UNIVERSITEIT GENT

FACULTEIT ECONOMIE
EN BEDRIJFSKUNDE

HOVENIERSBERG 24
B-9000 GENT
Tel. : 32 - (0)9 – 264.34.61
Fax. : 32 - (0)9 – 264.35.92

WORKING PAPER

The Cost-Effectiveness of Herceptin® in a Standard Cost Model for Breast-Cancer Treatment in a Belgian University Hospital

Mattias Neyt [1]

Johan Albrecht [1]

Bart Clarysse [2]

Veronique Cocquyt [3]

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[1] Ghent University, Faculty of Economics and Business Administration, Department of Economics.
[2] Ghent University, Faculty of Economics and Business Administration, Department of Operations and Technology Management; Vlerick Leuven Gent Management School
[3] Department of Medical Oncology, University Hospital Gent

Correspondence to: Mattias Neyt, Ghent University, Hoveniersberg 24, B-9000 Ghent, Belgium, phone +32 9 264 42 09, fax +32 9 264 35 99, e-mail: mattias.neyt@ugent.be.

The process of developing a standard breast-cancer treatment model required input from numerous persons. The authors wish to acknowledge the persons of the Ghent University Hospital, the peripheral hospitals Sint-Lucas (Assebroek) and Sint-Jan (Brugge) and Roche for their co-operation.

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Abstract

Objective:
The objective of this study was to set up a standard cost model for breast-cancer treatment to be able to complete a cost-effectiveness analysis of Herceptin®. This is a new biotechnological pharmaceutical developed by Genentech. Herceptin® is a humanized monoclonal antibody that targets the HER2 receptor, an important anticancer target.

Method:
A cost model with standard diagnostic and treatment options for breast cancer was set up for a Belgian university hospital to calculate monthly standard treatment costs from this hospital's point of view. With the exception of the hospital-stay price, all costs were measured in a direct way. Effectiveness was estimated through literature study. With an incremental cost-effectiveness analysis, differences in costs and effectiveness with and without Herceptin® were compared.

Results:
When looking at the period starting from diagnosis and ending in the metastatic phase, monthly costs for the hospital rose from € 113.06 to € 121.32 when adding Herceptin® to the model. When looking at the metastatic phase, these costs rose from € 1,132.33 to € 1,256.23. When observing the incremental cost-effectiveness ratio, an extra cost of € 3,981.44 per extra life-month was found. This cost was rather high because Herceptin® was quite expensive and the product was additive in its current use and did not completely or partially replace existing treatments.
Cost consequences were even more pronounced when this exercise was done for a hypothetical situation, in which Herceptin® was included in the metastatic phase of the treatment model as a single agent and in combination with Taxotere®.

Keywords: Herceptin®, breast cancer, cost model, cost-effectiveness, monthly costs, incremental cost-effectiveness ratio

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1. Introduction

Pressures on healthcare budgets have forced pharmaceutical companies to generate evidence on whether the use of their products creates value for money. In Australia and Ontario, governments require cost-effectiveness evidence of new products for decisions on reimbursement. As early as in 1990, Australia drafted guidelines for this type of economic analysis, which had to be followed since 1993 (Hess *et al*., 1999). In many other countries, discussions on the use of economic evaluation of pharmaceuticals are going on. A study of Nuijten (1999) points at the growing impact of health economic data to support pricing and reimbursement decisions. The proliferation of pharmaco-economic guidelines has intensified and the question of a possible consolidation to one global standard is circulating in the pioneering countries.

This paper demonstrates that a pharmaco-economic analysis provides essential information for decision makers. Each technological trajectory brings however specific problems and trade-offs into the outcome assessment. This is illustrated with a cost-effectiveness analysis for Herceptin®, a new biotechnological pharmaceutical developed by Genentech. Herceptin® is a humanized monoclonal antibody that targets the HER2 receptor, an important anticancer target[4]. HER2 overexpression occurs in 25% to 30% of human breast cancers (Berger *et al*., 1988).[5] In September 1998, Herceptin® was approved by the US Food and Drug Administration (FDA) for the treatment of women with HER2 positive metastatic breast cancer, both as a first-line therapy in combination with paclitaxel and as a single agent in second- and third-line therapy. In Belgium, Herceptin® is also registered as single agent therapy or in combination with paclitaxel. Reimbursement is only approved for Herceptin® as single agent if two previous treatments with chemotherapy have failed, in which at least one antracycline and one taxane were used. HER2-overexpression also has to be proven by a FISH-test[6] (Roche, 2002).

The future use of Herceptin® will among other things depend on the outcomes of the ongoing Herceptin® Adjuvant Trial or HERA. This important international study aims to evaluate the effectiveness of adjuvant Herceptin® in HER2-positive patients with primary breast cancer. Our cost-effectiveness analysis of Herceptin® is based on the actual use of the product, i.e. for metastatic breast cancer.

2. Cost-effectiveness analysis

Economic evaluation is a tool to assist decision-makers in achieving value for money from a limited healthcare budget. There are four main types of economic evaluation, each with its advantages and disadvantages: cost-minimisation analysis, cost-effectiveness analysis, cost-utility analysis and cost-benefit analysis (BESPE, 1995). Pharmaco-economic assessments

[4] The human epidermal growth factor receptor-2 (HER2) is considered to be an important mediator of cell growth, differentiation and survival (Slamon *et al*., 1987).

[5] In this study, calculations were made on the assumption that 30% of the population could be treated with Herceptin.

[6] FISH: Fluorescence In Situ Hybridisation test.

often use cost-effectiveness analysis (CEA) because it allows making use of the medical outcomes of research during the clinical trials. Clinical trials try to demonstrate health gains in disease-specific 'natural units', based on function measurements or life-years gained. In the case of independent interventions, cost-effectiveness ratios (CER) are calculated (Ceri *et al.*, 2001).

$$CER = \frac{costs\ of\ intervention}{health\ effects\ produced}$$

A lower CER is more favourable than a higher one. To decide which interventions to adopt, the available resources also have to be considered. In this study, the implementation of Herceptin® for treatment of metastatic breast cancer is compared to the alternative of not using Herceptin®.
For mutually exclusive interventions, incremental cost-effectiveness ratios (ICER) are calculated (Ceri *et al.*, 2001; BESPE, 1995). With this technique costs and effects are related to each other.

$$ICER = \frac{difference\ in\ costs\ between\ two\ interventions}{difference\ in\ health\ effects\ between\ those\ two\ interventions}$$

The present situation is mostly taken as one option and a new intervention as an alternative.
A disadvantage of CEA is that it is not possible to compare the relative cost-effectiveness of different groups of interventions for diseases affecting different patient groups. Decision-makers, therefore, need to specify in advance for which purpose they want to use the economic evaluation.

3. A standard cost model for breast-cancer treatment in a Belgian university hospital

3.1 Standard costs

When assessing the impact of Herceptin®, it is essential to compare treatment costs with and without Herceptin®. Herceptin® is currently used in the metastatic treatment phase of our university hospital. An economic evaluation without detailed cost information cannot provide reliable results since the use of this treatment option also involved indirect costs and had an influence on costs made earlier in the breast-cancer treatment model. Unfortunately, detailed real cost data for each specific phase in the complete breast-cancer treatment scheme are not available in Belgium. The real cost for hospitals is not necessarily equal to what they receive for a specific treatment from the healthcare budget. We found that the difference between the real costs for a specific treatment and what hospitals receive for it can amount to 40%. Even a persistent relation between hospital charges to patients for products or services and the actual costs of those products or services is not existing (Cramer *et al.*, 1997). We therefore opted to work with real costs for the average patient or standard costs. This approach is not only reliable but also yields results which will not be influenced by administrative decisions that impact how much hospitals can charge for specific treatments.

3.2 The cost model

The costs were calculated from the perspective of the hospital or care provider. We cooperated with a university hospital, located in Flanders, the northern part of Belgium. In

this paper, we present the standard diagnostic and treatment model of our university hospital. All data were drawn up, put together and checked in close collaboration with specialist of this hospital during 2002-2003, reflecting the situation of 2001-2002.[7]

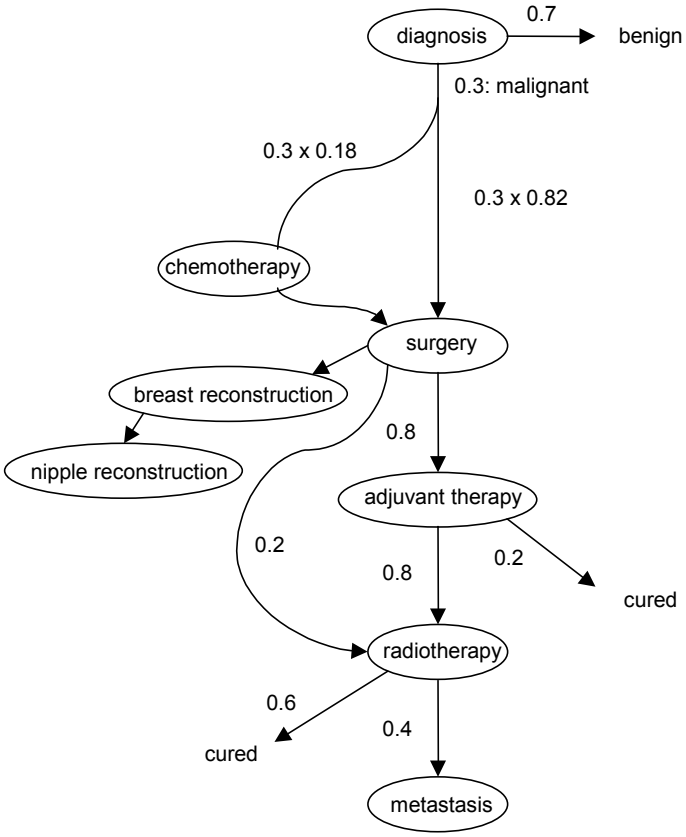

Figure 1: standard breast-cancer treatment model in a Belgian university hospital

We divided the model in different phases, starting with diagnosis and ending with metastasis (*Figure 1*). Diagnostic costs consisted of the costs of radiology and biopsy since these two phases occurred at almost the same time. If breast cancer was found in an early stage, surgery was performed. In certain cases pre-operative chemotherapy was given to make breast-conserving surgery possible. When the breast was removed, breast and nipple reconstruction could be further options. After this phase, adjuvant therapy or radiotherapy was started. If a patient had to follow both, treatment started with adjuvant therapy[8]. After adjuvant therapy and radiotherapy were completed, there was an outstream of cured patients. If the cancer progressed and became metastatic, the final phase of the model was reached.
For each of these steps the standard diagnostic and treatment options were taken into account. Once these different types of options were defined, costs were calculated. The main direct cost-drivers were the use of personnel, medication, material, equipment and the costs for the hospital-stay. Indirect costs made for preparing medication, sterilising material and maintaining apparatus were also taken into account since they were related to the specific treatment option. Costs caused by complications were not interpreted as standard costs and therefore not taken into account. Overhead costs and costs linked to research activities were disregarded since they are in the first place related to a specific department and not to a

[7] Only the result of our calculations for each diagnostic or treatment option are represented in this paper. Details of these calculations are available upon request.
[8] This could be different for other hospitals. But since this was a case specific exercise, we reflected the standard situation of our university hospital.

specific diagnostic or treatment option. In other words, the real costs were higher than our calculated standard costs and they only reflected a part of total department expenditures.
The personnel, medication, material and equipment costs were calculated directly by using the *bottom-up* or *micro-costing* method in which the costs are calculated by directly tracing resources. The personnel costs were estimated by multiplying the time different people were involved by their average labour cost. The costs of medication and disposable materials were based on the standard amounts used, multiplied by their unit prices. The costs for reusable material were divided over the number of times it was reused. Equipment costs were calculated by using a distributive code. Acquisition costs were distributed over the estimated years an apparatus would be used. This amount was then divided over the estimated number of times a year the equipment was used. If the equipment was used for different purposes, the amount of hours it was used was taken as distributive code. Besides acquisition costs, maintenance costs were also taken into account. Other cost-drivers such as the costs made by pharmacy for preparing medication, anaesthetic costs, costs for sterilising instruments, laboratory costs for investigating the cancer before treatment was started and checking the blood image before medication was administered were also taken into account with the micro-costing method.
The costs for hospital-stay were estimated indirectly by *top-down* calculation. We started by subdividing the hospital-stay price into its different components. To avoid double counting we adjusted this hospital-stay price by subtracting those parts already taken into account in a direct way.
Finally, the follow-up costs were also considered. Standard follow-up patterns were formulated for invasive and non-invasive breast cancer. The costs for the different follow-up investigations were worked out in the same way as the different standard diagnostic and treatment options, i.e. following the micro-costing method.
The average costs for each phase were calculated by multiplying the cost of each diagnostic or treatment option by its ratio of use. These ratios of use reflected the chance that a certain option was carried out in a specific phase of the model. The costs for the whole model were estimated by using flow through ratios, i.e. ratios, which showed how many patients on average went from one phase in the model to another phase (see *figure 1*). Costs, which can not be assigned to a certain phase of the model, such as the follow-up costs, were finally added to total costs. Were possible, the ratios of use and flow through ratios were based on databases of the university hospital. If such a database did not exist, we relied on information of the university experts based on their knowledge and perception of the current treatment and diagnostic options used in their department.

3.3 From diagnosis to metastasis

We set up the whole model starting from diagnosis until the metastatic phase for several reasons. First of all, the use of Herceptin® had consequences in an earlier stage of the model. To see whether treatment with Herceptin® could be effective, HER2-overexpression had to be proven by a FISH-test. There were other tests possible but this test was necessary to qualify for reimbursement. Since Herceptin® was used in a smaller group the costs of the test could not simply be added up. Next to this, we wanted to make a more nuanced evaluation of the product. Beside calculating monthly treatment costs for using Herceptin® it was useful to know what cost consequences were of using this product for the metastatic phase or for the total standard treatment costs. Therefore, different 'starting points' were used in our analysis: diagnosis confirms breast cancer, the metastatic phase and the moment Herceptin® was administered. Finally, it could be very interesting for decision makers to be able to assess possible medical and cost consequences of using Herceptin® in another way. In this paper we

did this for one hypothetical situation based on literature which only influenced the metastatic phase. An exhaustive study of realistic hypothetical situations influencing metastatic and adjuvant phase was kept for further research.

4. Results from the cost model

4.1 Phase 1 : diagnosis

Table 1 shows the diagnostic options for the university hospital. The first three options were the basic tests. At the moment of data collecting (2002), about 40% of the screening mammograms were done within the Flemish breast-cancer screening program. The sum of all use ratios exceeded unity because beside the mammogram, with or without an ultrasound scan, additional tests could be required.
When multiplying the total costs for each option with its ratio of use, the estimated costs for diagnosis became € 77.02. The costs for personnel (53.88%) and equipment (30.58%) were the highest.

Table 1: costs for breast-cancer diagnosis

Diagnostic options	Ratio of use	Total	Personnel	Material	Apparatus
Screening mammogram VBS[9]	0.4	€ 41.89	€ 34.34	€ 3.89	€ 3.66
Screening mammogram	0.1	€ 41.89	€ 34.34	€ 3.89	€ 3.66
Mammogram and ultrasound scan	0.5	€ 59.41	€ 36.09	€ 3.96	€ 19.36
Enlargement shot	0.01625	€ 37.29	€ 31.71	€ 1.91	€ 3.66
Specimen radiography	0.00625	€ 25.48	€ 18.59	€ 3.23	€ 3.66
Needle localisation under stereotaxy	0.005	€ 1,426.67	€ 66.71	€ 55.35	€ 1,304.61
Fine needle aspiration under ultrasound guidance	0.025	€ 39.56	€ 22.96	€ 0.90	€ 15.70
Core-biopsy under ultrasound guidance	0.0625	€ 81.41	€ 36.09	€ 28.52	€ 16.81
Needle localisation under ultrasound guidance	0.015	€ 98.69	€ 22.96	€ 56.37	€ 19.36
MR (magnetic resonance) breast	0.0625	€ 174.56	€ 34.27	€ 81.12	€ 59.17

4.2 Phase 2 : surgery

4.2.1 Initial breast surgery

Costs concerning the initial removal of the cancer are represented in *table 2*. As with the costs of diagnosis, the sum of ratios exceeded unity. Total average or standard costs were € 2,101.86 for the initial breast surgery. The largest part of these costs was the cost of the hospital-stay (79.64%). A much longer hospital-stay explains why mastectomy was more expensive than lumpectomy.

[9] VBS: 'Vlaamse Borstkanker Screening' program.

Table 2: initial breast surgery costs

Surgery options	Ratio of use	Total	Personnel	Material	Apparatus
Lumpectomy	0.1841	€ 866.93	€ 126.79	€ 62.45	€ 9.94
Lumpectomy and sentinel	0.2762	€ 901.49	€ 144.91	€ 72.88	€ 11.18
Lumpectomy and removal axillary nodes	0.2434	€ 2,676.46	€ 271.78	€ 82.07	€ 19.88
Mastectomy	0.0466	€ 2,566.75	€ 199.28	€ 68.85	€ 14.91
Mastectomy and sentinel	0.0698	€ 2,596.63	€ 217.40	€ 74.59	€ 16.15
Mastectomy and removal axillary nodes	0.1799	€ 2,678.21	€ 271.78	€ 83.78	€ 19.88
removal axilla after sentinel	0.1038	€ 2,496.72	€ 144.91	€ 72.88	€ 11.18
			Anaesthetics	Sterilization	Hospital-stay
Lumpectomy			€ 119.43	€ 16.59	€ 531.74
Lumpectomy and sentinel			€ 124.20	€ 16.59	€ 531.74
Lumpectomy and removal axillary nodes			€ 157.56	€ 18.22	€ 2,126.96
Mastectomy			€ 138.50	€ 18.26	€ 2,126.96
Mastectomy and sentinel			€ 143.26	€ 18.26	€ 2,126.96
Mastectomy and removal axillary nodes			€ 157.56	€ 18.26	€ 2,126.96
removal axilla after sentinel			€ 124.20	€ 16.59	€ 2,126.96

4.2.2 Breast reconstruction

After mastectomy, breast reconstruction was possible.[10] This only happened in about 5 to 10% of the patients that had a mastectomy.[11] In the university hospital, two types of breast reconstruction were performed: the DIEP[12] flap and GAP[13] flap. In the first method, fat and skin from the lower abdomen are used to reconstruct the breast. In the second technique fat and skin from the buttocks are used to reconstruct the breast.

Table 3: costs for breast reconstruction

Surgery options	Ratio of use	Total	Personnel	Material	Apparatus
DIEP flap	0.8632	€ 3,786.24	€ 874.78	€ 432.26	€ 48.04
GAP flap	0.1368	€ 4,061.35	€ 1,117.84	€ 432.26	€ 54.66
			Anaesthetics	Sterilization	Hospital-stay
DIEP flap			€ 265.61	€ 38.59	€ 2,126.96
GAP flap			€ 291.03	€ 38.59	€ 2,126.96

[10] Breast reconstruction could be performed at the same time of the initial breast surgery or later on, which were respectively called primary and secondary reconstruction. We calculated standard costs for secondary reconstruction.
[11] Since 29.63% of all patients had a mastectomy, this lead to a flow through ratio of 1.48% to 2.96%. This number was so low since a lot of patients did not want or were not well informed about breast reconstruction or because there was a long waiting list.
[12] DIEP: deep inferior epigastric perforator.
[13] GAP: gluteal artery perforator.

Table 3 represents the costs for breast reconstruction. Total average or standard costs were € 3,823.89. This is much higher than the average initial breast surgery. Material costs (11.30%) were almost € 450. With the initial surgery material costs never exceeded € 100. Anaesthetic costs[14] (7.04%) were about doubled due to the much longer operation time.[15] Personnel costs (23.75%) were much higher due to the long operation time and because more persons were necessary to execute the intervention. Finally, hospital-stay costs took the largest part for their account (55.62%).

4.2.3 Nipple reconstruction

The costs of plastic surgery to reconstruct the nipple are presented in *table 4*. The nipple reconstruction was performed in about 80 to 85% of all patients which had a breast reconstruction. The nipple reconstruction consisted of two phases that were executed at different times. The placing of the tattoo to colour the nipple and the areola took place about four weeks after the nipple reconstruction. The material (47.34%) and personnel costs (41.51%) took the biggest part of total average costs, which were € 214.99.

Table 4: costs for nipple reconstruction

	Ratio of use	Total	Personnel	Material	Apparatus
Nipple reconstruction	1	€ 130.99	€ 47.90	€ 66.28	€ 5.80
Colouring	1	€ 84.00	€ 41.35	€ 35.49	€ 7.12
			Sterilization	Hospital-stay	
Nipple reconstruction			€ 11.02	/	
Colouring			€ 0.04	/	

4.3 Phase 3 : adjuvant therapy

After surgery, about 80% of the patients started adjuvant therapy. Hormone therapy with Nolvadex D® (40%) and Zoladex® (20%) or chemotherapy (60%) were possible. Combinations of hormone therapy and chemotherapy were also possible. For chemotherapy, 80% followed the FEC[16] therapy and 20% followed the CMF[17] therapy. The FEC treatment was split up in two options depending on whether chemotherapy was already given before surgery. This was the case for 30% of the patients receiving chemotherapy. Therefore, costs for pre-operative chemotherapy had to be counted for 18% of all patients were diagnosis confirmed breast cancer. The costs of different treatment options for treating breast cancer as adjuvant therapy are given in *table 5*. On average, the total costs amounted to € 3,375.03 but there were very important differences. Treatment with Zoladex® cost more than four times as much as treatment with Nolvadex D®. Medication costs represented 84.93% of total costs. For chemotherapy, the costs of preparing the medication and performing a blood test before administration were also taken into account. These costs amounted to more than 16% of the costs for the FEC therapy and even more than 37% for the CMF cure.

[14] See table 10 for the composition of anaesthetic costs.
[15] Operation time was respectively 4h50 and 5h30 hours for DIEP and GAP flap compared to two hours for mastectomy in combination with the removal of axillary nodes.
[16] FEC: 5-Fluorouracil, Epirubicine and Cyclophophamide.
[17] CMF: Cytoxan, Methotrexate and 5-Fluorouracil.

Table 5: costs for adjuvant therapy for treating breast cancer

	Ratio of use	Total	Personnel	Material	Medication
Nolvadex D®	0.4	€ 1,423.50	€ 0.00	€ 0.00	€ 1,423.50
Zoladex®	0.2	€ 6,101.28	€ 0.00	€ 0.00	€ 6,101.28
FEC	0.3	€ 3,592.31	€ 411.75	€ 7.20	€ 2,594.76
FEC (pre- and post operative)	0.18	€ 1,796.16	€ 205.88	€ 3.60	€ 1,297.38
CMF	0.12	€ 1,536.47	€ 411.75	€ 7.20	€ 538.92
			Pharmacy	Laboratory (blood test)	
Nolvadex D®			€ 0.00	€ 0.00	
Zoladex®			€ 0.00	€ 0.00	
FEC			€ 187.22	€ 391.38	
FEC (pre- and post operative)			€ 93.61	€ 195.69	
CMF			€ 187.22	€ 391.38	

4.4 Phase 4 : radiotherapy

Next to adjuvant therapy, 20% of the patients followed directly radiotherapy and 80% of those who already followed adjuvant therapy continued therapy with radiotherapy. After 25 sessions, it was possible to give five extra sessions of radiation treatment on a smaller area. On average, two out of three patients received these five additional sessions. Out of *table 6* we can distract the average cost for radiation therapy which were € 1,278.86. Equipment and personnel costs stood for respectively 51.86% and 47.22% of total costs.

Table 6: costs for radiotherapy

	Ratio of use	Total	Personnel	Material	Apparatus
25 sessions	0.33	€ 1,075.97	€ 503.35	€ 11.52	€ 561.10
30 sessions	0.67	€ 1,378.78	€ 653.39	€ 11.81	€ 713.59

4.5 Phase 5 : metastasis

Progress of disease can lead to metastases. The costs during this phase are presented in *table 7*. The sum of use ratios strongly exceeded unity. About 40% of patients followed a FEC chemotherapy cure and 60% were treated with Taxotere®. When the FEC treatment was not effective, 70% of the FEC group were treated with Taxotere®. When the Taxotere® treatment failed, 30% of this group opted for Navelbine® and another 30% for Herceptin®. All other patients stopped treatment and received palliative care.
Total costs for this phase could be calculated with and without Herceptin® by just letting this option out. Notice that the Herceptin® option was additional and did not replace another option. Total average costs amounted to € 19,852.04 without Herceptin® and € 22,500.59 with Herceptin®. Most costs could be attributed to medication costs (91.65% with and 91.58% before Herceptin® was used).

Table 7: costs for breast-cancer treatment during metastasis

	Ratio of use	Total	Personnel	Material	Medication
FEC	0.40	€ 4,442.87	€ 411.75	€ 7.20	€ 3,445.32
Taxotere®	0.88	€ 19,301.87	€ 411.75	€ 7.20	€ 18,304.32
Navelbine®	0.264	€ 4,125.95	€ 617.63	€ 10.80	€ 2,629.62
Herceptin®	0.264	€ 10,032.38	€ 456.36	€ 7.98	€ 9,252.10
			Pharmacy	Laboratory (blood test)	
FEC			€ 187.22	€ 391.38	
Taxotere®			€ 187.22	€ 391.38	
Navelbine®			€ 280.83	€ 587.07	
Herceptin®			€ 207.50	€ 108.45	

4.6 Other costs

4.6.1 Laboratory

During breast cancer treatment some laboratory examinations were carried out. Concerning these costs, we based our calculations on data obtained in the peripheral hospital since they delivered us the necessary information in detail.
A first examination was referred to as 'colouring test'. After the presence of a malignancy was confirmed, a histology or tissue examination was used to select further treatment. *Table 8* shows that the average total costs of this test were € 146.05. The high personnel costs (68.09%) pointed out the labour intensive feature of this laboratory test. Further, there was the FISH-test. This test was indispensable in the model because first of all, this was the best test to predict HER2-overexpression, which determined the potential use of Herceptin®. Secondly, one of the conditions concerning reimbursement was that HER2-overexpression had to be proven by a FISH-test. This FISH-test could be performed in two ways. One was by making the products in the laboratory (option A). The other was by doing the test with Ventana apparatus and reacting agents (option B), which meant that the hospital had to pay for using these products. The consequences were not only a difference in product costs but also in personnel costs. This can be seen in *table 8*. With € 196.82, the first option was some € 30 more expensive than the second one. Finally, during follow-up and before administering chemotherapy, a blood test was performed. These laboratory costs were equal to € 32.62.

Table 8: laboratory costs

	Total	Personnel	Material	Products	Apparatus
Colouring tests	€ 146.05	€ 99.45	€ 42.38	/	€ 4.22
FISH-test A	€ 196.82	€ 77.34	€ 0.78	€ 103.64	€ 15.06
FISH-test B	€ 166.53	€ 57.73	€ 0.78	€ 92.96	€ 15.06
Bloodtest	€ 32.62	€ 13.80	€ 0.15	€ 18.67	

4.6.2 bone scan, ultrasound scan liver, RX Thorax

During the follow-up period (4.9.2) several specific examinations were performed. Costs for these examinations are presented in *table 9*. First of all, a bone scan was carried out. The total average costs were € 73.50. Apparatus costs were relatively high (61.34%) mainly due to the use of cameras, which were expensive in purchase and maintenance. Next to a bone scan, an ultrasound scan of the liver was performed during follow-up. The standard costs for this scan were equal to € 12.81. Finally, an X-ray of the chest was taken, which costs € 25.04.

Table 9: costs for bone scan, ultrasound scan liver and X-ray thorax

	Total	Personnel	Material	Apparatus
Bone scan	€ 73.50	€ 24.75	€ 3.66	€ 45.08
Ultrasound scan liver	€ 12.81	€ 8.33	€ 0.85	€ 3.63
X-ray thorax	€ 25.04	€ 9.34	€ 3.20	€ 12.50

4.6.3 Anaesthetic, pharmacy and sterilisation costs

The first row of *table 10* shows the anaesthetic costs. The costs for the anaesthetist and the anaesthetist nurse were not taken into account in this part but were already integrated in the personnel costs of different phases were anaesthesia was necessary. Total costs consisted of the start-up costs (€ 81.30) and increased for each extra hour during which the anaesthetic condition was maintained (€ 38.13 / hour).
Since an important part of the medication was prepared in the hospital's pharmacy, these costs were also integrated in the cost model. We found that total costs were € 15.60 per preparation. *Table 10* shows that the biggest part could be assigned to material costs (71.08%). This was due to the use of the Phaseal system, which is a system to protect personnel by preventing them to be exposed to cytotoxics. The Phaseal system cost € 9.59 and additional labour time for each time used.
Equipment sterilisation costs were calculated per sterilisation cycle and divided over the number of sets or instruments made sterile per cycle. Total costs added to € 9.74 and could be mainly ascribed to personnel costs (74.06%). When sets were incorporated, this cost had to be divided over eight sets, leading to a cost of € 1.22 for making one set sterile. With respect to instruments, about 240 units were sterilised in one cycle. The minimal sterilisation cost was € 0.04 per instrument.

Table 10: anaesthetic, pharmacy and sterilisation costs

	Total	Personnel	Material	Apparatus	Medication
Anaesthetic costs	€ 81.30 + € 38.13 extra per hour	Included in other phases	€ 34.03	€ 6.71 per hour	€ 47.27 + € 31.42 extra per hour
Pharmacy	€ 15.60	€ 4.12	€ 11.09	€ 0.39	/
Sterilisation costs per cycle	€ 9.74	€ 7.22	€ 2.34	€ 0.19	/

4.7 Hospitalisation-stay

An indirect method based on the hospital-stay price charged to the patient was used to account for hospital-stay costs. We looked at the composition of the hospital-stay price and adjusted it to avoid that several cost elements were counted twice. All cost elements that were taken into account in the previous phases were filtered out of the hospital-stay price. *Table 11* presents an overview of the filtered items of the hospital-stay price. The first column shows which parts were filtered. Columns two and three show respectively the original and adjusted numbers. After adjusting, the hospital-stay price was equal to € 303.85.

Table 11: adjusted hospital-stay costs

Filtered parts	Original amounts	Adjusted amounts
Depreciation cost medical equipment	€ 15.12	€ 14.74
For magnetic resonance	€ 1.98	€ 0.00
Surgery, sterilisation and emergency personnel. Medical products for surgery and emergency room. Adjustment for average wage costs	€ 174.76	€ 144.39
Operational costs NMR (nuclear magnetic resonance)	€ 4.64	€ 0.00
Operational costs dispensary	€ 6.89	€ 0.00
Total (remark: non-filtered parts are not shown)	€ 348.12	€ 303.85

4.8 Costs for the five phases of the treatment model

Table 12 presents the average treatment costs per patient. These costs could be considered as standard production costs for our university hospital. They included average costs of diagnosis, surgery, adjuvant therapy, radiotherapy and the treatment for metastatic breast cancer. The costs are presented for three reference points in the treatment scheme (*Figure 1*): the time of diagnosis, when treatment for metastatic breast cancer was started and finally when Herceptin® treatment was started. For each reference point, the costs of the following phases were included. The costs of previous treatments and examinations were not included. Flow through ratios indicate how many patients on average went from one phase in the model to another. The standard costs for each reference point was equal to the standard costs of the actual phase in the model plus the standard costs of the following phases times the flow through ratio from the actual phase to those following phases.

Table 12: costs for the five* phases of the model

Reference/starting point	With Herceptin®	Before[18] Herceptin®
Diagnosis confirms breast cancer	€ 13,925.57	€ 13,035.66
Metastatic phase	€ 22,500.59	€ 19,852.04
Taking Herceptin®	€ 10,032.38	/

* These five phases were diagnosis, surgery, adjuvant therapy, radiotherapy and the metastatic phase.

4.9 Additional costs : laboratory and follow-up costs

4.9.1 Laboratory costs

In addition to estimated average treatment costs for the different phases, laboratory and follow-up costs, which could not be assigned to these phases, needed also to be considered. Laboratory costs included the colouring test to investigate the cancer and the two types of FISH-tests to detect the HER2 overexpression (*Table 8*).[19] To allocate these costs in the model, it was essential to know that every patient should be tested for HER2 overexpression for prognostic purposes and to determine if treatment with Herceptin® would be appropriate. Without proper testing, the use of Herceptin® would not be effective. In most cases, no overexpression was found and no Herceptin® treatment was started. The HER2 overexpression testing costs of this group of patients also had to be allocated in the model to

[18] With 'before' Herceptin® we refer to the same treatment model but this time without the use of Herceptin® as treatment option.

[19] The costs of the blood tests were taken into account during the phases where chemotherapy was given and during the follow-up period.

the group of patients actually treated with Herceptin®. To allocate the costs to the 'taking Herceptin®' group, we multiplied the costs of the FISH-test with the reciprocal of the share of patients ending up in this phase. These numbers were 1/0.336 for the metastatic phase and 1/0.0887 from the point were treatment with Herceptin® was started. We did not do this for the colouring test since this test was performed earlier in the model and was not related to the use of Herceptin®. As a result, € 2,218.85 in *table 13* was equal to € 196.82 divided by 0.0887.[20]

Table 13: laboratory costs

Starting point	Without FISH-test	With FISH-test	
		Option A	Option B
Diagnosis confirms breast cancer	€ 146.05	€ 146.05*[a] + € 196.82*[b]	€ 146.05 + € 166.53
Metastatic phase	/	€ 585.78	€ 495.62
Taking Herceptin®	/	€ 2,218.85	€ 1,877.37

*[a] Costs due to the colouring test
*[b] Costs due to the FISH-test

4.9.2 Follow-up costs

Follow-up costs included basic check-up and blood test (*Table 8*), mammogram and ultrasound scan (*Table 1*, third option), bone scan, ultrasound scan of the liver and X-ray of the thorax (*Table 9*). All costs were calculated directly in this study. The basic check-up costs, which only contained personnel costs, are not presented. They amounted to € 13.
The follow-up schedule mentioned, next to which examinations were done, at which point of time these examinations had to be carried out. Differences between follow-up of invasive or non-invasive breast cancer were taken into consideration. In combination with the expected survival time (*Table 16*), we calculated the average follow-up costs. These are shown in *table 14*. It was obvious that the further we went in the model, the lower the follow-up costs were.

Table 14: follow-up costs

Starting point	Stage I	
	With Herceptin®	Before Herceptin®
Diagnosis confirms breast cancer	€ 1,348.58	€ 1,340.48
Metastatic phase	€ 553.91	€ 529.82
Taking Herceptin®	€ 91.25	€ 0.00*

* The point of time of 'taking Herceptin®' in combination with 'before Herceptin®' was equal to entering the final terminal palliative phase. In our study we excluded this terminal palliative phase concerning costs and effectiveness. Therefore, the costs were zero.

4.10 Estimated total average costs for breast-cancer treatment

Table 15 presents the estimated total average costs for treatment of breast cancer in our university hospital. This was the sum of the costs made during the five phases of the treatment model (*Table 12*) and the additional laboratory and follow-up costs (*Table 13* and *14*). Only costs during the terminal palliative phase were not included since this type of care varied from patient to patient. Consequently, it was not possible to set up a standard treatment scheme for this phase in our university hospital. A distinction was made on the basis of the point of time in the model and on whether or not Herceptin® was included. If Herceptin® was included, a

[20] We have to remark that we made our calculations using all numbers after the comma.

distinction was made on whether or not the FISH-test was used in one of its two possible options.

Table 15: total costs for treatment of breast cancer

Starting point	With Herceptin®			Before Herceptin®
	Without FISH	With FISH: option A	With FISH: option B	Without FISH
Diagnosis confirms breast cancer	€ 15,420.19	€ 15,617.01	€ 15,586.72	€ 14,522.18
Metastatic phase	€ 23,054.50	€ 23,640.28	€ 23,550.13	€ 20,381.86
Taking Herceptin®	€ 10,123.63	€ 12,342.48	€ 12,001.00	€ 0.00

5. Effectiveness

We conducted a literature review to assess the medical effectiveness of breast-cancer treatments and treatment with Herceptin®. The main conclusions are presented in *table 16*. Berkowitz *et al*. (2000) found that the average duration between the initial diagnosis of breast cancer and the progression to metastatic disease were 10.2, 7.9 and 4.3 years for respectively stages I, II and III disease.[21] A study of Honig *et al*. (1996) reported that the median survival time for metastatic disease was 18 to 24 months. Furthermore, a study of Cobleigh *et al*. (1999) concluded that prolongation of life due to the use of Herceptin® in a metastatic setting was 3.1 months. Finally, studies of Berkowitz *et al*. (2000) and Will *et al*. (2000) considered the last three months prior to death as the terminal phase of breast cancer patients.

Table 16: information for estimating effectiveness

Average duration between diagnosis and progression to metastases	Stage I	122.4 months
	Stage II	94.8 months
	Stage III	51.6 months
Median survival time for metastatic disease	18-24 months before Herceptin®	
Delay time to progression because of Herceptin®	3.1 months	
Terminal phase	3 months	

On the basis of these data, we calculated average lifetime for the different starting points in the model. A distinction was made on the basis of whether or not Herceptin® was used. The results are shown in *table 17*. With taking Herceptin® as a starting point, the average lifetime without inclusion of the terminal phase was 3.1 months. The terminal phase was not included since costs and effects had to be related to each other and the costs for the terminal phase were not included in this study. When taking the metastatic phase as starting point we came to an estimated lifetime with exclusion of the terminal phase of 18.8184 months. This was the sum of 18 months and an extra of 0.8184 months. The first part was obtained by subtracting the last three terminal months from the average time between metastatic breast cancer and

[21] One of the factors that helped to determine treatment decisions and influenced prognosis was the stage of breast cancer. An example of a commonly accepted staging system was the TNM staging system of the American Joint Committee on Cancer. It was based on the size of the Tumour, the presence of cancer in the lymph Nodes and the presence of Metastasis. Stage I meant that the size of the tumour was two centimetres or less without evidence of cancer in the lymph nodes. Stage II referred to a tumour, which measured two to five centimetres and had not spread to the lymph nodes. Stage III meant that several lymph nodes were involved. Once the cancer had spread beyond the breast to secondary tumours, stage IV or metastases was reached (Gorman, 2002).

death. The second part was the multiplication of the estimated prolongation of life due to Herceptin® treatment with the percentage of people in the metastatic phase treated with Herceptin®, which was 26.4 per cent.
If only looking to the group of people treated with Herceptin®, a simple addition of the 18 and the extra 3.1 months could be made (column two). Since we wanted to compare cost with and without Herceptin® for the same population group, we had to look at the estimated lifetime with and without Herceptin® for all patients (column three and four of *table 17*). To find the estimated lifetime from the moment of diagnosis, two numbers were added up. The first one was the average duration between the initial diagnosis of breast cancer and the progression to metastatic disease for stage I breast cancer, which was 122.4 months. The other number was the multiplication of the average estimated lifetime in the metastatic phase, with exclusion of the terminal phase, and the number of people flowing through to this phase, which was 33.6% in our model.

Table 17: estimated lifetime (with exclusion of terminal phase)

	With Herceptin®		Before Herceptin®
Starting point	Only looking at Herceptin® treated patients	all patients	all patients
Diagnosis confirms breast cancer	129.4896 months	128.723 months	128.448 months
Metastatic phase	21.1 months	18.8184 months	18 months
Taking Herceptin®	3.1 months	3.1 months	0* months

* The starting point of taking Herceptin before the use of Herceptin did not exist. It is equal to the moment were palliative care was started. Since we did not take this phase into account, the estimated lifetime was zero.

6. Utility and adaptibility of the model

As mentioned in the study of Russell (1999) a useful model should allow assessing changes in a large number of factors, which may influence results. In our model, these factors were treatment options, ratios of use, flow through ratios, amount of medication administered, scheme of administration[22], duration of administration[23], purchase price of medication, ratio of HER2 overexpression and effectiveness of treatment options. By changing these factors, the robustness of results could be tested and some worse- and best-case scenarios could be constructed. There were many possibilities to fill in the model. How the model would be filled in should be based on trial results and expert's opinion.
We demonstrated the utility of the model concisely by adding one hypothetical option to our original model. This option was based on literature information. *Figure 2* shows the standard treatment options and the ratios of use for metastatic breast-cancer treatment in our university hospital (see part 4.5). *Figure 3* represents a hypothetical model in which hypotheses out of literature are put into the present situation.

[22] For example every week or once three-weekly.
[23] For example, six cycles of four weeks.

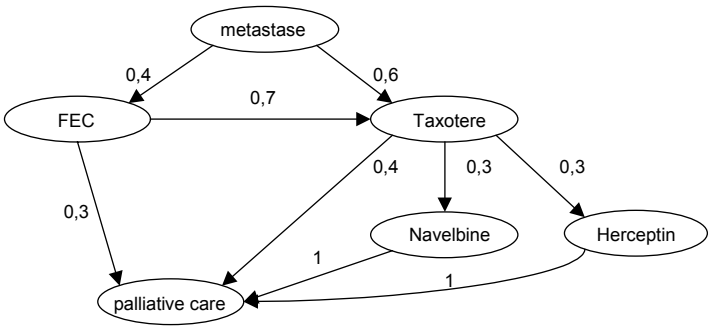

Figure 2: Treatment options and ratios of use in the university hospital

A first hypothesis put in the alternative model was the administration of Taxotere® and Herceptin® as a first-line treatment option for metastatic breast cancer. Data were collected from a study of Esteva *et al* (2002). Herceptin® was administered in the same way as in the university hospital, i.e. 4mg/m² loading dose and 2mg/m² weekly. Taxotere® was administered with a 35mg/m²/week dose.

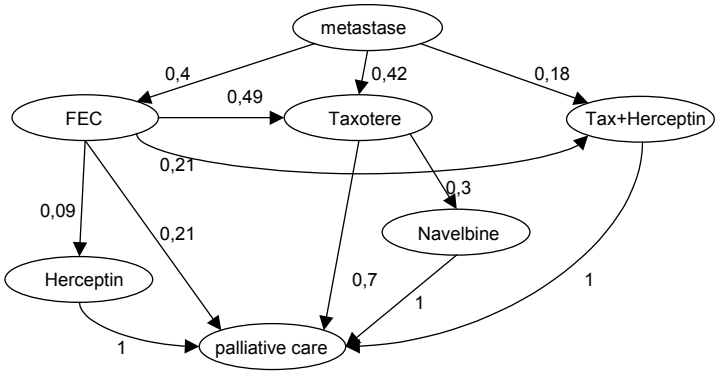

Figure 3: Treatment options and ratios of use in the hypothetical model

To keep the reasoning and presentation clear we only changed two variables in our hypothetical model in the group were Taxotere and Herceptin were administered together (*Table 18*).[24] In the group where Herceptin was given as monotherapy when previous chemotherapy had failed, we kept the data as they were before. The administration scheme was the first variable. In the study of Esteva *et al* (2002), in which Herceptin was administered in combination with Taxotere to patients with Her-2 overexpressing metastatic breast cancer, there was a break every fourth week. We varied this to weekly administration without intermission. The second variable was the duration of administration. Esteva *et al*. (2002) had a median of six cycles. We kept this number equal concerning Taxotere® since this administration scheme was equal to that of the university hospital for monotherapy with Taxotere®. Concerning Herceptin®, instructions for use mentioned that the product had to be administered until progression of the cancer was noticed (Roche, 2000). Since in the study of

[24] It should be clear that al the other variables could easily be changed in our model. Since the variety is so great, we will keep an extensive presentation of those results for future publications.

Esteva *et al* (2002) the median time to progression was 9 months we varied the duration of administration up to 39 weeks.

Table 18: hypothetical costs for metastatic breast-cancer treatment

Taxotere + Herceptin	Weekly, break in fourth week	Weekly, no break
Administration of Hercepting for 24 weeks	€ 21,641.38	€ 23,868.00
Administration of Hercepting for 39 weeks	€ 23,737.22	€ 26,662.44

These costs could be compared with costs from the metastatic phase presented in *table 12*. It was obvious that costs rose when adding Herceptin® as performed in our hypothetical model since it still did not replace other treatments completely. In the Taxotere®-Herceptin® combination (*Figure 3*) it was additive to the currently used Taxotere® treatment. In the single agent treatment option for Herceptin® (*Figure 2* and *3*), it represented an extra treatment option before starting 100% palliative care without replacing existing treatment options.
By using Herceptin® as currently applied in the university hospital, costs for the metastatic phase rose from € 19,852.04 to € 22,500.59. When applying Herceptin® as in the hypothetical model costs rose to € 21,641.38 in the cheapest application or up to € 26,662.44 in the most expensive one. When connecting this hypothetical model to estimated effectivity changes, based on clinical trial results or expert's opinion, a new cost-effectiveness study could be carried out. (see *table 19* and *20*). As mentioned before, we only changed the administration scheme and duration of administration in relation to the present situation. A more extensive incorporation of hypotheses will be kept for future publications. Estimating cost consequences caused by changes in one or more model variables can be an important tool for decision makers in hospital, government or business environments. It is clear that concerning for example reimbursement or price setting, such implications are very important.

7. Economic evaluation

7.1 Estimated average monthly costs for breast cancer treatment

Table 19 presents the estimated average monthly costs for breast cancer treatment in our university hospital. These numbers were obtained by dividing estimated total average treatment costs (*Table 15*) by estimated lifetime (*Table 17*). We did this for different starting points in our model. It was clear that the further we went in the model, the higher monthly expenses were. Next to different starting points we also made a distinction on whether Herceptin® was administered or not (*Table 19*, column 2-5 versus column six). If administered, we made a further distinction between the two options for performing the FISH-test (column three and four). The second column represents the results when Herceptin® was included in the model but the costs for the FISH-test were forgotten. The monthly costs for the hypothetical situation are presented with inclusion of the FISH-test costs. For this situation we used the most expensive alternative dealt with in section six.

Table 19: Estimated average monthly costs for breast-cancer treatment

Starting point	With Herceptin®			hypothesis	Before Herceptin®
	Without FISH	With FISH: option A	With FISH: option B	With FISH: option A	Without FISH
Diagnosis confirms breast cancer	€ 119.79	€ 121.32	€ 120.09	€ 132.19	€ 113.06
Metastatic phase	€ 1,225.10	€ 1,256.23	€ 1,251.44	€ 1,477.39	€ 1,132.33
Taking Herceptin®	€ 3,265.69	€ 3,981.44	€ 3,871.29	/	/

Since Herceptin® treatment did not replace other treatment options, it was obvious that estimated average monthly treatment costs rose. When comparing the situations of whether or not including Herceptin® in the model, the extra costs were very clear when looking at taking Herceptin® as starting point. These amounted about € 4,000 monthly. Instead of just looking at this final stage, it was more interesting to look at the numbers for the metastatic phase or the entire breast-cancer treatment model. With these starting points we could compare the results with the hypothetical situation. When looking at the period starting with diagnosis, monthly treatment costs rose with 7.31% or about € 8 in absolute numbers from € 113.06 to € 121.32 because of adding Herceptin® to the treatment model. In the metastatic phase, these costs rose with about 10.94% from € 1,132.33 up to € 1,256.23. Observing the hypothetical situation, this became an increase of 16.92% up to € 132.19 or an increase of 30.47% up to € 1,477.39 when looking at the estimated average monthly treatment costs from respectively the time of diagnosis and the metastatic phase.
The impact of not taking up the costs for the FISH-test on monthly costs was maybe not so clear when looking at diagnosis as starting point since the costs were spread over a wide range of months. But the shorter the remaining lifetime, the more clear it was that these extra costs should not be forgotten. When looking at the final stage where Herceptin® was taken, the FISH-test stood for an extra cost of about € 605 or € 715 per month, depending on which FISH-test was taken.
When taking the administration of Herceptin® as starting point, the costs and effectiveness were all caused by adding Herceptin® to the model. As a result, the monthly costs were equal to the incremental costs. It was not possible to take Herceptin® as a clear starting point for the hypothetical situation since one of the treatment options combined Herceptin® with Taxotere®. Therefore, we refer to the next part for the incremental cost-effectiveness analyses with inclusion of the hypothetical situation.

7.2 Incremental cost-effectiveness

The incremental cost-effectiveness ratio was calculated by taking the difference between total costs for treatment of breast cancer with and without Herceptin® (*Table 15*) and dividing this number by the difference in estimated lifetime with or without Herceptin® (*Table 17*). We did not make a distinction between different starting points since this did not affect the incremental cost-effectiveness ratio. The percentage of people treated with Herceptin® and influencing costs and effectiveness would change along with the chosen starting point. But once chosen a certain point in the model and calculating the incremental ratio, the percentage of patients influencing costs and effectiveness would be the same. Since numerator and denominator of the ratio would be influenced in the same order, the incremental cost-effectiveness ratio would not vary along with the chosen starting point.
Table 20 represents the incremental cost-effectiveness ratios for the current use of Herceptin® and for the hypothetical situation (see section six). A further distinction was made on the basis of the kind of FISH-test. The situation without the FISH-test is not presented since, as

mentioned before, real incremental costs would be underestimated. In the current situation, costs per extra month were estimated at € 3,981.44 or € 3,871.29 depending on the kind of FISH-test performed. The fact that this was rather high could be explained by the high costs of Herceptin® medication and especially by the fact that Herceptin® currently was additive to existing treatments and did not substitute them. When not changing estimated lifetime, the incremental costs became respectively € 9,066.79 or € 8,956.64 for the hypothetical situation. This even higher incremental cost could be explained by first of all, the expensive Taxotere® medication and secondly, the prolonged use of Herceptin®.

Table 20: Incremental cost-effectiveness ratios

	With Herceptin®		Hypothetical situation	
	With FISH: option A	With FISH: option B	With FISH: option A	With FISH: option B
Incremental cost-effectiveness ratio	€ 3,981.44	€ 3,871.29	€ 9,066.79	€ 8,956.64

8. Conclusions and further research

This study provides a cost model for breast cancer treatment in a university hospital in Belgium. We estimated costs from the hospital's point of view, using the micro-costing method. This was necessary since what hospitals receive from the healthcare budget differs from real costs. Only the hospital-stay costs were estimated indirectly through an adjustment of the hospital-stay price. Since this cost represents a large part of total costs in surgery procedures, it may be interesting for further research to set up a direct way to calculate this cost.

In the first part of our economic evaluation, based on our cost model, we estimated the influence of Herceptin® on the monthly standard costs for breast-cancer treatment. It was essential to mention the time period considered in the evaluation. When looking at the period starting from diagnosis and ending in the metastatic phase, costs rose from € 113.06 to € 121.32 per month when adding Herceptin® treatment to the model. When only looking at the metastatic phase, monthly costs rose from € 1,132.33 to € 1,256.23. Considering our hypothetical model, these monthly costs were estimated at respectively € 132.19 and € 1,477.39.

In the second part of our economic evaluation, we calculated the incremental cost-effectiveness ratio. The cost of the FISH-test strongly determined results. Instead of € 3,265.69 per extra life-month, € 3,981.44 was a more precise calculation of this extra life-month cost. Besides the price of the product, the fact that Herceptin® was additive in its current use and did not (partially) replace existing treatments made these costs rather high. The hypothetical situation with Herceptin® as single agent and in combination with Taxotere®, in which effectiveness was not changed, showed even higher costs per extra life month of € 9,066.79. This could be explained by the very high costs for both Herceptin® and Taxotere® treatment and the prolonged duration of Herceptin® administration.

We have to keep in mind that this was an evaluation of Herceptin® as an additional treatment option following on previous treatment possibilities. Herceptin® treatment did not yet replace other treatment options. If doing so, new cost-effectiveness studies can easily be carried out with our model. It is interesting to consider cost consequences that result from variations in a wide range of factors. We do not claim that decisions on treatment or diagnostic options should solely be based on costs. However, decision makers should be aware of the financial implications of these options. The question of what is reasonable in the relationship between costs and effectiveness is after all a matter of values.

We demonstrated the use of the model by implementing new treatment options with Herceptin® in the metastatic phase of the model and changing duration and scheme of administration. In further research we can analyse the influence of changing treatment options, ratios of use, flow through ratios, amounts of medication administered, scheme and duration of administration, price of medication and other variables. We will do this on the basis of literature study and reckon with expert's opinion. Next to using Herceptin® in metastatic phase, we will also do this with Herceptin® in adjuvant setting.

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UNIVERSITEIT GENT

FACULTEIT ECONOMIE EN BEDRIJFSKUNDE
HOVENIERSBERG 24
9000 GENT

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9000 GENT

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