (months)</b>    | 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   |
| <b>IC (euro)</b>      | 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 |
| <b>ICER (euro/LY)</b> | 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.

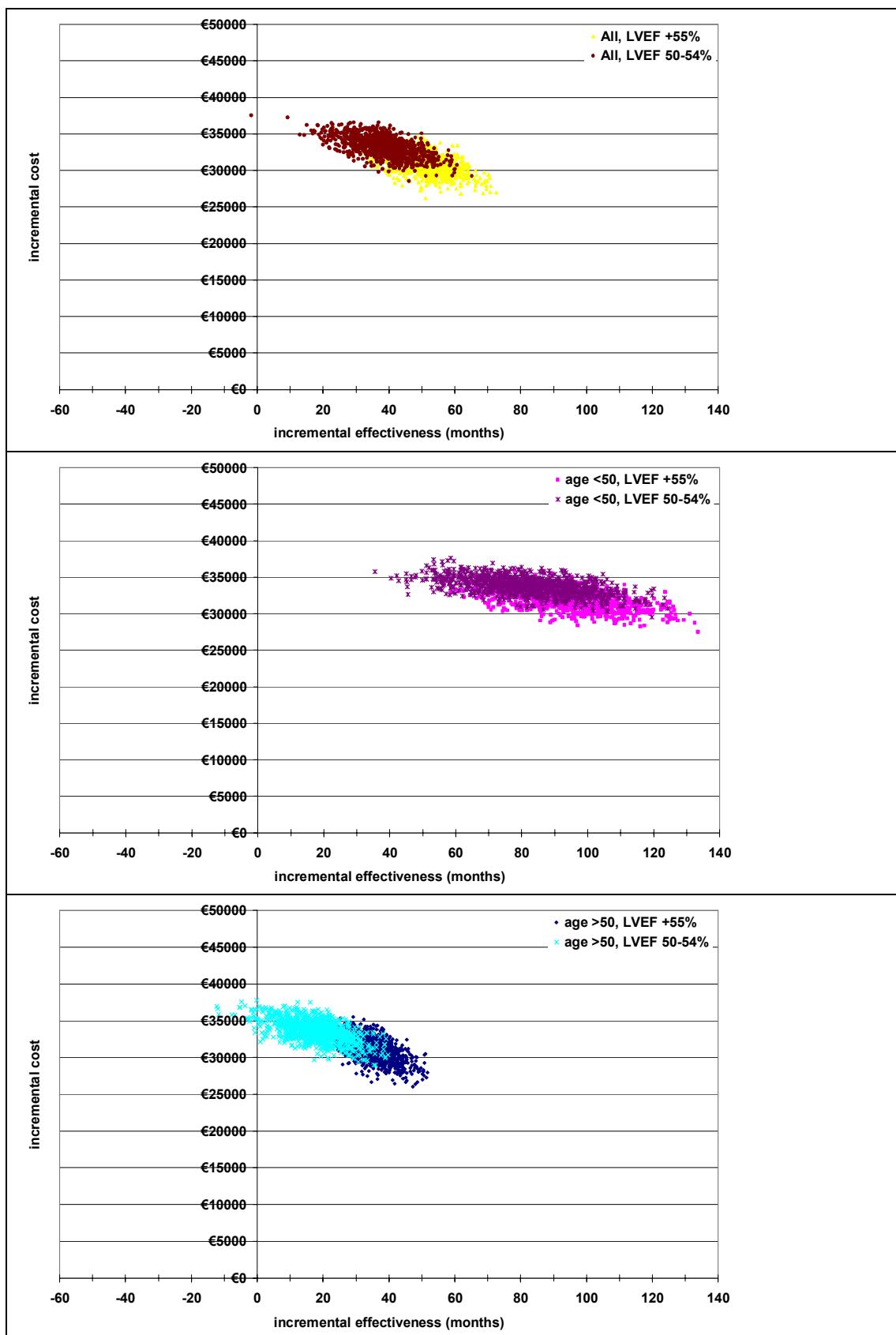
**Table 45.** The ICER and 95%CI for the B3I-N983I trial and stage III breast cancers

|                       | LVEF +55% |        |        | LVEF 50-54% |        |        |
|-----------------------|-----------|--------|--------|-------------|--------|--------|
|                       | All       | <50    | >50    | All         | <50    | >50    |
| <b>IE (months)</b>    | 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  |
| <b>IC (euro)</b>      | 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 |
| <b>ICER (euro/LY)</b> | 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 B3I 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 B3I/N9831 trial (stage III; according to age and LVEF)**



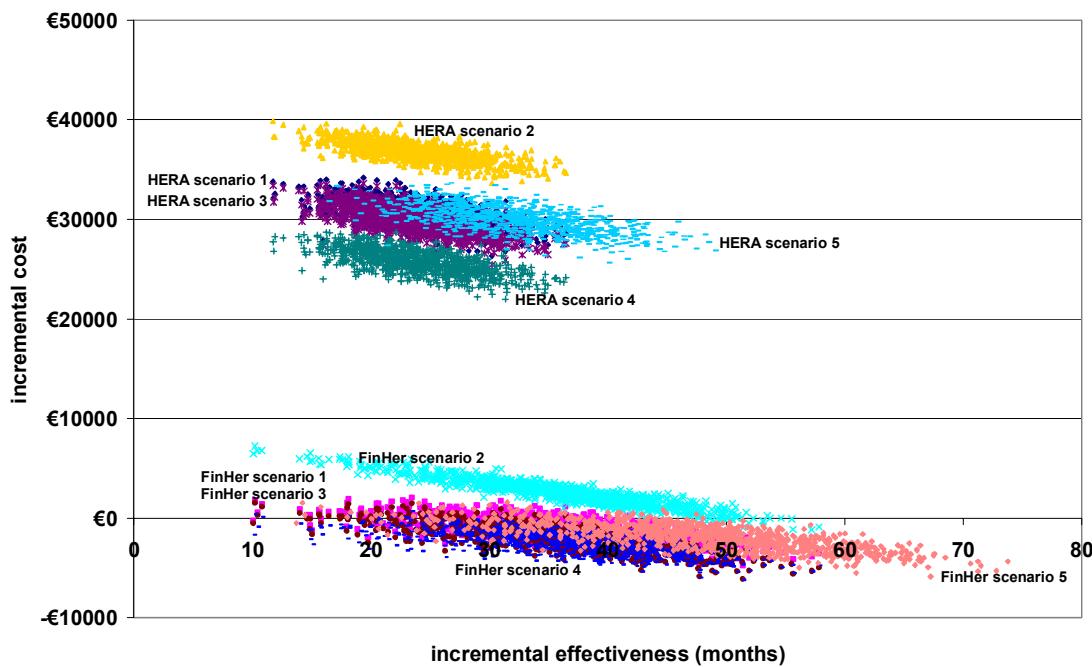
#### 4.1.2.4 Scenario analysis

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 |
|-----------------------|------------|------------|------------|------------|------------|
| <b>IE (months)</b>    | 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      |
| <b>IC (euro)</b>      | 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     |
| <b>ICER (euro/LY)</b> | 16 026     | 19 226     | 15 672     | 13 516     | 11 620     |
| 2.5%                  | 10 553     | 12 898     | 10 206     | 8 733      | 7 770      |
| 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)**

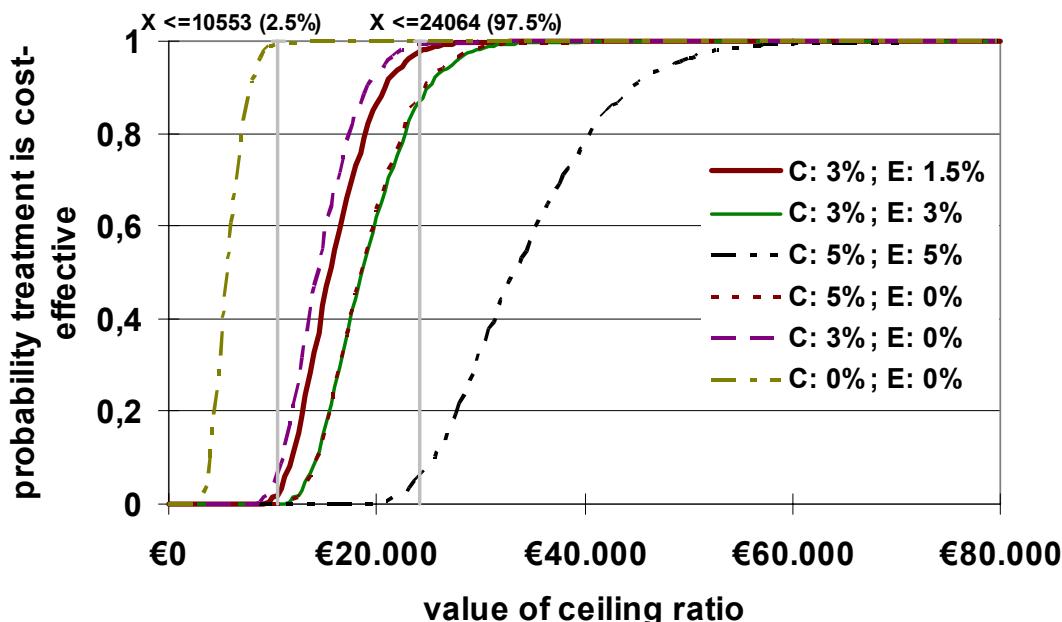
|                    | Scenario 1 | Scenario 2 | Scenario 3 | Scenario 4 | Scenario 5 |
|--------------------|------------|------------|------------|------------|------------|
| <b>IE (months)</b> | 36.09      | 36.09      | 36.09      | 36.09      | 47.53      |
| 2.5%               | 19.12      | 19.12      | 19.12      | 19.12      | 25.34      |
| 97.5%              | 50.15      | 50.15      | 50.15      | 50.15      | 65.31      |
| <b>IC (euro)</b>   | -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)**



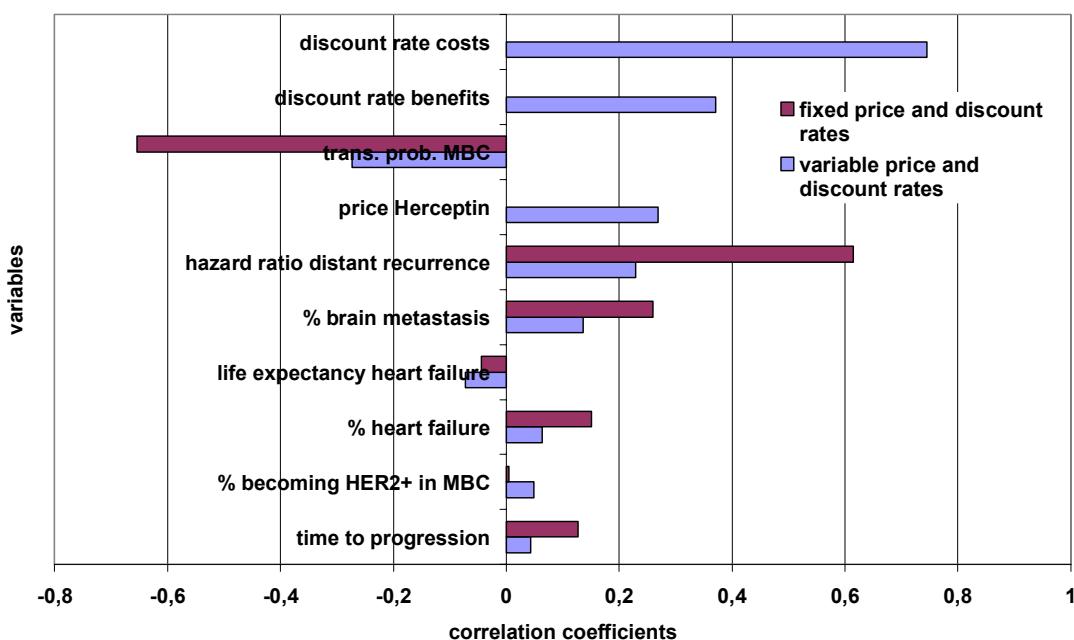
**Table 48. Discount rate scenarios (HERA trial, stage II, all patients)**

|                       | C: 3%;<br>E: 1.5% | C: 3%;<br>E: 3% | C: 5%;<br>E: 5% | C: 5%;<br>E: 0% | C: 3%;<br>E: 0% | C: 0%;<br>E: 0% |
|-----------------------|-------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| <b>IE (months)</b>    | 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           |
| <b>IC (euro)</b>      | 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          |
| <b>ICER (euro/LY)</b> | 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.<sup>70</sup>

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**

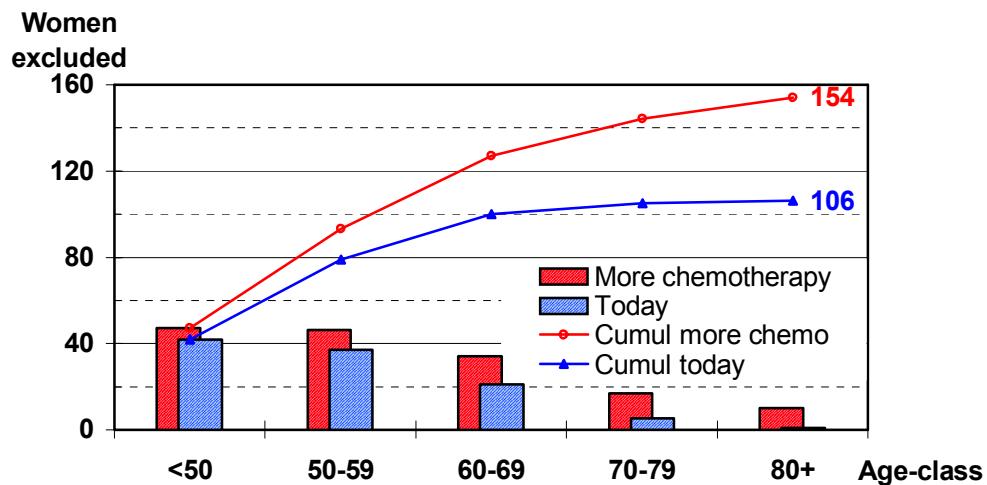
| Age-class | LVEF $\geq 50\%$ <sup>§</sup> | Before anthracyclines<br>LVEF $\geq 50\%$ | After anthracyclines*<br>LVEF $\geq 55\%$ |
|-----------|-------------------------------|---|---|
| <50       | 0.61%                         | 0.61%                                     | 17.94%                                    |
| 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<sup>2</sup> doxorubicin, 6.70% had a strong LVEF drop and 11.40% × (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 lose 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  $\geq 50\%$  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 $\geq 50\%$ | More chemo-therapy | Chemo & LVEF $\geq 55\%$ | 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  $\geq 50\%$  (or  $\geq 55\%$ ): Patients neu-HER2 FISH positive, treated with adjuvant chemotherapy and LVEF  $\geq 50\%$  (or  $\geq 55\%$ ) at start of trastuzumab treatment.

More chemotherapy: Actual chemo + 50% of the chemo naïve FISH positive patients & LVEF  $\geq 50\%$  (or  $\geq 55\%$ ) 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 Week | Diag 1       | 2 | 3 | 4                    | 1    | 2 | 3 | 4    | 5 | 6 | 7    | 8 | 9 | 10 | 11 | 12 | 13 | 1 | 14 | 15 | 16         | 2 | 17 | 18 | 19 | 3 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 |  |
|------------|--------------|---|---|----------------------|------|---|---|------|---|---|------|---|---|----|----|----|----|---|----|----|------------|---|----|----|----|---|----|----|----|----|----|----|----|----|--|
|            | Mast or Lump |   |   | H4 H2 H2 H2 H2 H2 H2 | F600 |   |   | F600 |   |   | F600 |   |   |    |    |    | E  |   |    |    | Rx therapy | N |    |    | D  |   |    |    |    |    |    |    |    |    |  |

Herceptin is administered immediately before anthracyclines.

D100-80 = Docetaxel 100-80 mg/m<sup>2</sup> every 3 weeks

H4 = Herceptin 4 mg/kg

H2 = Herceptin 2 mg/kg weekly

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

F60 = 5-fluorouracil 600 mg/m<sup>2</sup> every 3 weeks

E60 = Epirubicin 60 mg/m<sup>2</sup> every 3 weeks

C600 = Cyclophosphamide 600 mg/m<sup>2</sup> every 3 weeks

|         |                    |
|---------|--------------------|
| Surface | 1,75m <sup>2</sup> |
| Weight  | 63,9 kg            |

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

**Figure 22. Detailed costs of chemotherapy in the HERA setting**

| Cycle Week | Diag |                    |                    | 5 6 7              |              |    | 8 9 10 11 12 |    |    | 1 13 14 15                  |                             |                             | 2 16 17 18                  |                     |                    | 3 19 20 21          |                    |              | 4 22 23 24          |                    |    | 1 25 26 27 |    |    | 2 28 29 30 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
|------------|------|--------------------|--------------------|--------------------|--------------|----|--------------|----|----|-----------------------------|-----------------------------|-----------------------------|-----------------------------|---------------------|--------------------|---------------------|--------------------|--------------|---------------------|--------------------|----|------------|----|----|------------|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|
|            | 1    | 2                  | 3                  | 4                  | Mast or Lump |    |              |    |    | F500<br>E100 or A60<br>C500 | F500<br>E100 or A60<br>C500 | F500<br>E100 or A60<br>C500 | F500<br>E100 or A60<br>C500 | C600<br>M40<br>F600 | D100<br>or<br>P175 | C600<br>M40<br>F600 | D100<br>or<br>P175 | C600<br>D100 | C600<br>M40<br>F600 | D100<br>or<br>P175 |    |            |    |    |            |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Cycle Week | 3    | 31                 | 32                 | 33                 | 4            | 34 | 35           | 36 | 1  | 37                          | 38                          | 39                          | 2                           | 40                  | 41                 | 42                  | 3                  | 43           | 44                  | 45                 | 4  | 46         | 47 | 48 | 5          | 49 | 50 | 51 | 6  | 52 | 53 | 54 | 7  | 55 | 56 | 57 | 8  | 58 | 59 | 60 |
|            |      | D100<br>or<br>P175 | C600<br>or<br>F600 | D100<br>or<br>P175 | H8           |    | H6           |    | H6 |                             | H6                          |                             | H6                          |                     | H6                 |                     | H6                 |              | H6                  |                    | H6 |            | H6 |    | H6         |    | H6 |    | H6 |    | H6 |    | H6 |    | H6 |    |    |    |    |    |
| Cycle Week | 9    | 61                 | 62                 | 63                 | 10           | 64 | 65           | 66 | 11 | 67                          | 68                          | 69                          | 12                          | 70                  | 71                 | 72                  | 13                 | 73           | 74                  | 75                 | 14 | 76         | 77 | 78 | 15         | 79 | 80 | 81 | 16 | 82 | 83 | 84 | 17 | 85 | 86 | 87 | 18 | 88 |    |    |
|            |      | H6                 |                    | H6                 |              | H6 |              | H6 |    | H6                          |                             | H6                          |                             | H6                  |                    | H6                  |                    | H6           |                     | H6                 |    | H6         |    | H6 |            | H6 |    | H6 |    | H6 |    | E  |    | N  |    | D  |    |    |    |    |

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/m<sup>2</sup> every 3 weeks

E100 = Epirubicin 100 mg/m<sup>2</sup> every 3 weeks

C500 = Cyclophosphamide 500 mg/m<sup>2</sup> every 3 weeks

D100 = Docetaxel 100 mg/m<sup>2</sup> every 3 weeks

P175 = Paclitaxel 175 mg/m<sup>2</sup> every 3 weeks

C600 = Cyclophosphamide 600 mg/m<sup>2</sup> twice every 4 weeks

M40 = Methotrexate 40 mg/m<sup>2</sup> twice every 4 weeks

F600 = 5-fluorouracil 600 mg/m<sup>2</sup> twice every 4 weeks

H8 = Herceptin 8 mg/kg

H6 = Herceptin 6 mg/kg every 3 weeks

|         |                    |
|---------|--------------------|
| Surface | 1,75m <sup>2</sup> |
| Weight  | 63,9 kg            |

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

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 N983I & B3I settings****The N983I- B3I studies**

| Cycle Week | Diag 1 2 3     | 4              | 1 5 6 7        | 2 8 9 10       | 3 11 12 13     | 4 14 15 16     | 1 17 18 19     | 2 H2           | 3 H2           | 4 H2           | 5 H2           | 6 H2           | 7 H2           | 8 H2           | 9 H2           | 10 H2          | 11 H2          | 12 H2          | 13 H2          | 14 H2 |       |       |       |       |       |       |       |       |       |       |
|------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
| Cycle Week | Mast or Lump   | A60<br>C600    | A60<br>C600    | A60<br>C600    | A60<br>C600    | A60<br>C600    | H4<br>P80      | H2<br>P80      | Rx    |       |       |       |       |       |       |       |       |       |       |
| Cycle Week | 15 31          | 16 32          | 17 33          | 18 34          | 19 35          | 20 36          | 21 37          | 22 38          | 23 39          | 24 40          | 25 41          | 26 42          | 27 43          | 28 44          | 29 45          | 30 46          | 31 47          | 32 48          | 33 49          | 34 50 | 35 51 | 36 52 | 37 53 | 38 54 | 39 55 | 40 56 | 41 57 | 42 58 | 43 59 | 44 60 |
| Cycle Week | H2<br>H2<br>H2 | E     | N     | D     |       |       |       |       |       |       |       |       |

Herceptin is administered immediately after anthracyclines.

A60 = Doxorubicin 60 mg/m<sup>2</sup> every 3 weeksP80 = Paclitaxel 80 mg/m<sup>2</sup> weekly

Rx = Radiotherapy

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

C600 = Cyclophosphamide 600 mg/m<sup>2</sup> every 3 weeks

H4 = Herceptin 4 mg/kg

H2 = Herceptin 2 mg/kg weekly

|         |                    |
|---------|--------------------|
| Surface | 1,75m <sup>2</sup> |
| Weight  | 63,9 kg            |

|  | Dose                                       | Cost/cycle   | Cost per regimen                |                    | Cost per regimen  |
|--|--|--|---------------------------------|--------------------|---|
| <b>4 cycles</b><br>doxorubicin 60 mg/m <sup>2</sup><br>cyclophosphamide 600 mg/m <sup>2</sup><br>daycare (4)   | 105,0 mg<br>1.050 mg                       | 131,56 €<br>5,77 €<br>245,98 €                             | 526,24 €<br>23,09 €<br>983,92 € |                    |   |
| <b>12 cycles</b><br>paclitaxel 80 mg/m <sup>2</sup><br>daycare (12)  | 140,0 mg                                   | 547,12 €<br>245,98 €                                       | 6.565,44 €<br>2.951,76 €        |                    |   |
| <b>52 cycles of which 12 concurrent with paclitaxel</b><br>1 x trastuzumab 4 mg/kg<br>1 x unavoidable waste 22,2%<br><b>51 x trastuzumab 2 mg/kg</b><br>51 x unavoidable waste 26,7%<br>daycare (40) | 255,6 mg<br>56,7 mg<br>127,8 mg<br>34,1 mg | 1.143,23 €<br>253,80 €<br>571,62 €<br>152,62 €<br>245,98 € |                                 |                    | 1.143,23 €<br>253,80 €<br>29.152,38 €<br>7.783,69 €<br>9.839,20 € |
| <b>TOTAL DRUGS</b>   |  |  | 7.114,77 €                      |                    | 38.333,09 €   |
| <b>Daycare stays</b>   |  |  | 3.935,68 €                      |                    | 9.839,20 €  |
| <b>TOTAL</b>   |  |  | 11.050,45 €                     |                    | 48.172,29 €   |
| <b>GRAND TOTAL</b>   | <b>N983I - B3I</b>                         |  |                                 | <b>59.222,75 €</b> |   |

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 N983I/B3I 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<br>≥50%       | More<br>chemotherapy        | Chemo & LVEF<br>≥55%       | More<br>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€<br>for 98 patients | 2.82 M€<br>for 232 patients | 3.25 M€<br>for 80 patients | 8.26 M€<br>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<br>≥50%        | More<br>chemotherapy        | Chemo & LVEF<br>≥55%         | More<br>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€<br>for 324 patients | 4.30 M€<br>for 425 patients | 10.86 M€<br>for 267 patients | 14.59 M€<br>for 349 patients |

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

| Stage III | Chemo & LVEF<br>≥50%        | More<br>chemotherapy        | Chemo & LVEF<br>≥55%        | More<br>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€<br>for 175 patients | 1.96 M€<br>for 205 patients | 5.85 M€<br>for 144 patients | 6.99 M€<br>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<br>≥50%                | Chemo & LVEF<br>≥55%                 | More<br>chemotherapy                | More<br>chemotherapy                 |
|-------------------------------|-------------------------------------|--------------------------------------|-------------------------------------|--------------------------------------|
|                               | T 9 weeks                           | T 52 weeks                           | T 9 weeks                           | T 52 weeks                           |
| <b>Stage I</b>                | 0.85 M€                             | 3.25 M€                              | 2.82 M€                             | 8.26 M€                              |
| <b>Stage II</b>               | 2.81 M€                             | 10.86 M€                             | 4.30 M€                             | 14.59 M€                             |
| <b>Stage III</b>              | 1.52 M€                             | 5.85 M€                              | 1.96 M€                             | 6.99 M€                              |
| <b>Stages I, II &amp; III</b> | <b>5.17 M€<br/>for 597 patients</b> | <b>19.96 M€<br/>for 491 patients</b> | <b>9.08 M€<br/>for 862 patients</b> | <b>29.84 M€<br/>for 708 patients</b> |

## 5 APPENDICES

### 5.1 APPENDIX I: 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, (6<sup>th</sup> 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 |
|---|--------------------|-------------------|---|---|---|---------------|----|----|--------------|--------------------|---------|--------------|---------------|--------|-------|-----------|-----------------|
|   |                    |                   |   |   |   |               |    |    |              |                    |         |              |               |        |       |           |                 |
| <b>Menopausal status</b> Ante, Post, Unknown<br><b>T</b> 0, is, 1a, 1b, 1c, 2, 3, 4, x<br><b>N</b> 0, 1, 2, 3, x<br><b>M</b> 0, 1, x  |                    |                   |   |   |   |               |    |    |              |                    |         |              |               |        |       |           |                 |
| <b>Histologic grade</b><br>1 = well<br>2 = moderately<br>3 = poor / anaplastic<br>Unknown   |                    |                   |   |   |   |               |    |    |              |                    |         |              |               |        |       |           |                 |
| <b>ER</b> -, +, Unknown<br><b>PR</b> -, +, Unknown  |                    |                   |   |   |   |               |    |    |              |                    |         |              |               |        |       |           |                 |
| <b>HER2/neu</b> <b>IHC</b> -, 1+, 2+, 3+, Unknown<br><b>HER2/neu</b> <b>FISH</b> -, +, Unknown<br><b>or</b> <b>CISH</b> -, +, Unknown |                    |                   |   |   |   |               |    |    |              |                    |         |              |               |        |       |           |                 |
| <b>Surgery</b> Mastectomy, Lumpectomy   |                    |                   |   |   |   |               |    |    |              |                    |         |              |               |        |       |           |                 |
| <b>Radiotherapy</b> -, +, Unknown   |                    |                   |   |   |   |               |    |    |              |                    |         |              |               |        |       |           |                 |
| <b>Anthracycline</b> Doxorubicin, Epirubicine   |                    |                   |   |   |   |               |    |    |              |                    |         |              |               |        |       |           |                 |
| <b>Taxanes</b> Paclitaxel<br>Docetaxel  |                    |                   |   |   |   |               |    |    |              |                    |         |              |               |        |       |           |                 |
| <b>Other</b> Cyclophosphamide<br>5-Fluorouracil   |                    |                   |   |   |   |               |    |    |              |                    |         |              |               |        |       |           |                 |
| <b>Tamoxifen</b> -, +, Unknown  |                    |                   |   |   |   |               |    |    |              |                    |         |              |               |        |       |           |                 |
| <b>Arom. inhibitor</b> Anastrozol, Letrozol, Exemestan  |                    |                   |   |   |   |               |    |    |              |                    |         |              |               |        |       |           |                 |

**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 15<sup>th</sup> of May in spite of a request at the 9<sup>th</sup> 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 15<sup>th</sup>) 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 6<sup>th</sup> 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    |
| <b>TOTAL</b>  | <b>5254</b> |         |

### 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              |
| I | 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              |
| I | 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 (6<sup>th</sup> 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 (6<sup>th</sup> version vs 5<sup>th</sup> version). The 6<sup>th</sup> edition classifies some nodal categories as Stage III that were previously considered Stage II.<sup>a</sup>

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

| Stage            | KCE 2005 * (N=4528) |              |                    | NCR 2001 **(N=3767) |         |
|------------------|---------------------|--------------|--------------------|---------------------|---------|
|                  | 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              |                     |         |
| <b>Total II</b>  | <b>1792</b>         | <b>39.58</b> |                    | 1755                | 46.59   |
| IIIa             | 400                 | 8.83         | 86.42              |                     |         |
| IIIb             | 182                 | 4.02         | 90.44              |                     |         |
| IIIc             | 137                 | 3.03         | 93.46              |                     |         |
| <b>Total III</b> | <b>719</b>          | <b>15.88</b> |                    | 333                 | 8.8     |
| IV               | 296                 | 6.54         | 100.00             | 209                 | 5.55    |

\* staging definition based on TNM classification 2002 (6<sup>th</sup> edition)

\*\* staging definition based on TNM classification 1997 (5<sup>th</sup> edition)

<sup>a</sup> 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**

| Stage | N    | Analysis Variable : Age at diagnosis |        |               |         |         |
|-------|------|--------------------------------------|--------|---------------|---------|---------|
|       |      | 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**

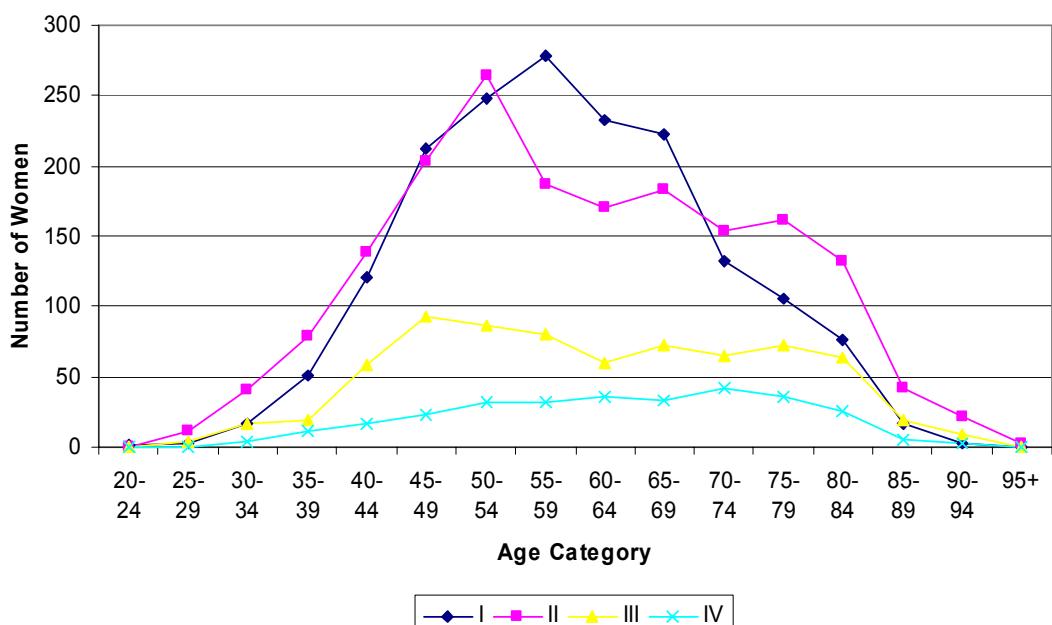
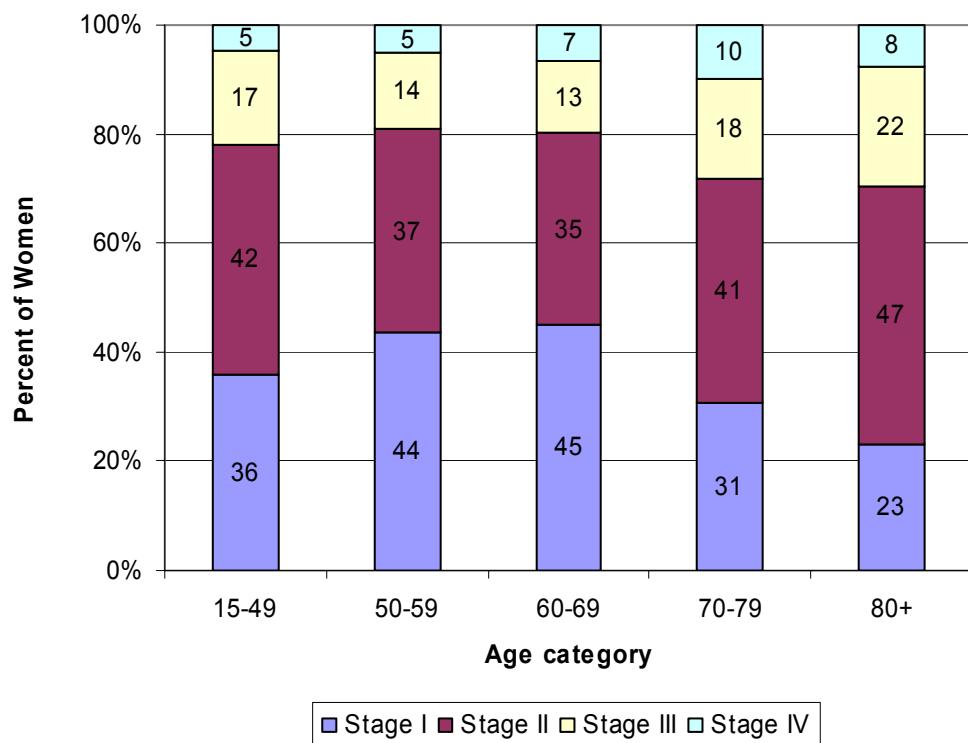


Table 64. Number and percent of patients per age and stage

| Age at diagnostic<br>Frequency<br>Percent | Table of age by stage |               |              |             | Total          |
|---|-----------------------|---------------|--------------|-------------|----------------|
|   | I                     | II            | III          | IV          |                |
| 15-49                                     | 405<br>8.94           | 474<br>10.47  | 192<br>4.24  | 55<br>1.21  | 1126<br>24.87  |
| 50-59                                     | 527<br>11.64          | 452<br>9.98   | 166<br>3.67  | 64<br>1.41  | 1209<br>26.70  |
| 60-69                                     | 456<br>10.07          | 353<br>7.80   | 132<br>2.92  | 68<br>1.50  | 1009<br>22.28  |
| 70-79                                     | 237<br>5.23           | 315<br>6.96   | 138<br>3.05  | 77<br>1.70  | 767<br>16.94   |
| 80+                                       | 96<br>2.12            | 198<br>4.37   | 91<br>2.01   | 32<br>0.71  | 417<br>9.21    |
| Total                                     | 1721<br>38.01         | 1792<br>39.58 | 719<br>15.88 | 296<br>6.54 | 4528<br>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 |       |      |       |       |      |       |       |       |       |       |     | ER    |       |      | All |  |
|----------|---|-------|-------|------|-------|-------|------|-------|-------|-------|-------|-------|-----|-------|-------|------|-----|--|
|          |   | I     |       | II   |       | III   |      | IV    |       | + All |       | - All |     |       |       |      |     |  |
|          |   | ER    | N     | ER   | N     | ER    | N    | ER    | N     | ER    | N     | ER    | N   | +     | 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 |       |      |       |       |      |       |       |       |       |       |     | PR    |       |      | All |  |
|----------|---|-------|-------|------|-------|-------|------|-------|-------|-------|-------|-------|-----|-------|-------|------|-----|--|
|          |   | I     |       | II   |       | III   |      | IV    |       | + All |       | - All |     |       |       |      |     |  |
|          |   | PR    | N     | PR   | N     | PR    | N    | PR    | N     | PR    | N     | PR    | N   | +     | 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<br>(N=4151) | Percent      |
|--------------------------------------|-----------------------|--------------|
| -                                    | 2561                  | 61.70        |
| 1+                                   | 610                   | 14.70        |
| 2+                                   | 496                   | 11.95        |
| 3+                                   | 484                   | 11.66        |
| <b>Total Positive tests (2+, 3+)</b> | <b>980</b>            | <b>23.61</b> |

(N = 377 missing IHC tests)

**Table 68. neu-HER2 overexpression in IHC by age**

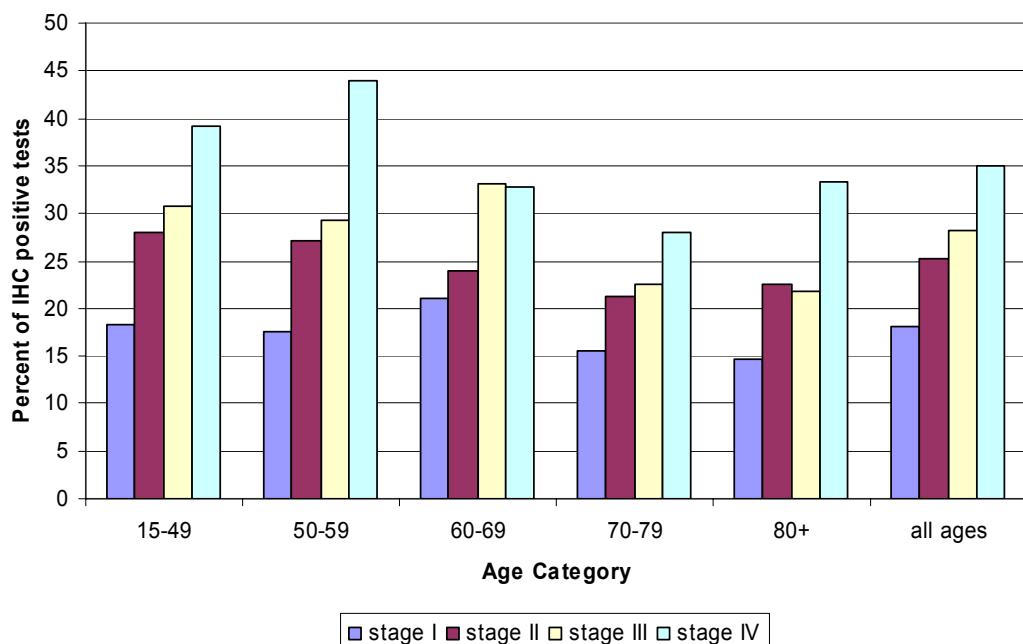
| Age<br>Frequency<br>Row Pct    | Table of age by IHC |            |             |
|--------------------------------|---------------------|------------|-------------|
|                                | HER IHC             |            |             |
| 15-49                          | -, 1+        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

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

| Age      |   | stage     |      |           |      |           |     |           |     |
|----------|---|-----------|------|-----------|------|-----------|-----|-----------|-----|
|          |   | I         |      | II        |      | III       |     | IV        |     |
|          |   | HER 2+ 3+ | n    | HER 2+ 3+ | n    | HER 2+ 3+ | n   | HER 2+ 3+ | 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<br>Frequency<br>Row Pct | FISH result  |              | Total      |
|------------------------------------|--------------|--------------|------------|
|                                    | Positive     | Negative     |            |
| -                                  | 0<br>0.00    | 22<br>100.00 | 22         |
| I+                                 | 2<br>14.29   | 12<br>85.71  | 14         |
| 2+                                 | 61<br>34.46  | 116<br>65.54 | 177        |
| 3+                                 | 199<br>80.89 | 47<br>19.11  | 246        |
| <b>Total</b>                       | <b>262</b>   | <b>197</b>   | <b>459</b> |
| <b>%</b>                           | <b>57.08</b> | <b>42.92</b> |            |

### 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**

| Age      | Stage             |        |                    |         |                     |          |                    |         | Surgery All |       |      |
|----------|-------------------|--------|--------------------|---------|---------------------|----------|--------------------|---------|-------------|-------|------|
|          | I<br>Surgery<br>n | I<br>N | II<br>Surgery<br>n | II<br>N | III<br>Surgery<br>n | III<br>N | IV<br>Surgery<br>n | IV<br>N |             |       |      |
| 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**

| Age      | Stage      |            |            |            |            |            |            |            | Radiotherapy + | All  |
|----------|------------|------------|------------|------------|------------|------------|------------|------------|----------------|------|
|          | 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      |      |            |      |            |     |            |     | All   |      |
|----------|---|------------|------|------------|------|------------|-----|------------|-----|-------|------|
|          |   | I          |      | II         |      | III        |     | IV         |     | n     | N    |
|          |   | Combi<br>n | N    | Combi<br>n | N    | Combi<br>n | N   | Combi<br>n | N   | n     | 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      |      |            |      |            |     |            |     | All        |      |
|----------|---|------------|------|------------|------|------------|-----|------------|-----|------------|------|
|          |   | I          |      | II         |      | III        |     | IV         |     | Combi<br>n |      |
|          |   | combi<br>n | N    | combi<br>n | N    | combi<br>n | N   | combi<br>n | N   | n          | N    |
| 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<br>n | N   | combi<br>n | N   | combi<br>n | N   | combi<br>n | N  |         |
| <b>Age</b>      |          |            |     |            |     |            |     |            |    |         |
| <b>15-49</b>    | <b>N</b> | 33         | 64  | 113        | 125 | 52         | 54  | 9          | 17 | 207 260 |
|                 | <b>%</b> | 51.56      |     | 90.40      |     | 96.30      |     | 52.94      |    | 79.62   |
| <b>50-59</b>    | <b>N</b> | 23         | 80  | 98         | 115 | 40         | 44  | 18         | 22 | 179 261 |
|                 | <b>%</b> | 28.75      |     | 85.22      |     | 90.91      |     | 81.82      |    | 68.58   |
| <b>60-69</b>    | <b>N</b> | 16         | 85  | 42         | 79  | 34         | 40  | 6          | 18 | 98 222  |
|                 | <b>%</b> | 18.82      |     | 53.16      |     | 85.00      |     | 33.33      |    | 44.14   |
| <b>70-79</b>    | <b>N</b> | 2          | 30  | 9          | 59  | 9          | 25  | 5          | 19 | 25 133  |
|                 | <b>%</b> | 6.67       |     | 15.25      |     | 36.00      |     | 26.32      |    | 18.80   |
| <b>80+</b>      | <b>N</b> | 0          | 11  | 0          | 37  | 1          | 17  | 0          | 8  | 1 73    |
|                 | <b>%</b> | 0          |     | 0          |     | 5.88       |     | 0          |    | 1.37    |
| <b>All ages</b> | <b>N</b> | 74         | 270 | 262        | 415 | 136        | 180 | 38         | 84 | 510 949 |
|                 | <b>%</b> | 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 |
|-------------------|-----------|---------|----------------------|
| <b>15-49</b>      | 244       | 25.28   | 244                  |
| <b>50-59</b>      | 288       | 29.84   | 532                  |
| <b>60-69</b>      | 238       | 24.66   | 770                  |
| <b>70-79</b>      | 137       | 14.20   | 907                  |
| <b>80+</b>        | 58        | 6.01    | 965                  |

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

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

Frequency Missing = 63

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

| Age          | Combination of Chemotherapies           |  |
|--------------|---|--|
|              | Only Patients Tested for IHC<br>n/N (%) | Only Patients Positive (2+, 3+) for IHC<br>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 (.92)                              | 0/8 (0.00)   |
| <b>Total</b> | <b>191/881 (21.68)</b>                  | <b>60/163 (36.81)</b>                              |

### 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

| Age                           | Table of age by HER_IHC |                     |            |
|-------------------------------|-------------------------|---------------------|------------|
|                               | HER_IHC                 |                     | Total      |
|                               | -, 1+                   | 2+, 3+              |            |
| 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         |
| <b>Total</b>                  | <b>508</b>              | <b>157 (23.61%)</b> | <b>665</b> |
| <b>Frequency Missing = 49</b> |                         |                     |            |

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

| Age          | Combination of chemotherapies           |  |
|--------------|---|--|
|              | Only patients tested for IHC<br>n/N (%) | Only patients positive (2+, 3+) for IHC<br>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 (.12)                              | 0/15 (0.00)  |
| <b>Total</b> | <b>267/650 (41.08)</b>                  | <b>78/151 (51.66)</b>                              |

## Addendum

**Stage undefined (too many missing data)**

| T  | N | M | Count |
|----|---|---|-------|
| Ic | X | 0 | 25    |
| Ic | X | X | 11    |
| Ix | X | 0 | 8     |
| Ix | 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  | I | 0 | 8     |
| X  | I | 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  | I | 0 | 1     |
| is | 0 | 0 | 292   |
| is | 0 | X | 21    |
| is | I | 0 | 1     |
| is | X | 0 | 70    |
| is | X | X | 42    |

**Stage I**

| T  | N | M | Count |
|----|---|---|-------|
| Ia | 0 | 0 | 136   |
| Ia | 0 | X | 12    |
| Ia | X | 0 | 11    |
| Ia | X | X | 4     |
| Ib | 0 | 0 | 433   |
| Ib | 0 | X | 35    |
| Ib | X | 0 | 13    |
| Ib | X | X | 4     |
| Ic | 0 | 0 | 910   |
| Ic | 0 | X | 55    |
| Ix | 0 | 0 | 92    |
| Ix | 0 | X | 16    |

**Stage IIa**

| T  | N | M | Count |
|----|---|---|-------|
| Ia | I | 0 | 17    |
| Ia | I | X | 2     |
| Ib | I | 0 | 67    |
| Ib | I | X | 6     |
| Ic | I | 0 | 320   |
| Ic | I | X | 28    |
| Ix | I | 0 | 13    |
| Ix | I | X | 4     |
| 2  | 0 | 0 | 668   |
| 2  | 0 | X | 46    |

**Stage IIb**

| T | N | M | Count |
|---|---|---|-------|
| 2 | I | 0 | 482   |
| 2 | I | X | 47    |
| 3 | 0 | 0 | 88    |
| 3 | 0 | X | 4     |

**Stage IIIa**

| T  | N | M | Count |
|----|---|---|-------|
| Ia | 2 | 0 | 1     |
| Ib | 2 | 0 | 12    |
| Ib | 2 | X | 1     |
| Ic | 2 | 0 | 46    |
| Ic | 2 | X | 5     |
| Ix | 2 | 0 | 2     |
| Ix | 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 |
|----|---|---|-------|
| Ib | 3 | 0 | 2     |
| Ic | 3 | 0 | 14    |
| Ic | 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     |
| Ia | 0 | 1 | 1     |
| Ia | 1 | 1 | 1     |
| Ib | 0 | 1 | 5     |
| Ib | 1 | 1 | 2     |
| Ib | 2 | 1 | 2     |
| Ic | 0 | 1 | 4     |
| Ic | 1 | 1 | 6     |
| Ic | 2 | 1 | 1     |
| Ic | 3 | 1 | 2     |
| Ic | X | 1 | 4     |
| Ix | 0 | 1 | 1     |
| Ix | 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 <sup>2</sup> and of epirubicin (E) is 720mg/m <sup>2</sup>   |
| Anthracyclines with no taxanes | <p>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).</p> <p><u>Minimum allowable starting doses of A or E associated with C with or without F:</u></p> <p>A: 60mg/m<sup>2</sup><br/> CAF/FAC: 50mg/m<sup>2</sup> (q21d or q28d)<br/> EC: 90mg/m<sup>2</sup><br/> FEC/CEF: 75mg/m<sup>2</sup> (day 1 q21d) if given for a minimum of 6 cycles<br/> 50mg/m<sup>2</sup> (days 1 and 8 q28d)<br/> 75mg/m<sup>2</sup> (day 1 q21d)<br/> 60mg/m<sup>2</sup> (day 1 q21d) if given for a minimum of 5 cycles</p> <p><u>Minimum allowable starting doses of A or E as single agents or combined with C and followed by CMF (described below):</u></p> <p>A: 75mg/m<sup>2</sup><br/> E: 90mg/m<sup>2</sup></p>  |
| Anthracyclines and taxanes     | <p>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.</p> <p><u>Minimum allowable starting doses of A or E (with or without C and/or F) followed by P or D (sequential regimens):</u></p> <p>A: 60mg/m<sup>2</sup><br/> FAC: 50mg/m<sup>2</sup><br/> E: 90mg/m<sup>2</sup><br/> FEC: 60mg/m<sup>2</sup> (day 1 q21d) if followed by D 100mg/m<sup>2</sup> (day 1 q21d) if given for a minimum of 5 cycles<br/> 75mg/m<sup>2</sup><br/> P: 175mg/m<sup>2</sup>/3-hour<br/> 75 mg/m<sup>2</sup> (q7d)<br/> D: 100mg/m<sup>2</sup></p> <p><u>Minimum allowable starting doses of A and E (with or without C and/or F), and P and D given concurrently (combined regimens):</u></p> <p>A: 50mg/m<sup>2</sup><br/> E: 75mg m<sup>2</sup><br/> P: 135mg/m<sup>2</sup>/3-hour<br/> D: 60mg m<sup>2</sup>/1-hour</p> |
| 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 <sup>2</sup> /day days 1-14 if given orally and 600mg/m <sup>2</sup> per injection if given intravenously. The recommended starting dose per injection of M is 40mg/m <sup>2</sup> and of F is 600mg/m <sup>2</sup> . 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 <sup>A</sup>  |

<sup>A</sup> 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%      |
| 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.<sup>42</sup>

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%**

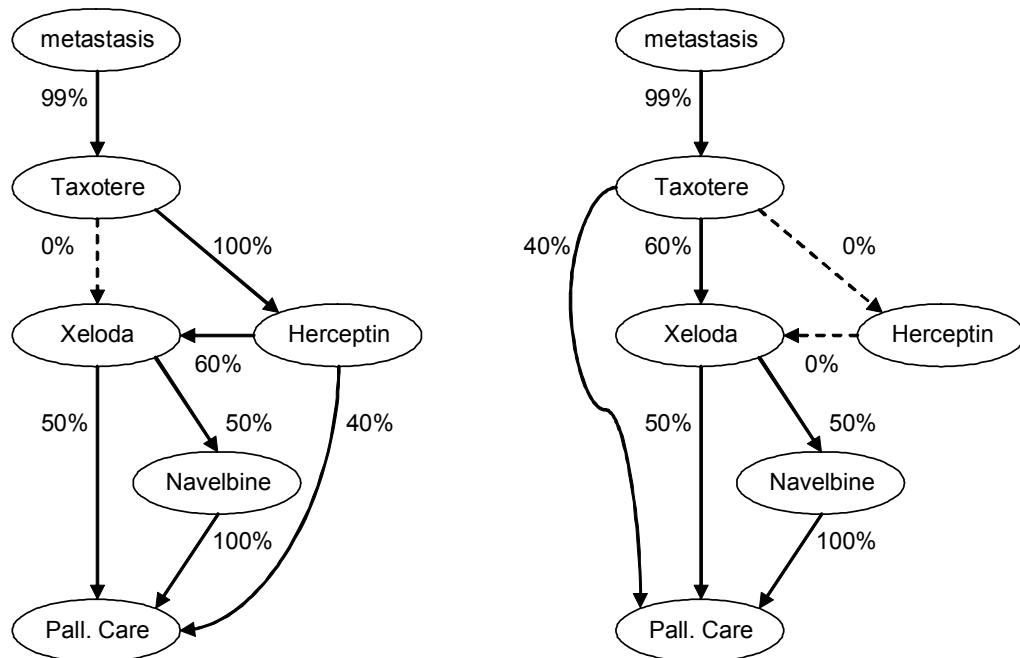
| <b>Age category</b>     | <b>Number of patients</b> | <b>Ejection fraction &lt;50%</b> |                                       |
|-------------------------|---------------------------|----------------------------------|---------------------------------------|
|                         |           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

## 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 Hospital 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 ( $100 \text{ mg/m}^2$ ) 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.<sup>71-74</sup> 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.<sup>75</sup> In another trial, this was 15% on a total of 1474 cycles.<sup>72</sup> 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.<sup>59, 58</sup> 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.<sup>76, 77</sup> We incorporated the weighted average of 13.65 weeks.

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

administered until disease progression or cumulative toxicity. Fumoleau and colleagues reported 126 patients who received a total of 874 cycles.<sup>78</sup> In another study 135 patients received a total of 700 cycles.<sup>79</sup> The weighted average of 6.03 cycles per patient was incorporated. Grade IV neutropenia only occurred very seldom.<sup>79, 78</sup> Concerning vinorelbine, in contrast to some trials who administered the drug until disease progression,<sup>80, 81</sup> 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%.<sup>80</sup> In our model, these 65.67% of patients received six cycles of vinorelbine. Furthermore, 6 on 67 patients had grade IV leukopenia and granulocytopenia,<sup>80</sup> 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.<sup>82, 83</sup> The weighted average of 18 weeks was used in our analysis. For anastrozole, a median time to progression of 21 weeks was taken.<sup>84</sup> 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.<sup>85</sup>

Finally, about 65-75% of patients had bone metastasis.<sup>86</sup> Bisphosphonates are an established standard of care for patients with bone metastases. As mentioned by Liberato,<sup>87</sup> 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.<sup>88</sup>

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 <sup>a</sup> | Number of patients | Age <sup>b</sup> | 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

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Wettelijk depot : D/2006/10.273/23

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