original article

Annals of Oncology 21: 2161–2168, 2010
doi:10.1093/annonc/mdq250
Published online 5 May 2010

Trastuzumab beyond progression: a cost-utility analysis

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Received 8 February 2010; revised 29 March 2010; accepted 30 March 2010

Background: The continuation of trastuzumab beyond progression in combination with capecitabine as secondary chemotherapy for HER2-positive metastatic breast cancer (MBC) prolongs progression-free survival without a substantial increase in toxicity.

Patients and methods: A Markov cohort simulation was used to follow the clinical course of typical patients with MBC. Information on response rates and major adverse effects was derived, and transition probabilities were estimated, based on the results of the Breast International Group 03-05 clinical trial. Direct costs were assessed from the perspective of the Swiss health care system.

Results: The addition of trastuzumab to capecitabine is estimated to cost on average an additional of €33 980 and to yield a gain of 0.35 quality-adjusted life years (QALYs), resulting in an incremental cost-effectiveness ratio of €98 329/QALYs gained. Probabilistic sensitivity analysis showed that the willingness-to-pay threshold of €60 000/QALY was reached in 12% of cases.

Conclusion: The addition of trastuzumab to capecitabine in MBC patients is more expensive than what is typically regarded as cost-effective but falls within the value ranges found for established regimens in the treatment of MBC.

Key words: cost-effectiveness, cost-utility, HER2 positive, metastatic breast cancer, second-line chemotherapy, trastuzumab

introduction

The prognosis for breast cancer patients with HER2-amplification (HER2+) has substantially improved since the introduction of trastuzumab into routine clinical treatment practice for metastatic disease. When added to first-line chemotherapy regimens (anthracycline plus cyclophosphamide, or paclitaxel) in a randomized, controlled trial, trastuzumab demonstrated significant improvement in survival (25.1 versus 20.3 months) and objective response rate (50% versus 32%), with acceptable additional toxicity [1]. Cardiotoxicity is the main side-effect observed with trastuzumab treatment, in particular when administered in combination with anthracyclines [1]. Subsequently, trastuzumab-based non-anthracycline chemotherapy has become a standard of care in the first-line therapy of HER2+ patients with metastatic disease. In a retrospective analysis, trastuzumab treatment seems to reverse the poorer prognosis for metastatic HER2+ patients compared with HER2-negative patients [2].

Nevertheless, the majority of trastuzumab-treated patients exhibit either *de novo* or acquired resistance to treatment or have early relapse [3]. In these patients, conventional chemotherapy, usually taxane based, is stopped and the patient is switched to a second-line treatment. Recently, the combination of lapatinib and capecitabine has been established as an additional HER2-directed treatment option for this group of patients. A significant prolongation of median time to disease progression (8.4 versus 4.4 months for capecitabine alone) could be achieved with this novel dual tyrosine kinase inhibitor of HER1 and HER2 [4]. Empirically, however, trastuzumab has been continued in many patients with disease progression, mainly due to its favorable safety profile and the assumption that progression was due to resistance to the co-administered chemotherapeutic agent but not trastuzumab itself [5]. Retrospective analyses provided some support for this treatment approach, at a weak level of evidence [6–9]. These findings have recently been confirmed by the German Breast Group 26/Breast International Group (BIG) 03-05 study, a randomized, controlled trial of trastuzumab treatment in combination with capecitabine continued beyond progression [10].

Given that cancer treatment costs have been increasing rapidly during the past few years and will continue to do so, it is essential to allocate the available resources as efficiently as possible [11]. Cost-effectiveness analyses for HER2+ metastatic breast cancer (MBC) have examined the role of trastuzumab as a first-line treatment [12–15] and of lapatinib as a second-line

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treatment [16], but costs associated with trastuzumab beyond progression have not yet been addressed.

The aim of this study is to examine the cost-effectiveness of trastuzumab beyond progression from the perspective of the Swiss health care system.

materials and methods

We constructed a Markov model to assess the cost-effectiveness of treatment strategies for patients with HER2+ MBC who progressed during treatment with trastuzumab. Chemotherapy with capecitabine alone was compared with capecitabine plus continuation of trastuzumab. Clinically, the modeling was based on the BIG 03-05 study [10]. Direct medical costs were based on Swiss national tariffs and covered chemotherapy treatment, major adverse events, laboratory tests and disease progression. The time horizon of the analysis was lifelong. Costs were assessed from the perspective of the Swiss health care system. Accordingly, indirect costs were not considered. Costs are reported in Euros (€). An exchange rate of €1.00 = CHF 1.52 was used (average exchange rate March 2009–October 2009). Utilities for the health states represented in the model were obtained from the literature [16–18]. Costs and benefits were not discounted given the short life expectancy of the patient population studied.

Patients were included in the BIG 03-05 study if they had pathologically confirmed, HER2++ (by immune histochemistry or FISH), locally advanced or MBC, if the duration of previous trastuzumab treatment was 12 weeks or greater and if the time since the end of the last trastuzumab cycle was <6 weeks [10]. Patients could have received up to one chemotherapy drug for metastatic disease. Patients with a Karnofsky performance status of less than 60%; a life expectancy of <3 months or inadequate hematologic, renal, hepatic, or cardiac function (left ventricular ejection fraction of <50%) were excluded. Enrolled patients were randomly assigned to receive either capecitabine 2500 mg/m^2 (1250 mg/m^2 twice-daily) on days 1 through 14 followed by 1 week of rest or the same capecitabine regimen plus 6 mg of trastuzumab per kilogram body weight (BW), given as a 30-minute infusion every 3 weeks. The calculated capecitabine dose was approximated by the closest possible dose achievable with 500-mg and 150-mg tablets (Table 1). Patients received the assigned therapy until disease progression or until unacceptable toxicity occurred.

The primary outcome measure of this analysis was the incremental cost-effectiveness ratio (ICER), expressed as cost per quality-adjusted life year (QALY) gained, of continuing trastuzumab in combination with capecitabine, compared with capecitabine alone, for advanced MBC that progressed under trastuzumab therapy. ICERs results were compared with a willingness-to-pay threshold of €60 000/QALY [24].

Secondary outcome measures included ICERs for subgroups of patients defined by different weight and body surface area (BSA) categories. A theoretical cost-effective price was calculated for multi-dose vials of trastuzumab (440 mg per vial).

One-way sensitivity analyses and probabilistic sensitivity analyses (Monte Carlo simulation) were carried out to test the robustness of the results.

model structure

The structure of the Markov model is shown in Figure 1. The model comprises three mutually exclusive health states: stable/responsive disease, disease progression and death. Cycle length was 3 weeks, to match the duration of chemotherapy cycles. At model entry, all patients were in the stable/responsive disease state. At the end of each cycle, they could stay in the stable/responsive disease state or move to the progressive disease state. Patients with progressive disease could remain in this state or die. We assumed constant hazards over time and used the median time spent in each stage to estimate hazard rates for the control arm, based on the following formula: hazard rate = $-\ln(0.5)/(\text{median time in state})$. Hazard rates were subsequently converted into Markov state transition probabilities, taking into account the Markov cycle length of 3 weeks. In order to model survival in the treatment arm, control arm hazard rates were multiplied with hazard ratios (HRs) for time to progression (TtP) and the median TtP [10]. HR for time from progression to death, which was not available from the publication, was kindly provided by the investigators (G. von Minckwitz).

model inputs

clinical data. The effectiveness data used in the modeling were based on the German Breast Group 26/BIG 03-05 study, as described above. In this study, no significant differences in the occurrence of grade 3–4 adverse events were reported. Therefore, only costly adverse events were taken into account in the modeling, namely suspected myocardial infarction (one patient in capecitabine + trastuzumab arm) and pericardium effusion (one patient in capecitabine + trastuzumab arm; Table 2).

Treatment delays occurred in both arms in an almost equal percentage of patients (8% capecitabine group, 9.3% capecitabine + trastuzumab group). As no data were available on the duration of these delays, no correction was applied in the modeling. As a reduction of capecitabine dose became necessary in an almost equal percentage of patients in both arms (58.9% of the patients in the capecitabine group and in 57.3% in the capecitabine plus trastuzumab group) this was not corrected for in the model. Due to lack of available detail, this was not corrected for in the model. Trastuzumab doses were not reduced in the study.

utilities. Preference-based utility scores for stable and progressive disease were derived from the literature [16–18]. The utility assumed for stable disease was 0.7 (range 0.5–0.8) and was both used for the control and treatment arm as no difference in quality of life for adding trastuzumab to capecitabine was expected [9, 25]. For time in progression, a utility of 0.5 (range 0.45–0.72) was used.

medical resource use. Assessment of medical resource use was based on the BIG 03-05 study [10] and on a study of the resource use and costs for patients with MBC conducted at the University Hospital of Zurich [23]. The types of medical resources included in the model were study medication (including prescription, preparation and administration), laboratory tests, medical resources used during disease progression and costs for major adverse events [22] (Table 1).

Capecitabine dosage and number of tablets was calculated for five BSA categories and based on the prescription information given on the Swiss label for Xeloda® (Roche Pharmaceuticals, Basel, Switzerland) [19]. Twice-daily administration was assumed. For the five BSA categories, corresponding mean BWs were established on the basis of data from 398 European women with breast cancer [26] and used to calculate corresponding trastuzumab (Herceptin®; Roche Pharmaceuticals) dosages. It was assumed that most of the central pharmacies in Swiss hospitals treating breast cancer patients provide the exact amount of trastuzumab required and that any leftovers are saved for later use, eliminating the necessity to correct for wastes.

In the BIG 03-05 study, the actual duration of treatment administration was shorter than the observed TtP in both arms. In the assessment of medical resource use, treatment duration was therefore corrected for the number of administered treatment cycles to fit the real data. In the control arm, patients received six cycles of capecitabine in the median, while, numerically, median TtP would have corresponded to 8.1 cycles. In the treatment arm, the median cycle number for capecitabine and trastuzumab was 9 and the median TtP would have corresponded to 11.8 cycles. Although trastuzumab was continued after discontinuation of capecitabine in 16 patients (20.8%), no additional correction was made for this monotherapy. The median-based correction was assumed to be comprehensive.

Table 1. Unit and cycle costs

Study treatment	Unit costs	Body weight (kg)–body surface (m^2)				
		51 kg, 1.39–1.52	58 kg, 1.53–1.66	66 kg, 1.67–1.78	75 kg 1.79–1.92	84 kg, 1.93–2.06
Capecetabine—Xeloda® [19]		Tablets per day				
Tablet at 150 mg/60 tablets	€77.43					
One tablet	€1.29	2× 2	0	2× 1	2× 2	
Tablet at 500 mg/120 tablets	€462.40					
One tablet	€3.85	2× 3	2× 4	2× 4	2× 4	2× 5
Total dose per day		3600 mg	4000 mg	4300 mg	4600 mg	5000 mg
Costs per cycle		€360	€432	€468	€504	€540
Trastuzumab—Herceptin® [19]		Trastuzumab 6 mg/kg, mg/cycle				
440 mg multiple dosing	€2310.39	306 mg	348 mg	397 mg	450 mg	504 mg
1 mg	€5.25					
Costs per cycle		€1611	€1828	€2084	€2363	€2646
Other resources/treatments						
Nadir blood count 1× per cycle [20]		€89.24	Costs per cycle	Treatment and control arm €89.24		
Chemotherapy prescription and preparation 1× per cycle [21]		€25.49	Costs per cycle	Treatment arm only €25.49		
Chemotherapy administration 1× per cycle [21]		€52.90	Costs per cycle	Treatment arm only €52.90		
Treatment of heart failure per month [22]		€354.00	Costs per cycle	Treatment arm only €245.00		
Treatment costs while in progression per month [23]		€1109.26	Costs per cycle	Treatment and control arm €768.00		
Echocardiography ones per stage [21]		€245.00	Treatment arm only			

One cycle = 3 weeks.

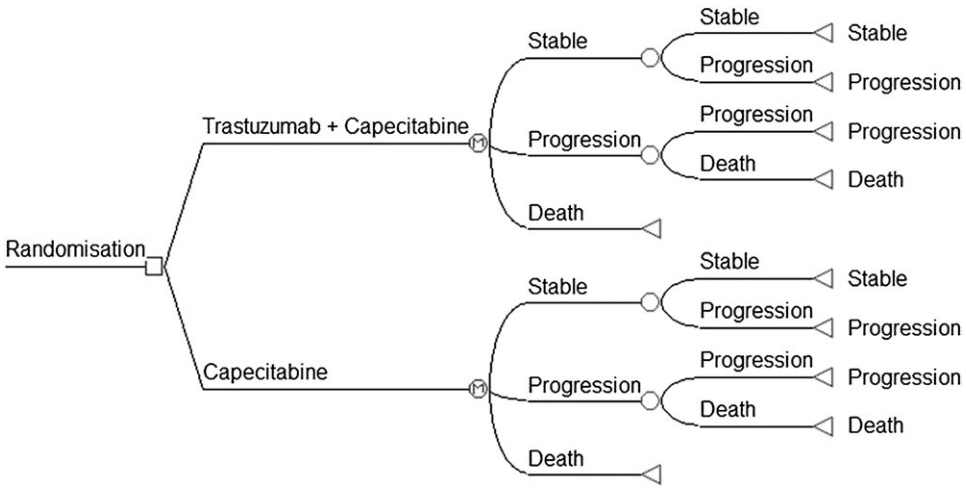

Figure 1. Structure of Markov model.

unit costs. Unit costs for treatment medication and concomitant treatments (Table 1) were taken from Swiss national drug price and tariff lists [19–21]. The per-cycle cost of treatment after disease progression was based on the total resource use observed during the first 5 years of treatment of patients with MBC as described by Dedes et al. [23]. This single-center experience is the best currently available Swiss source on the topic, and reported costs are comparable with data from other health care systems [27, 28].

sensitivity analysis

To assess the impact of statistical uncertainty around key model inputs, a series of univariate sensitivity analyses were carried out for the middle body surface area–body weight (BSA-BW) group (66 kg, 1.67–1.78 m^2), as this group includes the median BSA of 1.76 m^2 as calculated from the data of 398 European women with breast cancer [26] or for women with solid tumors (BSA 1.74 m^2) as described by Miller et al. [29]. In addition,

Table 2. Distributions

Variable	Distribution	Base case	
% Patients with echocardiography	Triangular	30%	Varied ±30%: min–max 21%–39%
% Patients with heart failure	Triangular	2.5%	Varied ±30%: min–max 1.8%–3.3%
Hazard ratio, time from progression to death	Lognormal	1.035	95% CI 0.64–1.68
Hazard ratio, time to progression	Lognormal	0.69	95% CI 0.48–0.97
Median number of treatment cycles, control arm	Triangular	6 cycles	Varied ±30%: min–max 4.2–7.8 cycles
Median number of treatment cycles, treatment arm	Triangular	9	Varied ±30%: min–max 6.3–11.3 cycles
Time from progression to death, control arm	Gamma	12.72 month	95% CI 9.67–16.75 month
Time to progression, control arm	Gamma	5.6 month	95% CI 4.2–6.3 month
Treatment costs per cycle during progression	Triangular	€768	Varied ±30%: min–max €539–998
Utility during stable	Triangular	0.7	Range: min–max 0.5–0.8
Utility during progression	Triangular	0.5	Range: min–max 0.45–0.72

CI, confidence interval.

probabilistic sensitivity analyses for all BS-BW groups were carried out. Additional scenario analyses were used to assess the impact of assumptions not primarily related to statistical uncertainty.

univariate sensitivity analysis. In univariate sensitivity analysis, median survival times, HRs, utility parameters and median numbers of treatment cycles as well as the costs of follow-up treatment were varied according to the distributions described in Table 2. The frequency of occurrence of the adverse event of heart failure and the performance of echocardiographies were also varied. In the absence of confidence intervals (CIs), the base-case values for these parameters were varied by ±30%.

probabilistic sensitivity analysis. Probabilistic sensitivity analyses (second-order Monte Carlo simulation) for all separate BSA-BW groups were based on the parameter distributions described in Table 2. For each BW-BS group, the probability of being cost-effective, based on a willingness-to-pay threshold of €60 000, was calculated.

additional scenario analyses. Drug prices may decrease over time due to price negotiations or expiring patent protection. As the original clinical effectiveness data from the BIG study [10] is promising and clinical relevant, acceptability curves as well as cost-effective prices for trastuzumab were calculated. These calculations were carried out for all BW-BS groups and using the base-case inputs for all other model input parameters.

model validation

The model was calibrated to match the original survival results of the BIG 03-05 study. Trackers for progression-free survival, overall survival and number of cycles were included in the model to assess correct reproduction of the original data. Additionally, all model outputs were reviewed for plausibility and key input parameters were subjected to extreme variation to test whether the model outputs behaved as expected.

technical implementation

The model was implemented and all Markov cohort and Monte Carlo analyses were carried out using TreeAge Pro Suite 2009® (TreeAge Software Inc., Williamstown, MA). Probabilistic sensitivity analyses were based on 5000 sets of randomly drawn input parameters.

results

After calibration, the effectiveness model outputs were comparable with the original clinical data of the BIG 03-05 study as shown in Table 3.

Table 3. Median time to progression and overall survival in model and original data

		Model	Original data
Time to progression	Control	5.89 month	5.6 month
	Treatment	7.96 month	8.2 month
Overall survival	Control	20.42 month	20.4 month
	Treatment	25.96 month	25.5 month

In the base-case analysis, the model indicated that continuing trastuzumab in combination with capecitabine, compared with capecitabine alone, in patients with locally advanced or MBC that progressed under trastuzumab therapy, leads to a gain of 0.35 QALYs per patient at an additional cost ranging from €27 502 (51 kg, 1.39–1.52 m^2) to €41 456 (84 kg, 1.93–2.06 m^2). Therefore, ICER for the continuation of trastuzumab in combination with capecitabine compared with capecitabine alone ranged from €79 581/QALY to €119 960/QALY gained, for the lowest to highest BW-BS groups.

sensitivity analyses

Univariate sensitivity analysis was carried out for the middle BW-BS group (66 kg, 1.67–1.78 m^2). The base-case ICER for this group was €98 329/QALY. Varying the HR for time from progression to death had the highest impact on the ICER and led to an ICER below the willingness-to-pay threshold of €60 000 for the lowest HR (0.64) input used. The second-most influential parameter was the HR for TtP. Reducing the number of treatment cycles in the trastuzumab + capecitabine arm reduced the ICER to €67 847/QALY; however, such a reduction would possibly impact negatively on the size of the clinical effect and therefore, such a low ICER may not be achievable. All other univariate sensitivity analysis results are summarized in a Tornado diagram (Figure 2). None of the other parameters tested resulted in an ICER below the willingness-to-pay threshold of €60 000.

Probabilistic sensitivity analyses resulted in a 26.94% probability of meeting the €60 000/QALY willingness-to-pay threshold in the lowest body weight–body surface group (BW-BS

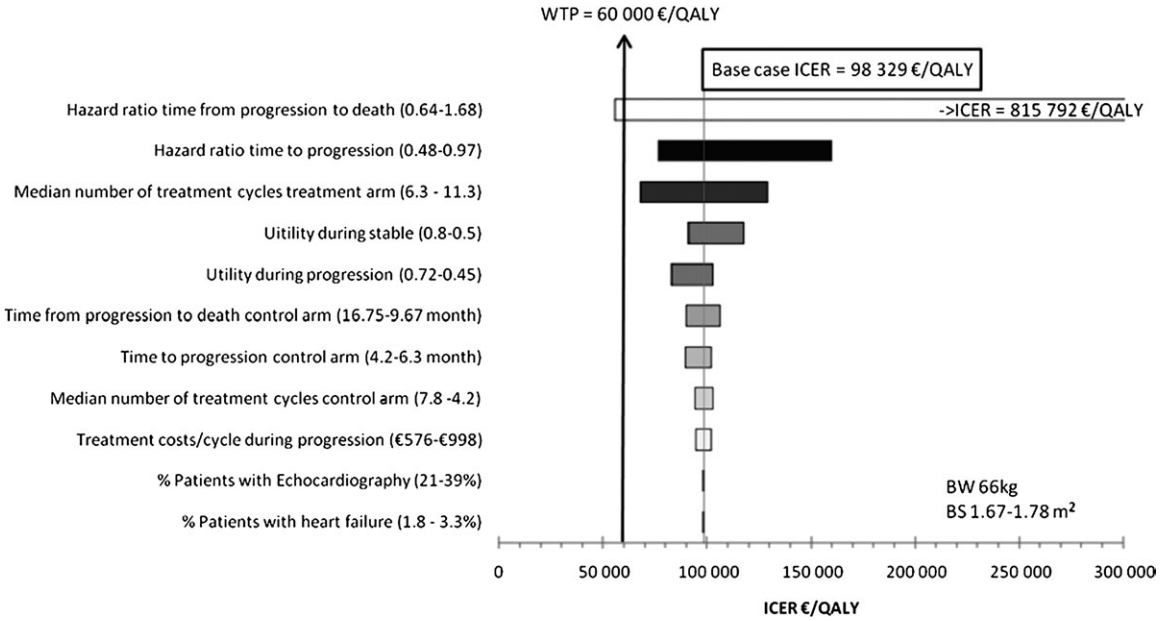

Figure 2. Tornado plot univariate sensitivity analyses for women with mean body weight of 66 kg and a body surface of 1.67–1.78 m^2. BS, body surface; BW, body weight; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; WTP, willingness to pay.

66 kg, 1.67–1.78 m^2 see Figure 3). The lowest probability (4.7%) of meeting the €60 000/QALY willingness-to-pay threshold was found for the highest BW-BS group (Table 4, Figure 4).

cost-effective trastuzumab price

In an additional analysis, cost-effective price for trastuzumab was calculated for all five BW-BS groups. Today the price for a 440-mg vial of trastuzumab is €2310. In order to reduce the ICER to the willingness-to-pay threshold of €60 000, a reduction of 30%–60% would be required, resulting in a price per vial between €1639 and €940, depending on BW and BSA of the patients (Figure 5).

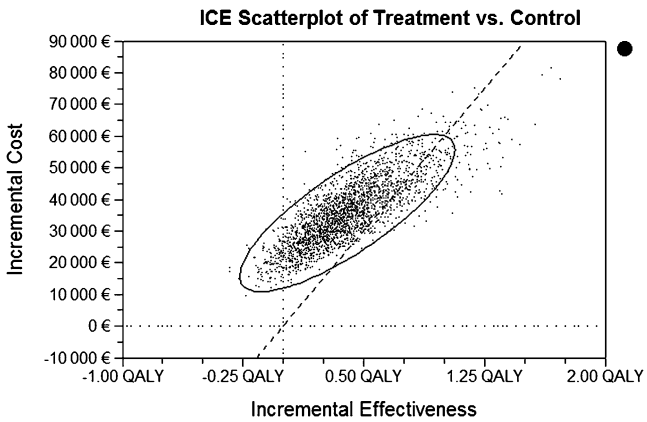

Figure 3. Monte Carlo for women with mean body weight of 66 kg and a body surface of 1.67–1.78 m^2. ICE, incremental cost effectiveness.

discussion

The addition of trastuzumab to capecitabine alone as a second-line treatment of HER2+ MBC patients who progress under trastuzumab-containing first-line chemotherapy results in a gain of 0.35 QALYs, based on the BIG 03-05 study and according to our model. This survival advantage is associated with an additional lifetime cost of €27 502–€41 456 per patient, resulting in an average ICER of ∼€98 500/QALY gained (range €79 581–119 960/QALY according to BW). The additional costs associated with the combination treatment are mainly the acquisition costs of trastuzumab, whereas the cost of administration and treatment of side-effects is negligible.

Available cost-effectiveness data on anti-HER2-directed drugs for MBC are limited. Norum et al. [12] published an analysis on trastuzumab for the first-line use from the perspective of the Norwegian health care system (with an ICER ranging from €63 137 to €162 417). For lapatinib use in the second line of treatment, Le and Hay [16] reported an ICER of USD 166 113 (€110 184), based on the clinical trial by Geyer et al. [4]. Le and Hay carried out their cost-utility analysis for the USA health care system. Although the inclusion criteria for this study and the BIG 03-05 study were similar, baseline characteristics of the included patients differed. For example, median age in the capecitabine-alone arm of the lapatinib trial was 51 years compared with 59 years in the trastuzumab trial. The percentage of patients with hormone receptor-positive cancers in the control arms was 47% versus 62%, respectively [4, 10]. The resulting median time for progression was shorter in the capecitabine-alone arm of the lapatinib trial (4.4 months) compared with the trastuzumab trial (5.6 months), reflecting the fact that patients with more aggressive breast cancers were included. Compared with targeted first-line treatment of HER2-negative cancers with bevacizumab (ICER of €189 500/QALY gained), our results for trastuzumab beyond progression are substantially more favorable [23].

Table 4. Base-case incremental cost-effectiveness ratios

BS-BW	Strategy	Costs, €	Incremental costs, €	Effect	Incremental effect	Cost/effect	ICER	Probability cost-effective[a], %
66 kg, 1.67–1.78 m^2	Control	23 217		2.06 YR		€11 253/YR		
	Treatment	57 198	33 980	2.64 YR	0.58 YR	€21 654/YR	58 762 €/YR	
	Control	23 217		1.17 QALY		€19 854/QALY		
	Treatment	57 198	33 980	1.51 QALY	0.35 QALY	€37 756/QALY	98 329 €/QALY	11.98
51 kg, 1.39–1.52 m^2	Control	22 263		1.17 QALY		€19 038/QALY		
	Treatment	49 764	27 502	1.51 QALY	0.35 QALY	€32 849/QALY	€79 581/QALY	26.94
58 kg, 1.53–1.66 m^2	Control	22 899		1.17 QALY		€19 582/QALY		
	Treatment	53 462	30 563	1.51 QALY	0.35 QALY	€35 290/QALY	88 439 /QALY	18.5
75 kg, 1.79–1.92 m^2	Control	23 535		1.17 QALY		€20 127/QALY		
	Treatment	61 228	37 692	1.51 QALY	0.35 QALY	€40 416/QALY	€109 070 /QALY	7.66
84 kg, 1.93–2.06 m^2	Control	23 853		1.17 QALY		€20 399/QALY		
	Treatment	65 309	41 456	1.51 QALY	0.35 QALY	€43 110/QALY	€119 960 /QALY	4.76

[a]Probabilistic sensitivity analysis.

BW, mean body weight; BS, body surface; ICER, incremental cost-effectiveness ratio.

In probabilistic sensitivity analysis, the probability to meet a willingness-to-pay threshold of €60 000 was between 4.7% and 26.9%, depending on the BSA and weight of the patients analyzed. HRs for time from progression to death and for TtP were the most influential parameters in univariate sensitivity analysis, driven by relatively wide CIs due to limited patient numbers in the BIG 03-05 study. They impacted on cost but more strongly on clinical effect estimates, i.e. the denominator of the cost-effectiveness formula. The median number of treatment cycles in the trastuzumab plus capecitabine arm was second-most influential. Considering that the BIG 03-05 study showed a substantial clinical benefit and that we found, for the continuation of trastuzumab beyond progression, a 5%–27% probability of cost-effectiveness better than the threshold of €60 000/QALY, the ICER range of €79 581–119 960/QALY should be interpreted with care. Judging the BIG 03-05 study only in relation to costs may undervalue the results of the study. It would, e.g. be relevant to calculate a parallel set of ICER results using patient-derived instead of general population-based health state valuations. However, this is currently precluded by a lack of appropriate input data.

An additional scenario analysis showed that decreasing the cost of trastuzumab by 30%–60% (depending on BW and BSA) would result in ICERs below the threshold of €60 000/QALY.

Reliance on data from a single randomized clinical trial [10] is the most important limitation of this analysis. The BIG 03-05 study, on which this cost-utility analysis had to rely on, had some particular limitations. For example, the initial protocol intended to randomly assign 482 patients in total but the trial was closed with 156 patients only [30]. One reason was the slow study accrual of patients and the other the early closure of the trial due to the availability of the lapatinib plus capecitabine data [4, 30]. Furthermore, another main criticism of this study is a possible investigator bias as responses or progressions defined by the RECIST criteria lacked independent assessment of responses [30]. Nevertheless, this trial is the best available evidence on which continuation of trastuzumab administration despite progression, a commonly practiced approach, can be based. Given that new anti-HER2-directed treatments are

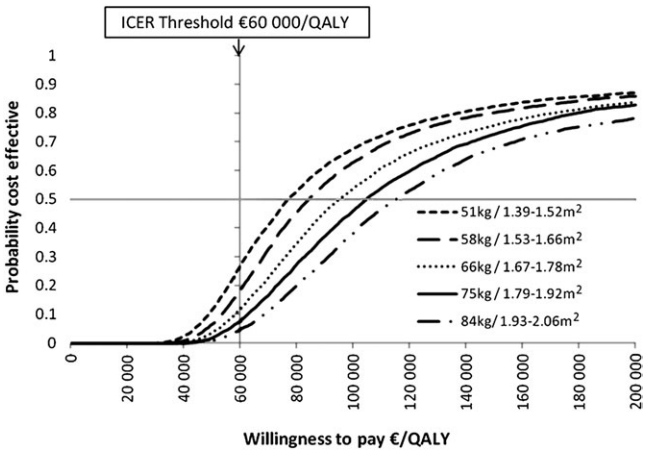

Figure 4. Acceptability curve for all body weight/body surface groups. ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

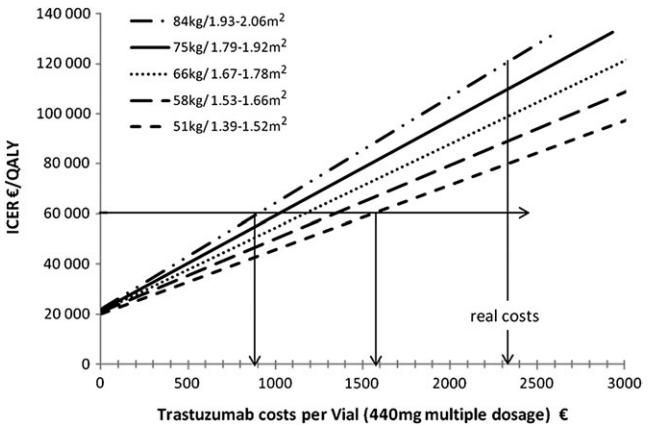

Figure 5. Costs of trastuzumab to be cost-effective, all body weight–body surface groups. ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

beginning to be tested for these patients [31], no further randomized, controlled trial-based evidence on continuation of trastuzumab treatment beyond progression is expected to be published in the near future. In the absence of additional trial data, a relevant amount of uncertainty remains. It should also be kept in mind that randomized clinical trial-based cost-effectiveness results may overestimate real-world effectiveness.

Some model input data had to be based on assumptions due to a lack of published data. For example, 58.9% of the patients in the capecitabine group and 57.3% in the capecitabine plus trastuzumab group had dose reductions for capecitabine. The extent and time of dose reduction in both groups, however, were not reported. Therefore, we assumed no difference between study arms and implemented no correction in the model.

When implications of cost-effectiveness and cost-utility results for reimbursement decisions are discussed, reference to cost-effectiveness thresholds (compared with different interventions or based on societal willingness-to-pay) is usually made. However, in Switzerland as well as most other countries, no such thresholds have formally been defined. In the USA threshold values of USD 50 000–100 000 per QALY gained are usually regarded as acceptable [32–34]. Taking into account differences in purchasing power, this range is roughly equivalent to CHF 50 000–100 000 (mean exchange rate 2009) or €32 900–65 800/QALY gained in Switzerland [35]. This threshold corresponds to 0.9–1.8 times the Swiss gross domestic product *per capita*. In the UK a factor of 1.4–2.1 times the gross domestic product *per capita* has tentatively been estimated as the threshold being used by the National Institute of Clinical Excellence.

In conclusion, in the patient group studied, administration of trastuzumab and capecitabine after progression under trastuzumab-containing chemotherapy is more expensive than what is typically regarded as cost-effective. The cost-effectiveness ratios identified, however, fall within the value ranges found for established regimens in the treatment of MBC, such as first-line trastuzumab plus chemotherapy, as well as second-line lapatinib plus chemotherapy, and are more cost-effective than first-line bevacizumab.

funding

Swiss government.

acknowledgements

We thank Gunter von Minckwitz, Neu-Isenburg, Germany, for kindly supporting us in collecting clinical data.

disclosure

The authors declare no conflict of interest.

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