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PHARMACOECONOMIC METHODS TO EVALUATE THE COST-EFFECTIVENESS AND BUDGET IMPACT OF CANCER TREATMENT

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ABSTRACT

Economic evaluations are being used increasingly often in attempts to meet the challenges of optimally allocating scarce health care resources. The cost-effectiveness of cancer treatments has been assessed widely perhaps because there is a global interest about the economic issues related to cancer. Cancer is one of the leading causes of morbidity and mortality worldwide, and thus, is a major challenge to health care funding. The burden of cancer is likely to increase due to ageing of the population, intensive care with targeted drugs, and increasing treatment costs. Thus, cancer consumes a large and potentially increasing proportion of the total health care budget.

The general aim of this thesis was to study pharmacoeconomic methods and to apply them to evaluate the cost-effectiveness and budget impact of cancer treatments in Finland. In most cases, new treatments are more effective but also more expensive compared to their predecessors. The thesis consists of studies trastuzumab in the treatment of HER2-positive early breast cancer. The studies include various elements of economic evaluations, including cost-effectiveness analyses, budget impact analyses, value of information analyses, and burden of illness estimates. The utilized methods were chosen individually in each of the studies.

The results of this thesis revealed that. Analyses of short-course trastuzumab demonstrated a good cost-effectiveness profile compared to treatment without trastuzumab, in HER2-positive early breast cancer. The value of information analysis illustrated that most of the uncertainty in the results was related to effectiveness parameters. Furthermore, the budget impact analysis indicated that treatment length has a major effect on the budgetimpact of trastuzumab.

Pharmacoeconomics methods represent a useful tool to support decision making related to the introduction of new cancer treatments. These studies revealed that the utilized cancer model was suitable for modeling the natural disease progression with respect to breast cancer. Although the results, based on modeling, are surrounded by uncertainty, this may be quantified to reduce decisionuncertainty. A probabilistic approach was applied to cost-effectiveness analyses and budget impact analysis. This approach can achieve a better recognition of uncertainty and it enhances the methodology currently used in budget impact analyses.

Introduction:

The cost of cancer is increasing due to the ageing of the population, increased survival times and introduction of novel cancer treatments. Economic evaluations are now being used to meet the challenges related to optimal allocation of scarce health care resources. In this study, Pharmacoeconomics methods were used to assess the quantity of health benefits gained with the resources invested in new cancer treatments, as well as the potential affordability of these treatments. Breast cancer is the most common cancer among women, and there are over a million new breast cancer cases in the world each year. In Finland it is the leading cause of cancer deathsin women, and accounts for 16% of all female cancer deaths (Statistics Finland 2007). Approximately 12-30% of breast cancer cases overexpress Human Epidermal Growth Factor Receptor 2 (HER2) (Slamon et

al. 1989, Joensuu et al. 2003, Owens et al. 2004). These HER2-positive (HER2+) cases are associated with an aggressive disease, and the prognosis is poorer compared with HER2-negative cases (Drucker et al. 2008, Herceptin: Summary of product characteristics). Recently, new targeted therapies have offered new alternatives in the treatment of HER2-positive patients, however, with increasing costs.

Trastuzumab is a monoclonal antibody used for the treatment of HER2-positive breast cancer patients (Herceptin: Summary of product characteristics). At first, trastuzumab was used only in the metastatic disease and, until recently, it has been the only targeted therapy for HER2-positive breast cancer. There are several studies concerning trastuzumab in adjuvant treatment of early breast cancer (Piccart-Gebhart et al. 2005, Romond et al. 2005, Slamon et al. 2005, Joensuu et al. 2006, Slamon et al. 2006, Perez et al. 2007, Smith et al. 2007). Today it is widely used in this indication. Together with the indication extension, the number of eligible patients grew substantially. This, in turn, increased concern about the affordability of trastuzumab, since the health care budget and resources are limited.

Trastuzumab is used in addition to existing therapies and does not replace them. Since it is an expensive drug, it causes a substantial impact on the health care budget. Recent reviews show that in most analyses, trastuzumab is considered to be cost-effective, despite the diversity of the results (McKeage and Lyseng-Williamson 2008, Younis and Skedgel 2008). However, cost-effectiveness analyses alone do not provide information on the drug's impact on the total health care budget, since this is dependent on the number of treated patients. Thus, the expected budget impact of a new treatment should be explicitly estimated, in addition to the traditional cost-effectiveness. A few of the cost-effectiveness studies of adjuvant trastuzumab have included evaluation of its budgetary impact (Liberatoet al. 2007, Neyt et al. 2008, Shiroiwa et al. 2008). Furthermore, the cost burden of monoclonal antibodies has been evaluated from the Canadian health care perspective (Drucker et al. 2008). However, a comprehensive budget impact analysis of trastuzumab that includes the estimated effectiveness of the treatment and probabilistic analysis, has not,to our knowledge, been previously published.

In this study we created an evaluation tool for estimating the budget impact of new cancer treatments. This was done on the request of the consortium of the Finnish Office for Health Technology Assessment (Finohta) and local hospital districts. In Finland, the health care system is publicly funded, and hospital districts are allowed to operate rather independently. Thus, there are concerns regarding the cost burden of trastuzumab, both at the national level and in hospital districts. In this study the new tool was used to explorethe budget impact of trastuzumab in early breast cancer in a single Finnish hospital district. Furthermore, we analyzed how different treatment protocols and changes in the number of patients affect the estimated budget impact.

Materials and methods

Perspective and Time Horizon. This study was conducted from the perspective of a single hospital district with ca. 250,000 inhabitants (payer's perspective). In the target organization(Hospital district of Northern Savo), all trastuzumab treatments are given in one hospital (Kuopio University Hospital). Only direct costs allocated to the hospital district were included in the study. The maximum follow-up time was set to be 4 years, since a longer perspective was not considered relevant for the budget holder. All results are depicted cumulatively from 1 to 4 years.

Population. Population-based epidemiological data were obtained from the Finnish Cancer Registry, which covers the vast majority of cancer cases in the country. The 5-year average yearly number of new breast

cancer cases (ICD-10 C50) in the hospital district was

176. The age-adjusted incidence of breast cancer in the whole country in 2006 was 86.6/100,000, which is slightly higher than in the target hospital district (Finnish cancer registry 2008). The prevalence of HER2+ was 18%, which reflects the 3-year average HER2+ incidence rate in the local district (Department of Pathology, Kuopio University Hospital 2008). Thus, there are approximately 32 new HER2-positive breast cancer cases in this district yearly. Previously diagnosed breast cancer cases were not included in the analysis. Ten percent of the HER2-positive patients were assumed not to receive trastuzumab because of other diseases and poor general condition, or because of a very small tumour size.

Model. A spreadsheet model was created to assess the budget impact of trastuzumab. A simplified structure of the model is presented in Figure 1**.** The model took into account thenumber of patients, HER2+ prevalence, the length and cost of treatment, and its effectiveness. Estimates concerning distant disease free survival (DDFS) were derived from the published data of a Finnish trial (Joensuu et al. 2006). These estimates were applied to the model in order to include the effectiveness of the treatment. Mortality was not included due to the short time horizon. The effectiveness of trastuzumab was assumed not to depend on the length of the treatment. The model utilized is a simple stage transition modeltypically used in cost-effectiveness analyses. The mutually exclusive health stages in the model are “free of distant recurrence” and “distant recurrence”. The number of new cases was used as the population entering the model each year. Yearly new cases were followed throughout the model, depending on the chosen time span. Each additional follow-up year increased the number of eligible patients and prolonged the time spent in the model. The results of the model apply to periods from 1 to 4 years. Consistent with the current recommendations for budget impact analyses, discounting was not incorporated in the model (Mauskopf et al. 2007).

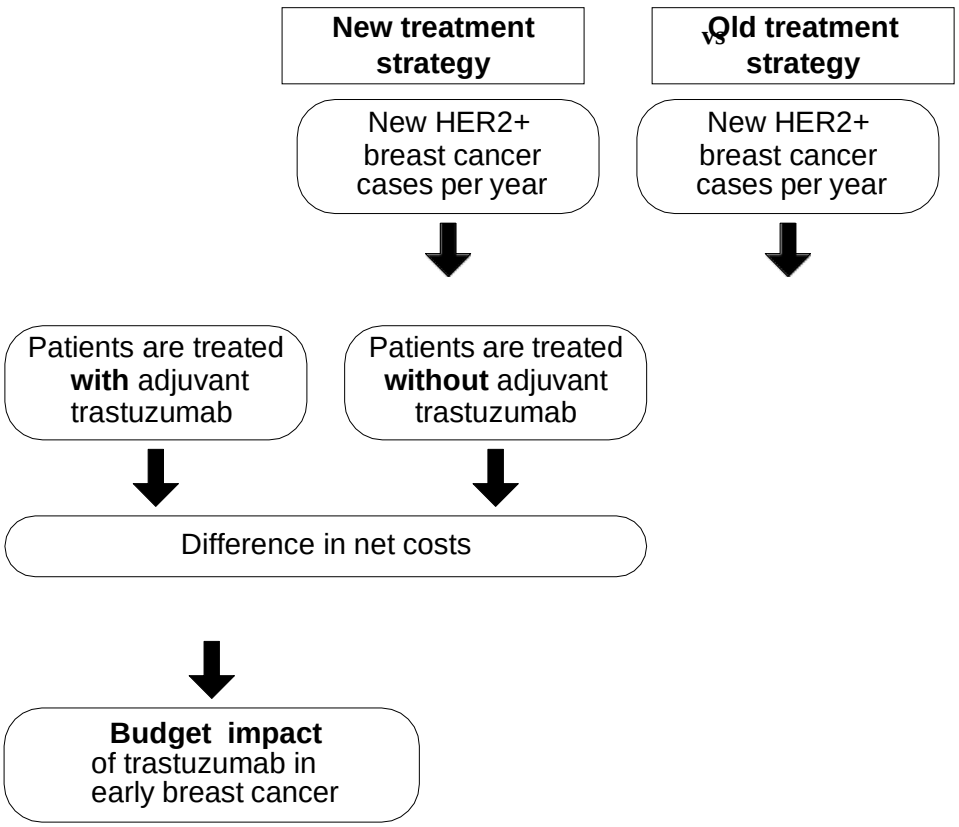


Figure 1. **Structure of the budget impact model of trastuzumab in early breast cancer**

Treatment mix and costs. The treatment mix and costs of breast cancer therapy are based on current clinical practice in the treating hospital. Activity-based costing was used as the costing method (in 2008 Euros, value added tax (VAT) excluded). Patient copayments attributable to hormonal cancer therapy and oral cytostatics were not included, since in Finland they are reimbursed by the Social Insurance Institute (SII). In the target hospital district, chromogenic in situ hybridization (CISH) is used to test the patient's HER2 status. Since all new cases are tested similarly, the cost of testing was not included in the analysis.

Treatment cost of HER2+ early breast cancer. The first year after diagnosis is more treatment-intensive than the following years. Average first-year adjuvant treatment without trastuzumab constituted a total cost of €9,540 per patient for the hospital district (Table 1). The treatment includes hormonal treatment (tamoxifen or aromatase inhibitor), but their cost is not allocated to the hospital district. Trastuzumab is given in addition to standard breast cancer treatment. In local clinical practice, adjuvant trastuzumab treatment in early breast cancer includes two treatment lengths – 9 weeks and 1 year. All patients initially receive 9 weekly doses of trastuzumab (1^{st} dose 4 mg/kg, then 2 mg/kg) together with chemotherapy. Subsequently, 40% of the patients receive an infusion every 3^{rd} week(1^{st} dose 8 mg/kg, then 4 mg/kg) for up to 1 year. The cost of a subsequent month with trastuzumab was €2,800, which adds up to €35,000 a year. All trastuzumab costs include the administration and preparation costs covered by the treating organization. Trastuzumab drug wasteage in the hospital is marginal due to the concentrated preparation practices, and is therefore not included. Since stable use of trastuzumab does not reflect real clinical practice, the developed model was adjusted to take into account variability in treatment lengths. Every 10^{th} patient was assumed to discontinue the trastuzumab treatment at 6 months due to adverse events or other reasons. All adverse events were assumed to be fullyreversible, and thus not to cause any additional costs to the hospital district.

Table 1. Annual average cost of adjuvant treatment of HER2+ early breast cancer in thehospital district

Resource use and treatment*	**1st year standard treatment**	**1st year adjuvant trastuzumab**	**Annual follow-up (no progression)**
Treatment without trastuzumab			
Initial medical assessment	€275		
Docetaxel treatment	€3,750		
FEC combination treatment#	€1,440		
Radiotherapy 2Gy (25 times)	€3,900		
Treatment control visits	€175		€350
Mammography follow-up			€60
9-week trastuzumab treatment (60%)		€7,000	
1-year trastuzumab treatment (40%)		€35,000	

Average cost (€/patient/year)*	€9,540	€18,200	€410

*Drug costs other than those of the hospital district are excluded. #FEC = fluorouracil+epirubicin+cyclophosphamide.

Treatment cost of HER2+ metastatic breast cancer. The use of trastuzumab in metastatic disease was included in the model according to local clinical practice. All HER2-positive patients with metastatic breast cancer were assumed to receive trastuzumab, even if they had received it earlier in the adjuvant setting. In the treatment of metastatic breast cancer, trastuzumab is given in 3-week cycles for one year, which constitutes an average cost of €33,600 per patient per year. The average treatment mix and cost are described in Table 2**.**

Table 2. Average treatment mix and cost of metastatic HER2+ breast cancer by year fromprogression

Treatment*	**Cost peryear**	**Proportion Year 1**	**Proportion Year 2-4**
Hormonal (tamoxifen)	€1,500†		5 %
Hormonal (aromatase inhibitor)	€1,500†		10 %
Cytostatic (FEC)#	€10,000		10 %
Cytostatic (vinorelbine) + trastuzumab	€38,400†	50 %	20 %
Cytostatic (capesitabine)	€2,500		20 %
Cytostatic (docetaxel) + trastuzumab	€54,725	50 %	20 %
Other	€10,000		15 %
Weighted average cost (€/patient/year)†		€46,563	€21,850

* All treatment costs include follow-up visits and imaging (ultrasound and radiography).

† Drug costs other than those of the hospital district are excluded.

FEC = fluorouracil+epirubicin+cyclophosphamide

Sensitivity analyses. Sensitivity analyses were performed in order to evaluate uncertainty attributable to the applied assumptions and model parameters. Uncertainty related to the assumptions was explored by performing a series of "what-if" scenarios, which consisted ofthe following one-way sensitivity analyses. In scenario A, all patients were assumed to receive trastuzumab according to the 1-year treatment schedule. In scenario B, a short, 9- week treatment schedule was applied to all patients. The prevalence of HER2+ was assumed to be 12% in scenario C and 25% in scenario D. In scenario E, the cost of the trastuzumab treatment decreased by 40%. Finally, in scenario F, the effectiveness of the treatment was discarded from the model. These extreme scenarios were assumed to reflect the range of circumstances that the budget holders may face.

In addition to the traditional deterministic sensitivity analyses, a probabilistic sensitivity analysis was also performed. It takes into account the degree of variability and uncertainty related to these parameters simultaneously. In the model, probability distributions were assigned to all key parameters (i.e. number of patients, HER2+ prevalence, transition probabilities and treatment costs).

Results

Base-case results. The introduction of trastuzumab in the treatment of HER2-positive early breast cancer caused substantial costs to a rather small hospital district with 250,000 inhabitants and around 29 patients receiving adjuvant trastuzumab each year. In a 4-year follow-up period the net budget impact was €1,302,000, and in one year the figure was approximately €474,000. The additional cost per treated patient was around €16,000 in the first year. The total net costs included adjuvant treatment, the cost of the follow-up period, and treatment of metastatic disease. Most of the additional costs were accrued from the acquisition costs of adjuvant trastuzumab. However, there were also savings related to adjuvant trastuzumab treatment due to improved cancer recurrence rates. Thus, the acquisition costs were partially offset by the reduction in costs associated with the treatment of cancer recurrence and metastatic disease. However, the majority of these savings were due to the reduction in late-stage trastuzumab use. Figure 2 shows the contribution of each cost type to the total net budget impact when trastuzumab is added to the treatment of early breast cancer.

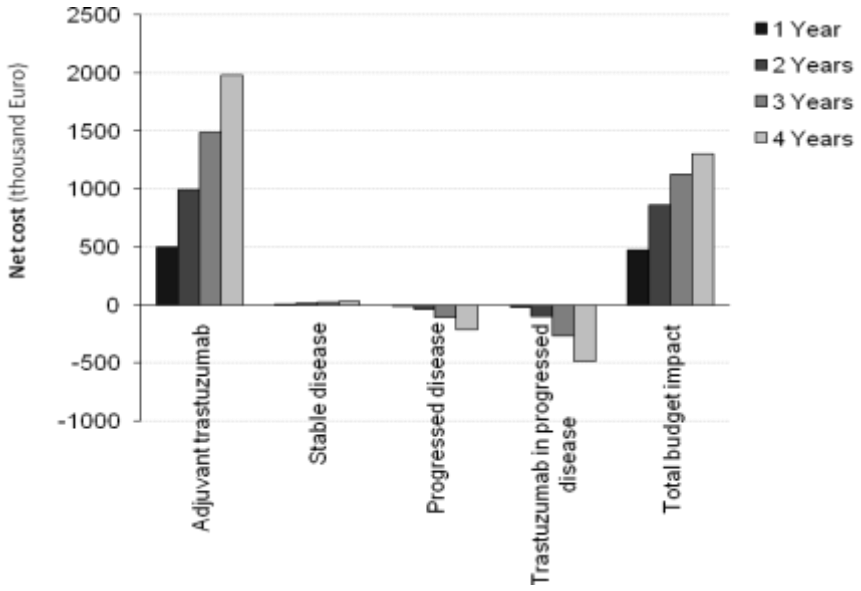
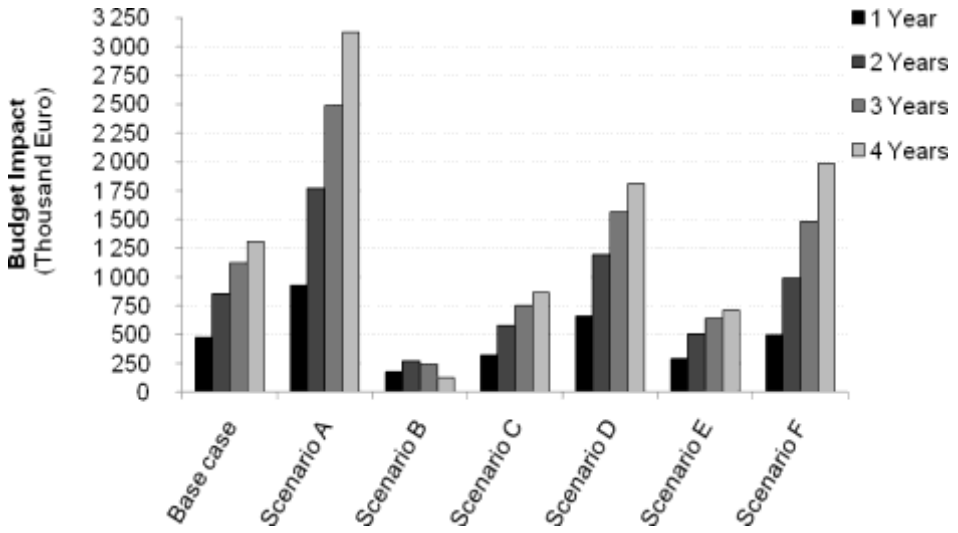


Figure 2. **Cumulative changes in different cost types by time, along with the net budget impactof trastuzumab in early breast cancer**

Sensitivity analyses. The sensitivity of the results was studied through alternative case scenarios (Figure 3). The short treatment schedule (scenario B) gave a smaller budget impact than the other scenarios. The budget impact of this 9-week treatment decreased overtime when effectiveness, in terms of disease progression, was included in the model. The difference between short (B) and prolonged (A) therapy was around €750,000 in one year, and €3M in 4 years. In scenario E, the treatment cost of trastuzumab was reduced by 40%. This constituted a 46% reduction in the 4-year budget impact compared with the base-case. When the prevalence of HER2+ was altered from 12% to 25%, the 4-year budget impact varied between €868,000 and €1,808,000. As assumed, the results of the study were fairly sensitive to the length of the trastuzumab treatment and the number of patients. Also, whenthe effectiveness of the treatment was excluded from the model (scenario F) the budget impact was notably higher than in the base-case.



Scenario A: All patients receive trastuzumab according to a 1-year schedule Scenario B: All patients receive trastuzumab according to a short 9-week schedule Scenario C: Prevalence of HER2+ is 12%

Scenario D: Prevalence of HER2+ is 25%

Scenario E: Cost of the trastuzumab treatment is reduced by 40% Scenario F:

Efficacy is not included in the analysis

Figure 3. Cumulative net budget impact of trastuzumab in the selected what-if scenarios and base-case analysis (in a population with 176 annual breast cancer cases)

The results of probabilistic sensitivity analysis are presented as affordability curves (Figure 4), which depict the probability of staying within a certain budget (Sendi and Briggs 2001). The information provided by these curves can be expected to be useful for the budget holders who make decisions under uncertainty. For example, if the annual budget constraint is €500,000, there is around a 70% probability that the budget will not be exceeded in the first year. In four years the same level of confidence is reached when the budget constraint is €1,350,000. However, these particular results hold only with the base- case assumptions. Uncertainty related to the results grows along with the longer time horizon.

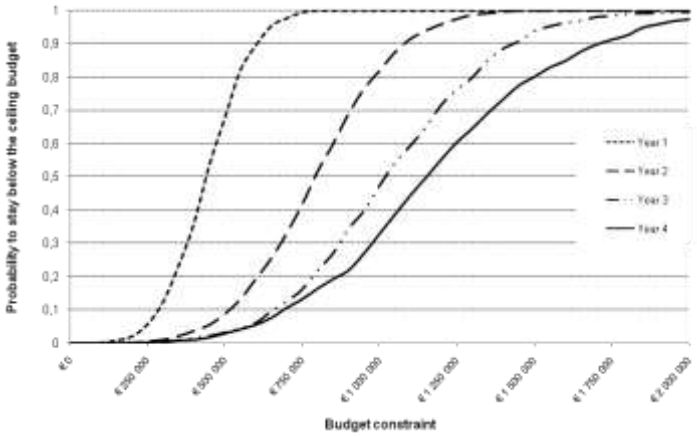


Figure 4. Affordability curves showing the probabilities that trastuzumab is affordable as a function of the budget constraint

7.1.1 Discussion

Evaluation of both cost-effectiveness and budget impact of new treatments is necessary due to limited health care resources. Economic evaluations are needed, not only to ascertain the best possible value for money, but also to assess to what extent the treatments are affordable. Nevertheless, the means for performing timely economic evaluations are currently limited. In this study, an evaluation model was developed to assess the budget impact of new cancer treatments. We found that adjuvant trastuzumab causes substantial costs even for a rather small hospital district. The net budget impact was greatly influenced by the number of treated patients, and the length and cost of the treatment.

Trastuzumab has proven its clinical efficacy in HER2-positive breast cancer. The aim of adjuvant treatment is to destroy micrometastases, and thus to prevent recurrences and improve the survival of the patients.

Most clinical evidence regarding adjuvant therapy is from a 1-year treatment (Piccart-Gebhart et al. 2005, Romond et al. 2005, Slamon et al. 2005, Slamon et al. 2006, Perez et al. 2007), but a shorter 9-week treatment has also been studied (Joensuu et al. 2006). However, the optimal duration or dosing frequency of trastuzumab is still not known.

In the future, longer follow-up data of adjuvant trastuzumab treatment will be available from ongoing trials. Survival estimates are also dependent on patient characteristics, including age and disease stage. However, currently available information did not enable us to do a patient subgroup analysis. In this budget impact analysis the effectiveness of the trastuzumab treatment was estimated according to the published data of the FinHer (Finland Herceptin) trial (Joensuu et al. 2006). The health benefit gained from the treatment was assumed to be the same despite the length of the treatment. However, if the 1-year treatment would be clinically better than the 9-week treatment, it would also lead to bigger savings during the follow-up than evaluated in this analysis. Furthermore, treatments given together with trastuzumab, and possible synergism with certain chemotherapy regimens, can be of significance to the treatment outcomes. Nevertheless, the most reliable data concerning the best way to give the trastuzumab treatment in early breast cancer will be acquired from randomised studies comparing short and long trastuzumab treatment.

Effectiveness of treatment is seldom included in budget impact models, though it has been considered to be important (Skedgel et al. 2008). In devastating and progressing diseases such as cancer, improved outcomes should be accounted for in order to depict real treatment practice. In local clinical practice the trastuzumab treatment was continued beyond disease progression. This was also included in the analysis. The financial impact of late-stage trastuzumab may, however, be easily discarded from the total net budget impact. A budget impact analysis that is solely based on acquisition costs ignores the effects of the treatment. It simply describes how much money is spent on the drug within a certain time horizon, but, at the same time it fails to include other possible costs or savings related to the treatment. After adjuvant treatment, patients without relapsed disease will be able to continue their everyday life and return to work. However, productivity losses or time costs were not included in the study. The complex nature of reality cannot be completely captured in economic evaluations. However, using the best available information and modeling techniques, this complexity may, to some extent, be taken into account.

Hospitals are not always able to manage in the pressure of increasing costs of new pharmaceuticals if costs

grow faster than the budget assigned for the drug. Unrestricted reimbursement of expensive and relatively widely used pharmaceuticals, such as trastuzumab, may lead to inequality in treatment access.

In the Netherlands, it has been already demonstrated that trastuzumab was unevenly distributed among patients in different hospitals, largely due to limited drug budgets. Nevertheless, budget impact estimations may play a role in preserving patient equality (Niezen et al. 2006, Niezen et al. 2009).

Budget impact analyses are usually performed from the perspective of a target organization (e.g. a hospital district in this study). However, it is important to note that costshifting between a hospital and other financing bodies, such as municipalities and SII in Finland, may lead to suboptimal decisions from the social perspective or the perspective of overall health care planning (Häkkinen 2005). This budget impact model was created to depict the current situation in one Finnish hospital district.

Thus, the results are not necessarily applicable to other jurisdictions due to possible differences in treatment practices and related costs. Furthermore, treatment practices may change over time, and thus affect the applicability of the results of economic evaluations. In addition, the results may need to be updated if new products are introduced for the same indication, since they may affect both the proportion of patients receiving the treatment and the actual price ofthe treatment. By using a relatively short time horizon, the number of assumptions does notgrow to be excessive.

The markets are volatile and may change when new products are introduced. Long-term budget impact analyses do not necessary depict the true future situation, which leads to instability in long-term results. In our analysis the market diffusion rate was considered to be stable, although the possibility to vary the annual diffusion rate was enabled in the model. Possible market changes should be recognised when budget impact estimations are performed.

When new products are introduced they usually slowly replace older treatments. This releases resources to fund the new treatment to some extent. However, in respect of add-on medicines, all costs will have to be compensated with additional funding or sacrifices madeelsewhere. Due to the large potential financial impact of trastuzumab, there was an increased need for more comprehensive budget impact analysis. Despite the favorableincremental cost-effectiveness rations concerning trastuzumab, the eventual economic consequences of the treatment are substantial.

Practical evaluation tools offer a great help for decision-makers and budget holders - especially with respect to new and expensive targeted therapies that add significant costs to the health care system. Alternative scenarios are an essential part of results in budgetimpact analyses. The model developed in this study was used in only one hospital district. However, when local epidemiological and treatment data are obtained, the model may be used similarly in other jurisdictions. The treatment costs of different stages of breast cancer were those of a single hospital, and were derived from an average treatment protocol practiced in the target organization. In order to provide real-time estimates of the economic impact of novel treatments and to allow fluent data collection, more attention should be paid to improving the usability and coverage of electronic databases.

The present analysis found that the budget impact of trastuzumab is considerable, from the perspective of a Finnish hospital district. However, when the effectiveness of the treatment is taken into account, there are also savings related to adjuvant trastuzumab treatment. The length of the treatment has a strong effect on the eventual budget impact. Future trials will show to what extent the duration of trastuzumab treatment affects its

effectiveness and the cost-effectiveness of the therapy.

Short-Course Adjuvant Trastuzumab Therapy In Early Stage Breast Cancer In Finland: Cost-Effectiveness And ValueOf Information Analysis Based On The 5-Year Follow Up Results Of The Finher Trial (Study V[5])

Introduction

Breast cancer is currently the most common cancer in Finland. There were 4,318 newly diagnosed cases in 2008 and the number is expected to rise to 5,247 by 2015 (Mäklin and Rissanen 2006, Finnish Cancer Registry 2010). According to the predictions of the Finnish Cancer Registry, in 2015 breast cancer will account for 42% of all female cancer incidence. In 2004, breast cancer alone caused costs of €65M, and the costs are assumed to double by 2015. It is currently responsible for 12% of all cancer-related costs in Finland. Approximately 12–30% of breast cancers over-express human epidermal growth factor receptor 2 (HER2) (Slamon et al. 1989, Joensuu et al. 2003, Owens et al. 2004). These HER2- positive cases are associated with a more aggressive form of disease, and in adjuvant setting they are currently treated with trastuzumab, together with conventional breastcancer treatment.

Trastuzumab, a humanised monoclonal antibody, has proven its clinical efficacy as an adjuvant therapy in several trials (Piccart-Gebhart et al. 2005, Romond et al. 2005, Joensuu et al. 2006, Smith et al. 2007, Joensuu et al. 2009, Slamon et al. 2009). However, there is no consensus about the optimal treatment schedule or the length of adjuvant treatment. Also the duration of treatment benefit has remained unclear. Most of the randomised controlled trials have focused on 12-month treatment (Piccart-Gebhart et al. 2005, Romond et al. 2005, Smith et al. 2007, Slamon et al. 2009), but also a shorter 9-week treatment regimen has been studied in Finland Herceptin trial (FinHer) (Joensuu et al. 2006, Joensuu et al. 2009). In addition, a trial comparing the 9-week and 12-month trastuzumab treatment regimens is currently ongoing (SOLD 2008).

Trastuzumab is a relatively expensive drug. It was first introduced for the treatment of HER2-positive metastatic breast cancer, but later the indication was extended to adjuvant treatment in early stage of the disease. The increasing number of eligible patients, after the indication extension, has led to concerns about the cost-effectiveness and affordability ofthe treatment. Cost-effectiveness of adjuvant trastuzumab has been assessed in several studies, and in most cases it has been deemed as a cost-effective treatment (Chan et al. 2009,Reed and Schulman 2009). However, most of these economic evaluations have been based on published interim results of clinical trials, having a relatively short follow-up. Evaluations using data from FinHer trial are few (Dedes et al. 2007, Millar and Millward 2007, Neyt et al. 2008), and there are no studies assessing the cost-effectiveness of short course trastuzumab in the light of the updated results.

The aim of this study was to assess the potential cost-effectiveness of adjuvant 9-week trastuzumab treatment, compared to treatment without trastuzumab, applying the final 5- year follow-up results of the FinHer trial (Joensuu et al. 2009). In addition, due to uncertainty related to the effect size of the 9-week treatment regimen and other model parameters, value of information (VOI) methods were used to combine the probability and consequences of a wrong adoption decision. Expected value of perfect information (EVPI) and expected value of perfect partial information (EVPPI) analyses were performed inorder to address the question whether and what additional evidence is required to support an adoption decision. (Barton et al. 2008)

Materials and methods

A health-economic modeling approach was utilized in the study. The model was used to simulate a

hypothetical cohort of 1,000 HER2-positive patients of an average age of 50 years matching the inclusion criteria and baseline population characteristics of the FinHer trial (Joensuu et al. 2009), the primary source of effectiveness data for this study. In the published results of the FinHer trial, the hazard ratio for distant disease progression was

0.65 (95% CI 0.38–1.12) and for death 0.55 (95% CI 0.27–1.11) after a follow-up of 5 years (Joensuu et al. 2009). Clinical parameters were extracted from published clinical trials. The analysis was performed from a societal perspective that included all direct, but no indirect costs (such as productivity losses). Costs and health outcomes were discounted by 3% as recommended in the Finnish guidelines. The evaluation model was built in Microsoft Excel 2007.

Model structure and clinical parameters. The applied model consists of two parts. The first part concerns the first 5 years from the initiation of treatment, and the second part continues onwards from year 5 to lifetime. This partition is driven by the available data on effectiveness, i.e. the actual survival curves, obtained from the final results of the FinHer trial (Joensuu et al. 2009), which were used to inform the clinical outcomes of the first partof the model. The second part of the model is a traditional Markov stage-transition model (Briggs and Sculpher 1998), which was used to extrapolate the costs and health outcomes over the lifetime of the patients. The initial Markov-stages (at the end of year 5) were populated using the information from model part 1. A scheme of the evaluation model is presented in Figure 5.

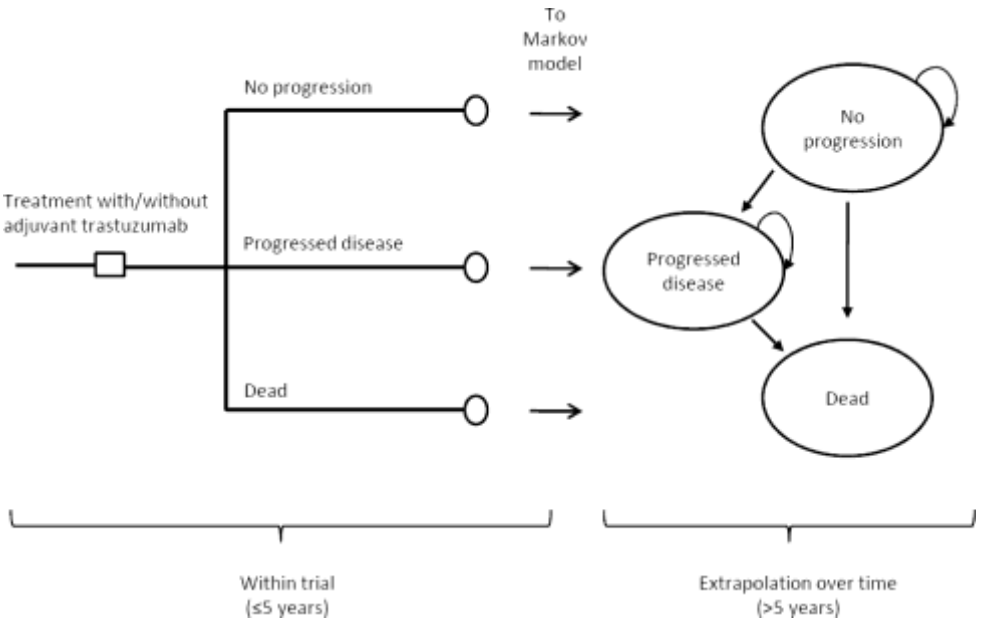


Figure 5. **Scheme of the cost-effectiveness model**

Since the published Kaplan-Meier curves of overall survival (OS) and distant disease- free survival (DDFS) in the FinHer trial (Joensuu et al. 2009) were not presented in a format suitable to health-economic analysis, a parametric (log-logistic) survival model was fitted toa manual trace of the curves, using statistical package R. The log-logistic model was chosen above other survival models (Weibull, exponential) because it provided the best fit to data (Figure 6). Probabilities of being in one of the three health states at a certain point in time were derived from this model, together with the associated measures of uncertainty. The treatment effect of trastuzumab was estimated as a regression coefficient. Because neither the summaries of OS conditional on DDFS nor patient histories have been published, the conditional nature of the sequence of events (time from

DDFS to OS) was imposed through a constraint in the simulation model.

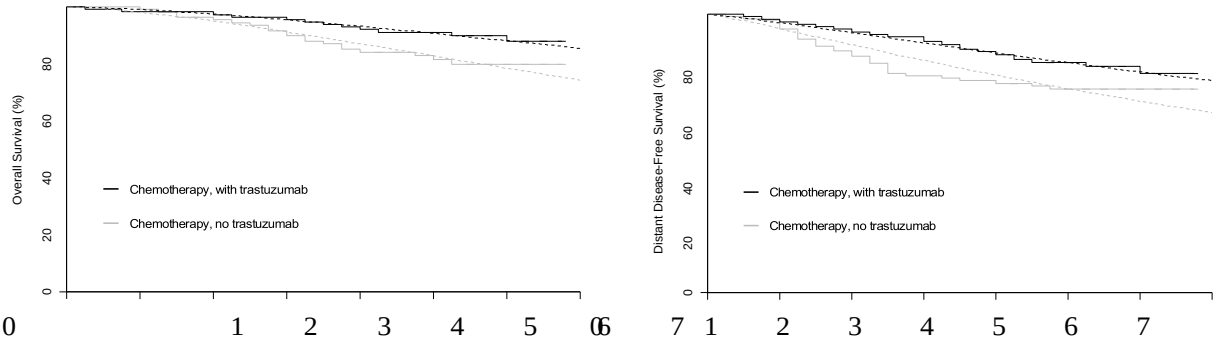


***Figure 6*. Kaplan-Meier survival curves (continuous lines) and the fitted log-logistic model (dashed lines) for overall survival and distant disease-free survival for 9-week adjuvant trastuzumab. Vertical lines represent drop-outs. Original survival curves obtained from the FinHer trial (Joensuu et al. 2009).**

Reliable follow-up data from clinical trials was lacking from 5 years onwards, and thus a Markov model was populated with data on disease progression. Patients enter the Markov model (part 2 of the model) at the beginning of year 6 according to the proportions in each of the health states estimated in model part 1. The Markov model utilizes monthly transition probabilities between health stages to represent the natural flow of the disease. The mutually exclusive health states are "No disease progression", "Progressed disease", and "Dead". Only distant progressions are included in the definition of "disease progression". The risk of disease progression is assumed to gradually decrease over time, and no new distant progressions are assumed to occur after 20 years of disease-free survival. Distant disease progression is assumed to be treated with trastuzumab, regardless of initial treatment assignment. Transition probabilities utilized in the Markov-model are presented in Table 3. The transition probability from progressed disease to death was based on median overall survival (25.1 months) among patients with HER2+ metastatic breast cancer treated with trastuzumab (Slamon et al. 2001). Disease progression and its treatment are modeled as tunnel states in order to allow variations in treatment length. Official Finnish life-tables, adjusted for breast cancer, were used to capture background mortality due to other causes than breast cancer (Statistics Finland 2008). In the base-case analysis, the treatment effectiveness of adjuvant trastuzumab was limited to 5 years, and beyond this point there were not assumed to be any differences in the treatment effectiveness between the compared groups (i.e. risk of disease progression was assumed to be same after 5 years in both groups). The modeled population contributes costs andoutcomes each month according to the modeled health stages during the entire model presented in earlier.

Quality of life parameters. Since appropriate Finnish quality of life data was not available, the applied utility weights were based on a study with 361 Swedish breast cancer patients (Lidgren et al. 2007). The utility weights were measured with the EQ-5D quality of life instrument. The model calculates quality-adjusted life-years (QALY), which is a common outcome measure used in economic evaluations.

Cost parameters. Treatments of localised and disseminated cancer can be distinguished. Breast cancer-specific treatment costs (in 2008 Euros) were previously obtained from a Finnish university hospital (study IV). In addition, patient co-payments were added to the present analyses in order to be consistent with the study perspective. The aggregated per- cycle costs, used in the analysis, are presented in Table 3. Adjuvant trastuzumab is used in addition to standard breast cancer treatment, and it is given as an infusion. The short, 9-week, treatment protocol begins with a loading dose of 4mg/kg and continues with a weekly 2mg/kg. Upon disease progression, patients receive trastuzumab in 3-week cycles for a maximum of 52 weeks similarly in both groups. The costing includes acquisition, administration and preparation costs.

Table 3. **Model parameters and their probability distributions**

Transition probability per cycle	**Probability**	**Distribution**		**Source**
Disease progression				
cycles 1–60 base-case survival model (part 1)		Log-logistic regression		(1)
cycles 1–60 (w/ trastuzumab)^	0.0031^			(1)
cycles 1–60 (w/o trastuzumab)^	0.0048^			(1)
cycles 61–120	0.0038	beta	α(0.441) β(115.56)	(1, 5)
cycles 121–180	0.0030	beta	α(0.348) β(115.65)	(1, 5)
cycles 181–240	0.0027	beta	α(0.313) β(115.69)	(1, 5)
cycles 241->	0.0000			assumption
Progressed disease to death	0.0272	beta	α(6.39) β(228.6)	(2)
	0.0336†	beta	α(7.89) β(227.1)	(2)
Treatment cost per cycle (1 month)	**Cost**			
Early breast cancer				
trastuzumab(a)*	€3,500	normal	SE ±10%	(3)
trastuzumab(b)*	€2,800	normal	SE ±10%	(3)
other cancer-related treatment				
cycles 1–12	€817	gamma	α(25) β(32.68)	(3)
cycles 13–60	€57	gamma	α(25) β(2.28)	(3)
cycles 60->	€5	gamma	α(2) β(0.2)	(3)
Advancer breast cancer				
trastuzumab(c)	€2,800	normal	SE ±10%	(3)
other cancer-related treatment	€1,122	gamma	α(25) β(44.88)	(3)
Quality of life (EQ-5D)	**Utility weight**			
Primary breast cancer, 1st year	0.696	beta	α(177.5) β(77.1)	(4)
Primary breast cancer, subsequent years	0.779	beta	α(472.3) β(134.0)	(4)
Metastatic breast cancer	0.685	beta	α(171.1) β(78.7)	(4)
Dead	0.000			

^ Used in a sensitivity scenario to depict treatment effect from 1 to 10 years.

†Used only in a sensitivity scenario.

* Only in trastuzumab group.

(a) During cycles 1-2 (9 week treatment)

(b) During cycles 1-12 (Only in sensitivity analysis for 12 month treatment)

(c) At maximum 12 months from disease progression

SE=Standard error; SE ±10% = [(Mean±10%)/(1.96*2)]

References: (1)Joensuu et al. 2009, (2)Slamon et al. 2001, (3)Study IV, (4)Lidgren et al. 2007, (5)Clarke et al. 2005

Sensitivity analyses. The model was made probabilistic in order to take into account the uncertainty related to all individual model parameters, and to convert this parameter uncertainty into decision uncertainty. In a probabilistic sensitivity analysis all model variables are allowed to vary simultaneously according to their probability distributions. Probability distributions were applied for all model inputs (probabilities, quality of life, costs). Beta distributions, whose benefit is the unit interval (0 to 1), are applied for each of the probabilities and quality weights. The cost of trastuzumab was assumed to follow normal distribution because the dosing of trastuzumab is weight-related, and weight can be assumed to be normally distributed. Gamma distributions were used for all other treatment costs. The fitted survival curves were varied by drawing the correlated regression coefficients using Cholesky decomposition. With this method, the uncertainty in the clinical data can be explored without breaking the correlation structures imposed by the chosen parametric survival model (log-logistic in this case).

The model was calculated repeatedly for 1,000 times in order to elicit the real variation of the results, rather than a single point estimate. The results of the simulation are presented in a cost-effectiveness plane. The uncertainty surrounding the cost-effectiveness of trastuzumab is depicted in a cost-effectiveness acceptability curve (CEAC), which plots the probability that trastuzumab is cost-effective for a range of cost-effectiveness thresholds.

In addition to the probabilistic sensitivity analysis, a variety of other sensitivity analyses were performed. In conventional one-way sensitivity analyses individual model parameters were altered one at a time. In one scenario, the assumption of trastuzumab being used after disease progression was tested by excluding the cost of trastuzumabtreatment in advanced disease from the model. At the same time, the observed treatment benefit in advanced disease was also excluded, and the transition probability was based on median survival of 20.3 months (Slamon et al. 2001). In another scenario, adjuvant trastuzumab was given for 12 months (€2,800/month), while the treatment effect remained at the base-case level. In the final sensitivity scenario the first part of the model was removed, and the 3-stage Markov model (part 2) was used for the entire comparison. Here, the transitions based on fitted survival curves were replaced with constant transition probabilities. With this modified model, we aimed to illustrate the uncertainty related to different assumptions of the effect of treatment benefit persisting beyond treatment duration.

Value of information analysis. The applied probabilistic model characterises the uncertainty related to the decision problem, and it was also used to establish the value of additional research aimed at obtaining more precise model parameters. Increased precision of the model parameters would reduce the decision uncertainty, i.e. minimise opportunity losses. In addition, value of additional research for a set of model parameters (i.e. clinical, quality of life, and cost parameters) was estimated to determine what type of additional research would be most valuable. Additional research may be considered worthwhile if the value of additional research in monetary units exceeds the cost of conducting such research.

7.1.2 Results

In the probabilistic base-case analysis, 9-week adjuvant trastuzumab treatment led to 0.66 incremental QALYs or 0.85 life-years gained (LYG) with an additional lifetime cost of €7,900, compared to treatment without adjuvant trastuzumab. Thus, the incremental cost- effectiveness ratio (ICER) of the 9-week treatment was €12,000 per QALY, and €9,300 per LYG. The total QALYs gained with and without adjuvant trastuzumab were 8.37 and 7.71, and the costs were €61,600 and €53,700, respectively. The probability that the 9-week course provides additional benefits at additional costs is high, but the hypothesis of minimal or even negative treatment effect cannot be excluded entirely (Figure 7). Most (70%) of the 1,000 iterations for incremental effectiveness lie between 0.3 and 1.0 QALY. Similarly, 70% of the estimates for incremental costs lie between €2,900 and €12,300.

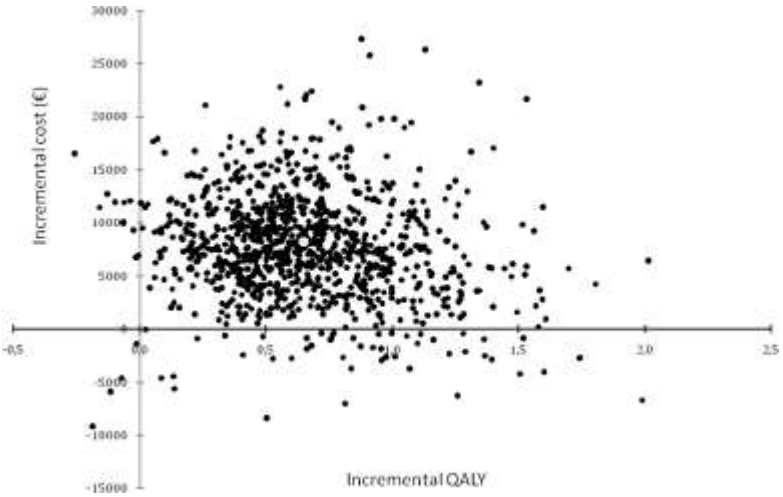


Figure 7. **Incremental cost-effectiveness plane of adjuvant 9-week trastuzumab in early stage breast cancer in Finnish settings. QALY=Quality-adjusted life year.**

According to these results, the short 9-week trastuzumab treatment is likely to be cost- effective already in relatively low willingness to pay (WTP) threshold levels. There is, for example, 87% probability of being a cost-effective option at WTP of €30,000 per QALY . This figure also shows the observed variation of cost-effectiveness with chosen discount rate. The impact of the discount rate reflects the nature of the treatment, in a sense that health benefits in terms of survival will be received in distant future.

The value of information (VOI) analysis indicates that the patient-level expected value of perfect information (EVPI) is, for example, €870 at WTP of €30,000 per QALY. The EVPI informs the consequences of making a wrong decision in monetary units, combined with the probability of that decision. With the WTP threshold of €30,000 and a population of 10,000 HER2-positive breast cancer patients, the population EVPI would be €8.7M. The EVPI is at its maximum at the point of ICER, where the decision uncertainty is greatest. The expected value of perfect partial information (EVPPI) showed that more than 90% of this can be attributed to the effectiveness parameters.

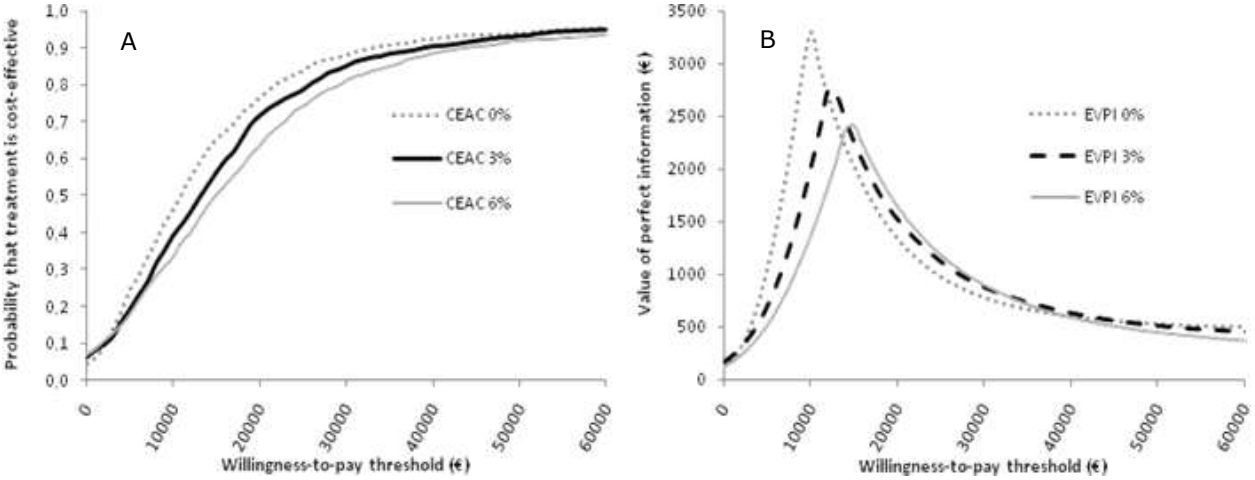


Figure 8. **A) Cost-effectiveness acceptability curves (CEACs) and B) expected value of perfect information (EVPI) of adjuvant 9-week trastuzumab in early stage breast cancer in Finnish settings. Presented with discount rates 0%, 3% and 6% for future costs and outcomes.**

Sensitivity analyses. In the deterministic one-way sensitivity analyses the modelparameters were altered one at a time. The results were relatively sensitive to the alteration of discount rate and trastuzumab treatment costs. Most parameter uncertainty, however, was related to the treatment effectiveness of adjuvant trastuzumab. When the bounds of 95% confidence interval of treatment co-efficient during years 0–5 were used, the ICER varied from €2,500/QALY to being dominated. The inclusion of costs of cardiac monitoring or additional travel costs did not have any significant impact on the results.

Assumptions related to trastuzumab use in advanced disease were tested in a scenario, where trastuzumab was discarded from treatment of advanced disease in both groups. This had only a marginal effect on the cost-effectiveness results, largely due to the fact that both groups were assumed to be treated similarly after disease progression. The impact of treatment length was studied in another scenario. When trastuzumab was used accordingto the 12-month treatment schedule, the ICER was €49,600 per QALY, assuming that the treatment benefit was the same as in the base-case.

Another important aspect related to the treatment effect is the assumption of the length of clinical benefit received beyond the duration of treatment. Our cost-effectiveness model utilized fitted survival data, and thus no further assumptions of the carry-over time of treatment effect were needed. However, to demonstrate how assumptions related to the length of treatment effect could affect the cost-effectiveness results, model part 1 was replaced with constant transition probabilities for disease progression (0.0031/0.0048 per cycle). These probabilities were applied for different durations, as illustrated in Figure 9. There is a strong dependence with the assumed length of treatment effect and cost- effectiveness of the treatment. Thus, it is clear that a conclusion on a treatment's cost- effectiveness may depend on the assumptions related to carry-over time of treatment benefit.

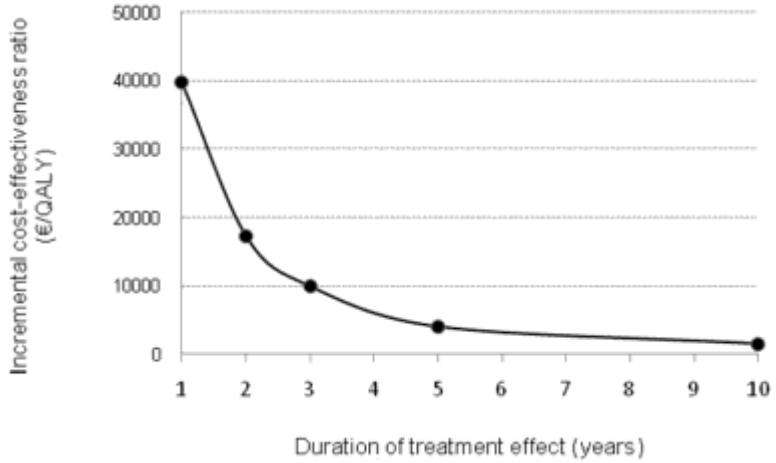


Figure 9. The impact of the assumptions related to length of treatment effectiveness in respect of incremental cost-effectiveness of 9-week adjuvant trastuzumab

7.1.3 Discussion

The aim of the current study was to assess the potential cost-effectiveness of adjuvant 9- week trastuzumab treatment in Finnish settings using the final results of FinHer trial, which have not, to our knowledge, been previously utilized in economic evaluations. We found that 9-week adjuvant trastuzumab is likely to be a cost-effective treatment option in early breast cancer compared to treatment without trastuzumab, despite the uncertainty related to the treatment effect. The value of information analyses show that more investment should be directed especially to research related to treatment effect in order to reduce the uncertainty related to adoption decision. The maximum acceptable cost (population EVPI) for a trial that would eliminate all uncertainty depends on the number ofpatients and society's willingness to pay threshold level.

The first published results from the clinical trials concerning adjuvant trastuzumab treatment were with relatively short follow-up (from 1 to 3 years) (Piccart- Gebhart et al. 2005, Romond et al. 2005, Joensuu et al. 2006, Slamon et al. 2009).

The more recently updated results show that the treatment effect of trastuzumab may be less favourable as previously expected. In the Herceptin Adjuvant (HERA) trial, using 12-month regimen, the hazard ratio (HR) for the risk of an event increased from 0.54 to 0.64 as the follow-up periodchanged from 1 year to 2 years (Piccart-Gebhart et al. 2005, Smith et al. 2007). The updated results of FinHer trial show similar change with the 9-week treatment. After 3-year follow- up, the women treated with 9-week trastuzumab+chemotherapy had more favourable overall survival (OS) compared to those treated with chemotherapy alone (Hazard Ratio [HR] = 0.41; 95% CI 0.16 to 1.08) (Joensuu et al. 2006). However, after a 5-year follow up, thecorresponding HR was 0.55 (95% CI 0.27 to 1.11) (Joensuu et al. 2009). In the FinHer trial,the patient subgroup with HER2 over-expression was small (n=232) compared to the other studies. Despite of the size of the patient population, the short course adjuvant treatment has shown positive signs about its efficacy, compared to chemotherapy only.

Nevertheless, the level of statistical significance, related to survival estimates, needs to be considered. In the current study, adjuvant trastuzumab led to 0.66 additional QALYs or 0.85 life-years. If our analysis would have been based on subgroup that received docetaxel+FEC+ trastuzumab, instead of any chemotherapy+trastuzumab, the cost-effectiveness results would have been more favourable to trastuzumab.

In this subgroup both the distant disease-free survival and the overall survival were greater than in the pooled analysis (Joensuu et al. 2009). However, this was not used since it does not reflect the current treatment practice, and also the population would have been considerably smaller. In addition, no patient subgroup analyses were performed due to lack of adequate information and sample size. The potential impact of patient cross-over from control group to receiving active treatment has not been addressed in the current study.

Economic evaluations are being used increasingly often in attempt to meet the challenges of optimally allocating the scarce health care resources. Cancer presents a challenge to health care funding both due to more expensive treatments and rising incidence rates. Furthermore, due to ageing of the population the annual number of new cases is increasing more rapidly than the age adjusted incidence. When expensive drugs are used in a number of patients, the economic issues become even more important.

Trastuzumab has been available for metastatic breast cancer from year 2000, and in 2006 the indication was extended for the adjuvant treatment of HER2-positive early breast cancer. This indication extension multiplied the number of potential patients. Since then, the cost-effectiveness of adjuvant trastuzumab has been investigated in several publications, and it has been estimated to be cost-effective in most of the analyses. However, a large part of these analyses are based on interim results of efficacy, and thus may need to be updated. Results from cost-effectiveness analyses based on the 1-year HERA results (Piccart-Gebhart et al. 2005) have varied from €6,000 per QALY to £18,000 (€22,000) per QALY (Reed and Schulman 2009). Analyses based on the 2-year HERA results (Smith et al. 2007) havepresented results from €17,000 per LYG to 127,900 Canadian dollars (€96,000) per QALY (Reed and Schulman 2009). From UK perspective, an ICER of £25,803 (€31,600) per QALY has been recently reported when 2-year follow-up was included in the analysis (Hall et al. 2010). Based on the above mentioned results, it seems these cost-effectiveness results are strongly associated with the follow-up time in the original study. However, the analyses based on shorter follow-up currently outnumber those using longer follow-up. A similar phenomenon may now be detected from economic evaluations based on 9-week treatment. In an Australian study, 9-week treatment had an ICER of A$1,700 (€1,300) per QALY (Millar and Millward 2007), and in a Swiss study it was found to be cost-saving (Dedes etal. 2007). A Belgian study showed that 9-week adjuvant treatment is most of the times cost-saving (in 11 out of 15 subgroups), and has ICER above €30,000/LYG in only one of the patient subgroups (age 80+, stage I disease) (Neyt et al. 2008). In the present analysis, we found a very low probability of 9-week trastuzumab being cost-saving, though the ICER was still on an acceptable level.

Trastuzumab use and its economic consequences have been studies in Nordic countriesin recent years. In Norway, the incremental cost per life-year saved ranged between €8,148 and €35,947 for a 1-year adjuvant treatment. The study assumed 10% or 20% improvement in absolute overall survival with trastuzumab treatment (Norum et al. 2007). The actual use of trastuzumab has been studied in Swedish Health Care Regions (Wilking et al. 2010), and from Swedish societal perspective the ICER for 1-year adjuvant trastuzumab was estimated to be €36,000 or €41,500 per QALY, in base-case analysis, depending on the HER2-testing strategy (Lidgren et al. 2008).

The current study was based on modeling, which inherently leads to simplification of real life circumstances. The model structure was driven by the available information in the primary data source. In the utilized Markov model (part 2), three mutually exclusive healthstages were used, following the partition in model part 1. Since

the analysis was based on published results of the FinHer trial, the inclusion of additional health stages would have led to number of assumptions leading to unnecessary uncertainty. For example, the local recurrences could not have been reliably included in the model, since little information has been published on this in the original data source (Joensuu et al. 2009). Moreover, distant recurrences are more closely associated with mortality than local ones (Joensuu et al. 2009). Nevertheless, the modeled health outcomes in the present study were of a same magnitude with those reported in previous studied assessing adjuvant trastuzumab.

In studies based on 12-month treatment, the incremental life-years gained with trastuzumab ranged from 0.12 (Dedes et al. 2007) to 4.1 (Millar and Millward 2007) years depending on the timeline and discount rate. Similarly, in studies using the interim results of FinHer trial (Joensuu et al. 2006) the incremental life-years ranged from 0.27 (Dedes et al. 2007) to 5.9 years (Millar and Millward 2007). If subgroup analyses were taken into account (e.g. age and disease stage) the variation in additional health benefit would be larger than the above mentioned (Neyt et al. 2008). The utilized cost data was based on a previous Finnish study (study IV). When compared with other economic evaluations of adjuvant trastuzumab, the stage specific costs were of similar magnitude to those used by others. Cost of HER2-testing was not included in the analysis since all new patients are equally tested. Similarly, cardiac toxicity was not taken into account in the analysis, because in the FinHer trial no significant differences existed between patients treated with or without trastuzumab (Joensuu et al. 2009). In addition, relatively fewer cases with cardiac toxicity were observed during the short course treatment in FinHer (Joensuu et al. 2009), compared to trials using 12-month treatment (Telli et al. 2007).

Quality of life was based on Swedish breast cancer patients (Lidgren et al. 2007), because suitable information was not available from local patients. However, due to close geographical and cultural proximity of Finland and Sweden, we believe that the utilized values were adequate to be used in the analyses.

In a sensitivity scenario we illustrated how different assumptions may affect the result of cost-effectiveness analyses. This is a key tool to determine the impact of various assumptions on the results, and is essential in complicated models, where the individual impact of each assumption on the observed results is difficult to infer analytically. Similar observations regarding the impact of assumed length of treatment benefit have been reported by others (Hall et al. 2010). In previously published cost-effectiveness analyses, 5 years has been the most used duration of benefit (Reed and Schulman 2009). In the current study we applied information directly from the published survival curves for OS andDDFS, which were used to estimate the natural flow of the disease for the first 5 years. Thus, we demonstrated that, despite their drawbacks, published Kaplan-Meier curves can be an appropriate source for fitted survival data in economic evaluations. Because of the statistical non-significance of the difference in treatment effects, our model included the possibility that adjuvant trastuzumab would lead to worse outcomes than the comparator. However, eventually only a small minority of the modeled cases showed negative effect.

Economic issues related to cancer treatments are multifaceted and even politically sensitive due to equity issues and the social value of the disease (Drummond et al. 2009). The Pharmaceutical Management Agency of New Zealand restricted trastuzumab funding to cover only 9-week of treatment, in July 2007 (Metcalfe et al. 2007). However, this turned into a juridical and political issue, and eventually the funding was extended to include 12- month treatment. (PHARMAC 2010, Herceptin 2010).

There is currently no evidence comparing the efficacy of the 9-week and 12-month treatment regimens, and thus therelative efficacy of these treatments cannot be evaluated directly. With the currently available data,

economic evaluations based on an indirect comparison of these treatments would support the 9-week treatment. However, with the current level of information and uncertainty, such evaluations would not be sufficiently credible to aid decision-making. The 9-week treatment may be a promising option in economic terms, compared with the 12-month treatment, if the treatment effect observed in existing studies is confirmed in additional studies. The ongoing SOLD-trial will eventually provide an important answer to this question. Since the duration of the treatment benefit is one of the driving forces of cost-effectiveness, such studies with longer follow-up are needed for more precise evaluations. Economic analyses on adjuvant trastuzumab should be updated when new data is available.

In conclusion, the current study shows that 9-week adjuvant trastuzumab is likely to be

Cost-effective in Finnish setting at relatively low willingness to pay threshold levels. The sensitivity analyses and the value of information analysis show that more research should be focused on the long-term effectiveness of treatments.

Conclusions and implications

- The utilized cancer model with three mutually exclusive health stages was suitable for modeling the disease progression of metastatic renal cell carcinoma, and early stage breast cancer. Additional research will be needed in applying the model to other types of cancer. If future cancer treatment moves towards increasing number of multiple subsequent treament lines, this will lead to difficulties in detecting an individual treatment's effect on the long-term end-points, such as overall survival.

- The length of the treatment has a strong effect on the eventual budget impact of trastuzumab. The short 9-week treatment with trastuzumab has a reasonable cost- effectiveness profile compared to treatment without trastuzumab. Future trials will reveal to what extent the duration of trastuzumab treatment affects its effectiveness and the cost-effectiveness of the therapy. According to current clinical trials, the short 9-week treatment is a promising option compared to the 12-month treatment in the adjuvant treatment of HER2-positive early breast cancer.

- A budget impact model using local data can be an effective tool to allow hospital districts to estimate the future cost burden of expensive medications. Budget impact estimations can help planning budgets within the hospital district, or within individual clinics.

- The probabilistic approach in budget impact analysis offers better recognition of uncertainty, and is a step forwards in the methodology used in budget impactanalyses.

- Further research on the cost-effectiveness, budget impact, as well as the cost and burden of different types of cancers are needed globally, but especially nationally.

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