EUROPEAN JOURNAL OF CANCER 45 (2009) 1397–1406

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Bevacizumab in combination with paclitaxel for HER-2 negative metastatic breast cancer: An economic evaluation

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ARTICLE INFO

Article history:
Received 5 October 2008
Received in revised form 1 December 2008
Accepted 12 December 2008
Available online 13 January 2009

Keywords:
Bevacizumab
Metastatic breast cancer
Cost-effectiveness
Quality of life

ABSTRACT

The addition of bevacizumab to weekly paclitaxel as primary chemotherapy for HER-2 negative metastatic breast cancer (MBC) prolongs progression-free survival without a substantial increase of toxicity.

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 E2100 clinical trial. Direct costs were assessed from the perspective of the Swiss health system.

The addition of bevacizumab to weekly paclitaxel is estimated to cost an additional 40,369€ and to yield a gain of 0.22 quality-adjusted life years (QALYs), resulting in an incremental cost-effectiveness ratio of 189,427 €/QALY gained. Probabilistic sensitivity analysis showed that the willingness-to-pay threshold of 60,000€ was never reached.

The addition of bevacizumab to paclitaxel in MBC patients is expensive given the clinical benefit in terms of QALYs gained.

1. Introduction

Antibody-based targeted therapies have brought forward the approach to breast cancer treatment. Trastuzumab, a humanised monoclonal antibody that targets HER-2, has become the standard for HER-2 over-expressing early and metastatic breast cancer and prolongs both progression-free survival and overall survival.[1] Recently, bevacizumab, a humanised monoclonal antibody targeting vascular endothelial growth factor (VEGF), has been approved in combination with chemotherapy for metastatic breast cancer not expressing HER-2. VEGF, the ligand to the VEGF receptor, plays a central role in promoting tumour angiogenesis.[2] Similarly to HER-2, over-expression of VEGF leads to poor outcomes in patients with breast cancer. Preclinical studies have shown that bevacizumab can reduce tumour angiogenesis, and inhibit the growth of breast cancer, either alone or in combination with chemotherapy. Table 1 provides an overview of the randomised phase III trials studying bevacizumab in this indication. In a randomised phase III trial conducted in pre-treated breast cancer patients, the addition of bevacizumab to capecitabine resulted in a significant increase in response rates (19.8% versus 9.1%) and was well tolerated.[3] However, this did not translate into improved progression-free survival

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doi:10.1016/j.ejca.2008.12.016

Table 1 – Summary of published randomized controlled trials of bevacizumab in metastatic breast cancer.

Trial	Miller (2005[3])	Miller (2007[4])	Miles (2008[5])	
Number of patients	462	722	736	
Experimental arm	Bevacizumab 15 mg/kg q3w + capecitabine 2500 mg/m^2/d × 1–14 q3w	Bevacizumab 10 mg/kg d 1.15 q4w + paclitaxel 90 mg/m^2 1815 q4w	Bevacizumab 7.5 mg/kg + docetaxel 100 mg/m^2 q3w	Bevacizumab 15 mg/kg + docetaxel 100 mg/m^2 q3w
Control arm	Capecitabine 2500 mg/m^2/d × 1–14 q3w	Paclitaxel 90 mg/m^2 1815 q4w	Docetaxel 100 mg/m^2 q3w	Docetaxel 100 mg/m^2 q3w
Median progression-free survival, month	4.86 versus 4.17	11.8 versus 5.9	8.7 versus 8.0	8.8 versus 8.0
Hazard ratio	0.98	0.6	0.69	0.61
P-value	0.857	<0.001	0.0035	0.0001
Median overall survival, month	15.1 versus 14.5	26.7 versus 25.2	Not reported	Not reported
Hazard ratio		0.88		
P-value	ns	0.16		

(4.86 months versus 4.17 months) or overall survival (15.1 months versus 14.5 months).

More encouraging results came from the E2100 randomised phase III trial examining bevacizumab in addition to paclitaxel weekly as primary therapy for metastatic breast cancer.[4] The addition of bevacizumab to paclitaxel alone significantly prolonged progression-free survival (11.8 months versus 5.9 months), although not overall survival (26.7 months versus 25.2 months) (Table 1). Furthermore, interim data on a phase III trial studying bevacizumab in combination with docetaxel were recently presented at a major conference.[5] The reported hazard ratio for disease free survival in the bevacizumab arm was encouraging; however, data for overall survival are immature yet. Although further phase III trials of bevacizumab for metastatic breast cancer are underway, market approval for the treatment of primary metastatic breast cancer in combination with paclitaxel has already been granted in many countries.

Cancer treatment costs have been increasing rapidly during the past years and will continue to do so.[6] Some expensive cancer therapies with small clinical benefits have become accepted treatments.[7] The introduction of novel and expensive systemic therapies together with the increasing prevalence of cancer in an ageing population requires allocating the available resources as efficiently as possible.

When the implications of cost-effectiveness and cost-utility results for reimbursement decisions are discussed, reference to cost-effectiveness thresholds (derived from comparison of different interventions or based on societal willingness-to-pay) is usually made. However, neither Switzerland nor other countries have formally defined such thresholds. In analyses for the USA, threshold values of USD 50,000–100,000 per QALY gained are usually regarded as acceptable.[7–10] If differences in purchasing power are taken into account, this range is roughly equivalent to CHF 50,000–100,000 (€31,000–62,000) per QALY gained in Switzerland.[11] This threshold corresponds to 0.9–1.8 times the Swiss gross domestic product (GDP) *per capita* while the use of a factor of 1.4–2.1 times the GDP *per capita* has been tentatively estimated for the United Kingdom (UK).

The cost-effectiveness of bevacizumab in metastastic breast cancer has not yet been examined. The objective of this analysis was to examine the cost-effectiveness of bevacizumab for primary metastatic breast cancer from the perspective of the Swiss health care system and to compare it with a willingness-to-pay threshold of 60,000€ per QALY gained.

2. Materials and methods

We constructed a Markov model to assess the cost-effectiveness of the addition of bevacizumab (Bev) to paclitaxel (Pac) alone as primary chemotherapy for HER-2 negative metastatic breast cancer (MBC), from the perspective of the Swiss health system. The time horizon of the analysis was life-long. Modelling of time from treatment start to disease progression and time from disease progression to death was based on the survival data from the E2100 clinical trial.[4] Direct medical costs (based on Swiss national tariffs) of chemotherapy treatment, major adverse events, laboratory tests and disease progression were taken into account. Costs were assessed from the perspective of the Swiss health system. Consequently, indirect costs were not considered. Costs are reported in 2008 Euros (€). An exchange rate of 1€ = CHF 1.62 was used. Utilities for health states were obtained from the literature. Costs and benefits were not discounted given the short life expectancy of this patient population.

The treatment strategies compared were equivalent to those used in the E2100 study. Patients were included into this trial if they had histologically or cytologically proven metastatic breast cancer and had not received previous cytotoxic therapy for metastatic disease. Previous hormonal treatment for metastatic disease or adjuvant cytotoxic chemotherapy and concurrent bisphosphonate administration were allowed. Exclusion criteria were ECOG performance status $\geqslant 2$ or central nervous system involvement.[4] HER-2 positive metastatic breast cancer was not a formal exclusion criterion but was hardly represented in this trial. Only 1.4% of patients in the experimental arm and 0.9% in the control arm were HER-2 positive. Further information on trial design, eligibility criteria and results can be obtained from the original E2100 trial publication.[4]

The patients enrolled into this study were randomised to receive 90 mg of Pac per square metre body-surface area

(mg/m^2 BSA) on days 1, 8 and 15 of a four-weekly cycle, either alone or in combination with 10 mg of Bev per kg body weight on cycle days 1 and 15. The Pac alone strategy represents an accepted standard in the treatment of MBC.[12] Patients received the assigned therapy until disease progression or until prohibitive toxic effects occurred. Patients in the Bev + Pac arm without disease progression but who discontinued Pac due to toxic effects could continue on Bev monotherapy. Patients in the Pac alone arm could not receive Bev at any time.

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 adding Bev to Pac alone treatment for metastatic breast cancer. In the present case, the resulting ICERs were compared with a willingness-to-pay threshold of 60,000 €/QALY.

Secondary outcome measures were ICERs for different age groups. The effect of different Bev doses on the ICER was assessed under the simplifying assumption of no change in clinical effectiveness. This assumption is supported by the interim data of a phase III trial showing a comparable disease free survival in patients receiving 7.5 mg q2w or 15 mg q3w of Bev per kg body weight.[5]

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

2.1. Model structure

The structure of the Markov model is shown in Fig. 1. The model comprised three mutually exclusive health states: stable/responsive disease, disease progression and death (see Fig. 1). Cycle length was one month. At model entry, all the patients were in the stable/responsive disease state. At the end of each cycle, they could remain stable or develop disease progression. Patients with progressive disease could remain in this state or die. Transition probabilities were estimated using the clinically observed median time in a given state, using the formula[13,14]:

$$\text{Transition probability} = 1 - 0.5^{(1/\text{median time in state})}$$

2.2. Model inputs

2.2.1. Clinical data

The effectiveness data used in the modelling were based on the E2100 study.[4] Median progression-free survival and overall survival were directly extracted from the main trial publication. Median time from progression to death and survival data by age group were kindly provided by the authors (personal communication Kathy Miller, see Table 4). Data on the frequency or number of patients with Pac dose reductions were not available. We, therefore, assumed that patients with Pac discontinuation did not restart on a lower dosage of Pac at a later point in time, as in clinical practice, chemotherapy is usually switched to another chemotherapeutic agent instead of awaiting the resolution of neuropathy. Major adverse events with statistically significant differences in frequency of occurrence, such as hypertension, infections and cerebrovascular ischaemia, were accounted for in the model (see Table 3).

2.2.2. Utilities

Preference-based utility scores for stable and progressive disease, derived from a Canadian population using the time trade-off technique, were taken from the literature.[15] For stable disease, the utility used was 0.61. As the limited quality of life data from the E2100 trial showed no influence on quality of life for the treatment combination of Pac + Bev, this utility was applied for stable disease in both arms.[4] The utility for progressive disease was 0.26.

2.2.3. Medical resource use

Assessment of medical resource use was based on the E2100 trial and on a study of the resource use and cost for patients with metastatic breast cancer conducted at the University Hospital of Zurich.[4,16] The types of medical resources considered in the model were study medication (including prescription, preparation and administration), concomitant medication during chemotherapy, laboratory tests, medical resources used due to disease progression, and medical resources used due to major adverse events (Tables 2 and 3).

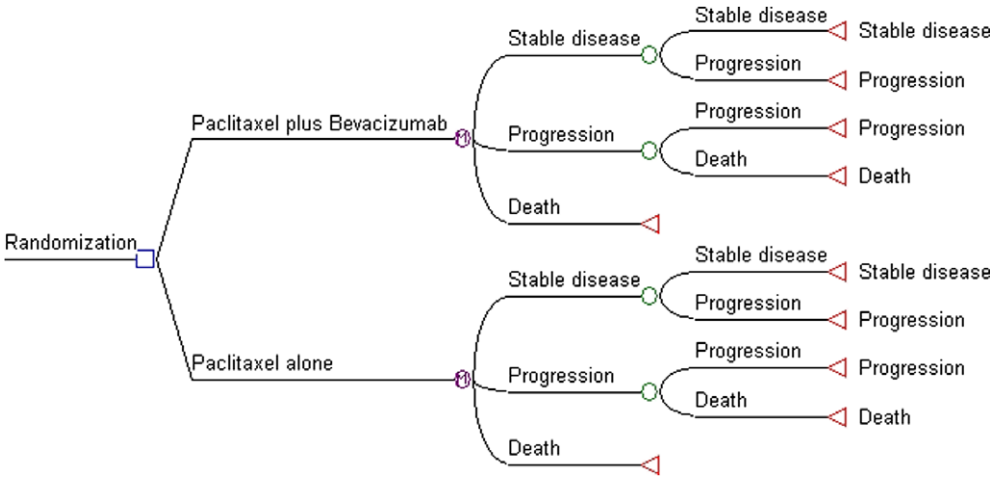

Fig. 1 – Structure of Markov model.

Table 2 – Medical resource use and cost data.

Type of resource	Dosage or units per 28 d	Units per month	Vials required and cost per-vial	Cost[d] per unit (€)	Cost per month (€)
Bevacizumab,10 mg/kg body weight	2 times 650 mg[a]	2.17	3 vials à 100 mg 410.46€/vial 1 vial à 400 mg 1404.91€/vial 3.77€/mg[c]	2447.99	5303.92
Paclitaxel,90 mg/m^2 body-surface	3 times 154.8 mg[b]	3.25	2 vials à 30 mg 54.23€/vial 1 vial à 100 mg 154.91€/vial 1.65€/mg[c]	254.80	828.11
Chemotherapy prescription and preparation	3	3.25		€ 25.49	82.85
Chemotherapy administration	3	3.25		€ 52.90	171.93
Antiemetics, steroids inclusive of infusion	3	3.25		€ 74.07	240.74
Nadir blood count	1	1.08		€ 89.24	96.68
Total bevacizumab + paclitaxel arm	6724.23 €				
Total paclitaxel arm	1420.31 €				
Treatment during progression[16]		1		1109.26	1109.26

a Assuming a bodyweight of 65 kg.
b Assuming a bodyweight of 65 kg and height of 1.64 m, resulting in a body-surface area of 1.72 m^2.
c The central pharmacies of most swiss hospitals deliver the exact amount of paclitaxel and bevacizumab in mg per patient, i.e. no waste occurs.
d Swiss national tariff list (tarmed),[19] analysenliste,[20] arzneimittelkompedium.[18]

Table 3 – Frequency and costs of adverse events.

Adverse events[a]	Patient incidence in Bev + Pav arm[4] (%)	Patient incidence in Pac arm[4] (%)	Cost	Further assumptions on occurrence
Hypertension	14.80	0	39.44€/month[18]	From second cycle on
Infection	9.30	2.90	61.73€/occurrence[18]	Once per time in stable/responsive disease
Cerebrovascular ischaemia	1.90	0	56370.00€/occurrence[28]	Once per time in stable/responsive disease

a Adverse events which showed statistically significant differences between the treatment arms of the E2100 trial.[4]

Treatment of adverse events was only considered for side-effects which showed statistically significant differences in occurrence between the treatment arms of the E2100 trial. Calculation of Bev and Pac dosages assumed a typical patient with a body weight of 65 kg and a height of 1.64 m, resulting in a body-surface of 1.72 m^2.[17] The treatment schemes of the E2100 study were based on a cycle length of 28 d. In order to achieve a harmonisation with the cycle length of the

Table 4 – Median progression-free survival, overall survival and treatment time: comparison of model outputs and published E2100 study results.[4]

	Treatment arm		All	Age 27–49	Age 50–64	Age 65–85
Overall survival, months	Paclitaxel	Base case	25.22	24.80	25.20	25.61
		Study E2100	25.2	24.8	25.2	25.6
	Paclitaxel + bevaczumab	Base case	26.74	28.71	29.42	20.82
		Study E2100	26.7	28.7	29.4	20.8
Progression-free survival, months	Paclitaxel	Base case	5.92	5.51	6.74	7.91
		Study E2100	5.9	5.5	6.7	7.9
	Paclitaxel + bevacizumab	Base case	11.84	12.56	11.34	11.90
		Study E2100	11.8	12.5	11.3	11.9
Time treated in progression-free/stable, month	Paclitaxel	Base case	5.12	4.76	5.82	6.84
		Study E2100	5.1	Not available		
	Paclitaxel + bevacizumab	Base case	7.13	7.56	6.82	7.17
		Study E2100	7.1	Not available		

model, we implemented an adjustment to ensure correct assessment of resource use per month (resource use per 28 d * 30.33/28), assuming that the mean number of days per month is 30.33.

In the E2100 study, the actual treatment times with Pac and Pac + Bev were shorter than the observed progression-free survival times. Treatment duration was therefore corrected to fit the real data. For the Pac + Bev group the median treatment time was 7.1 months (60.2% of time in stable disease), followed by Bev monotherapy for 3 months in 21% of the patients. For the Pac group the median treatment time was 5.1 months (86.4% of time in a stable disease).

2.2.4. *Unit costs*

Unit costs were taken from Swiss national drug price and tariff lists.[18–20] As most of the central pharmacies in the Swiss hospitals treating breast cancer patients provide the exact amount of drug required and as any leftovers are saved for later use, no waste occurs. Therefore, the cost of Bev and Pac could be based on a simple multiplication of absolute dose in mg and drug price in EUR/mg. The drug price per mg was calculated as a weighted average of vial size-specific prices per mg, based on the vials needed for a woman with a body weight of 65 kg and a height of 1.64 m. The monthly costs of treatment after disease progression were based on the total resource use observed during the first 5 years of treatment for patients with metastatic breast cancer, in the above-mentioned study at the University Hospital of Zurich.[16] This single centre experience is the best currently available Swiss source on this topic, and the costs are comparable to data from other health care systems.[21,22]

2.3. *Sensitivity analysis*

In order to assess the impact of statistical uncertainty around key model inputs, we performed a series of univariate sensitivity analyses and probabilistic sensitivity analysis. Scenario analyses were used to assess the impact of additional assumptions not primarily related to statistical uncertainty.

2.3.1. *Univariate sensitivity analysis*

In univariate sensitivity analysis, we varied the median survival times and utility parameters, the costs of the main treatment strategies and of follow-up treatment, treatment duration (which according to the E2100 study was shorter than the time spent in a stable disease), and the proportion of patients in the Pac + Bev strategy, who received Bev monotherapy after Pac was discontinued. The frequency of occurrence of the adverse effects of hypertension, infection and cerebrovascular ischaemia was also varied. As no confidence intervals were available for most of these parameters, their base case values were varied by ±30%. Median time to progression and median time from progression to death, as key input parameters, were varied by ±50%.

2.3.2. *Probabilistic sensitivity analysis*

Probabilistic sensitivity analysis (second-order Monte Carlo simulation) was based on triangular distributions for all parameters. The lower and upper values of these distributions corresponded to the ranges of variation used in a univariate sensitivity analysis. The probabilistic analysis was conducted in two ways. Initially, parameter values were simultaneously sampled from all probability distributions. Subsequently, the median times to progression and from progression to death for the Pac strategy were kept constant at their base case values. The reason for this second analysis was that the transition probabilities for the Pac + Bev arm were modelled independently from the Pac alone arm, as relative risk estimates were not available. Therefore, independently varying the transition probabilities for both arms may have resulted in an overestimation of variability.

2.3.3. *Additional scenarios*

Sub-group analyses by age group were also performed after estimating transition probabilities from the progression-free and overall survival data observed in the E2100 study, as described above.

As the model's clinical input parameters were derived from the results of a single trial, uncertainty around the time from progression to death, which was much shorter in the Bev + Pac arm of the E2100 study than in the Pac alone arm, may be an important issue. Therefore, an alternative analysis assumed the time from progression to death to be the same in both arms.

The per-vial costs of Bev were not subject to parameter uncertainty, but as the body weight of patients differs, we performed additional scenario analyses to assess the effect of body weight on the ICER. Body weight was varied from 45 kg to 85 kg. For simplicity, only body weight effects on the costs of Bev were analysed.

Finally, the effect of reducing the Bev dosage was evaluated under the simplifying assumption of no changes in clinical effectiveness.

2.4. *Model validation*

The model was calibrated to match the original survival results of the E2100 study. Trackers for progression-free survival, overall survival and treatment time were included in the model to check for the correct reproduction of the original data. In addition, all model outputs were reviewed for plausibility and key input parameters were subjected to extreme variation to check if the model outputs behaved as expected.

2.5. *Technical implementation*

The model was implemented and all Markov cohort and Monte Carlo analyses were performed using TreeAge Pro 2008 Suite® (TreeAge Software Inc., Williamstown, MA, USA). Further analyses were performed using SAS 9.1® (SAS Institute Inc., Cary, NC, USA). Probabilistic sensitivity analyses were based on five thousand sets of randomly drawn input parameters.

3. Results

3.1. *Model validation*

After calibration, the model outputs matched the original clinical data of the E2100 study, as shown in Table 4.

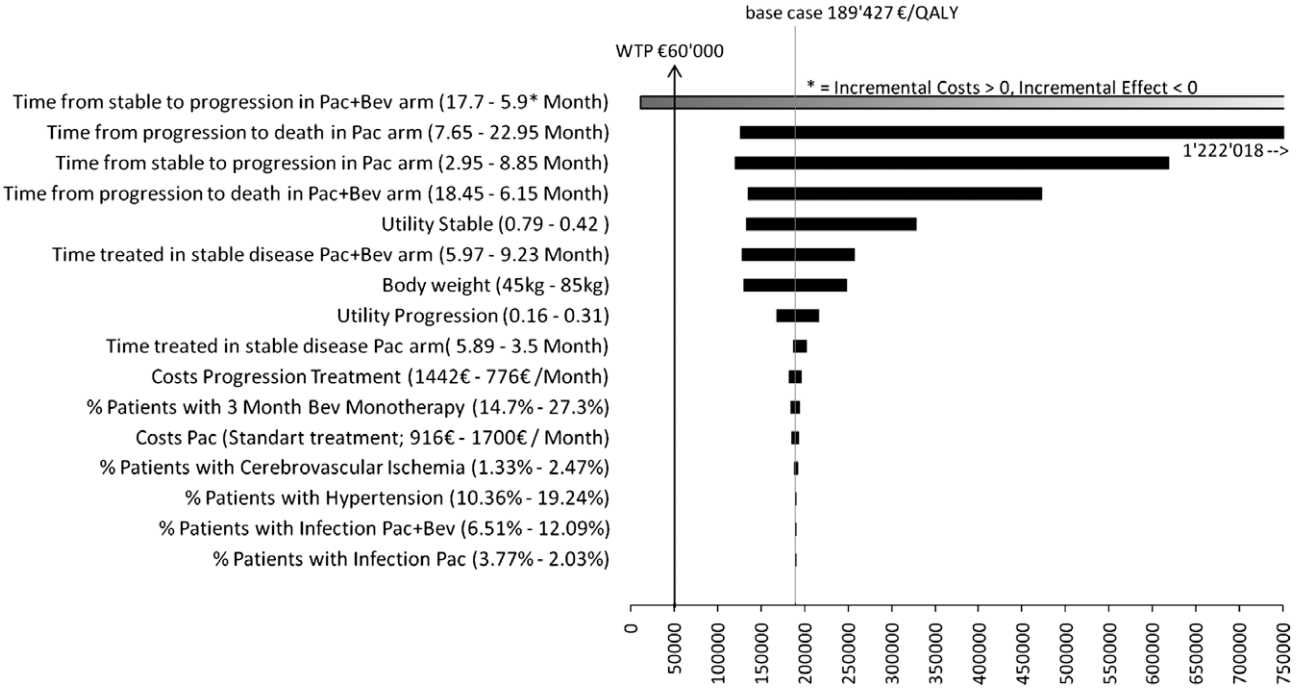

Fig. 2 – Tornado plot of the one-way sensitivity analysis for all parameters.

3.2. *Base case analysis*

In the base case analysis, the model indicated that the addition of Bev to Pac alone treatment would lead to a gain of 0.21 QALYs per patient at an additional cost of € 40,369. The incremental cost-effectiveness ratio (ICER) for Pac + Bev versus Pac alone was € 189,427 per QALY gained.

3.3. *Sensitivity analysis*

Varying time to progression in the Pac + Bev arm led to domination of the Pac + Bev strategy (incremental costs >0, incremental effect <0) when the lowest parameter values were used. For the longest time from stable to progression (17.7 months), however, an ICER of 11,502€ was achieved, which is below the WTP if 60,000€. The other univariate sensitivity analysis results are summarised in a Tornado diagram (Fig. 1). Variation of time to progression and time from progression to death in the Pac alone arm had the second-biggest influence overall, while variation of the percentage of patients with diverse adverse events and of the costs for the Pac standard treatment had only marginal impact. Except for varying the time from stable to progression in the Pac + Bev arm, none of the other performed analyses resulted in an ICER below the

Table 5 – Base case model analysis, all ages.

Strategy	Costs €	Progression-free, month	Overall survival, month	QALYs	ICER €/QALY
Pac	28,673	5.92	25.22	0.69	
Pac + Bev	69,042	11.84	26.74	0.90	
Incremental	40,369	5.92	1.52	0.21	189,427

Table 6 – Sub-group analysis according to age groups.

	Treatment	Age 27–49	Age 50–64	Age 65–85
Costs €	Pac	28,161	28,752	29,344
	Pac + Bev	73,326	70,539	62,605
	Incremental	45,165	41,788	33,262
Effect QALY	Pac	0.67	0.71	0.76
	Pac + Bev	0.96	0.94	0.78
	Incremental	0.30	0.23	0.03
ICER €/QALY		152,894	184,823	1,226,615

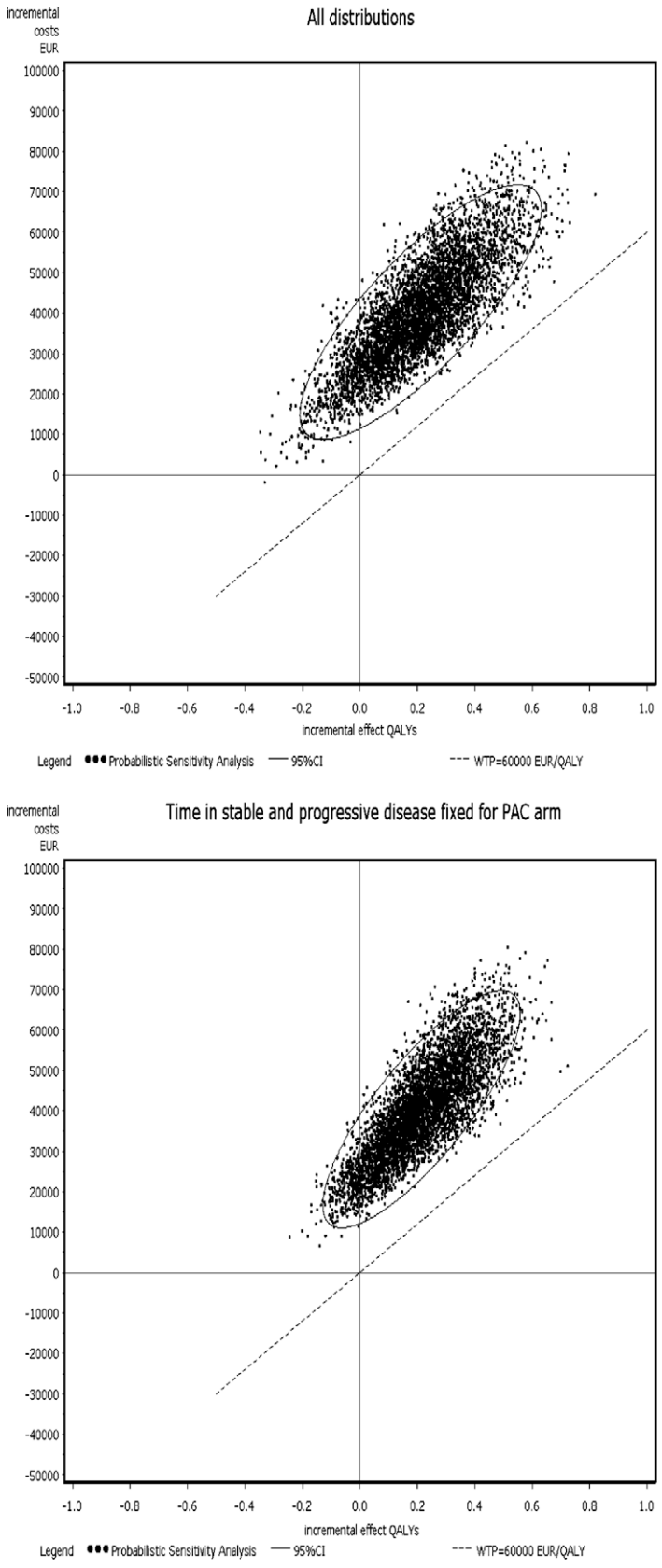

Fig. 3 – Probabilistic sensitivity analysis without and with fixing time in stable and progressive disease for the Pac arm.

WTP threshold of 60,000 €/QALY. Probabilistic sensitivity analysis with and without fixing median time to progression and median time from progression to death in the Pac arm, for all ages combined and for three separate age groups, always re-

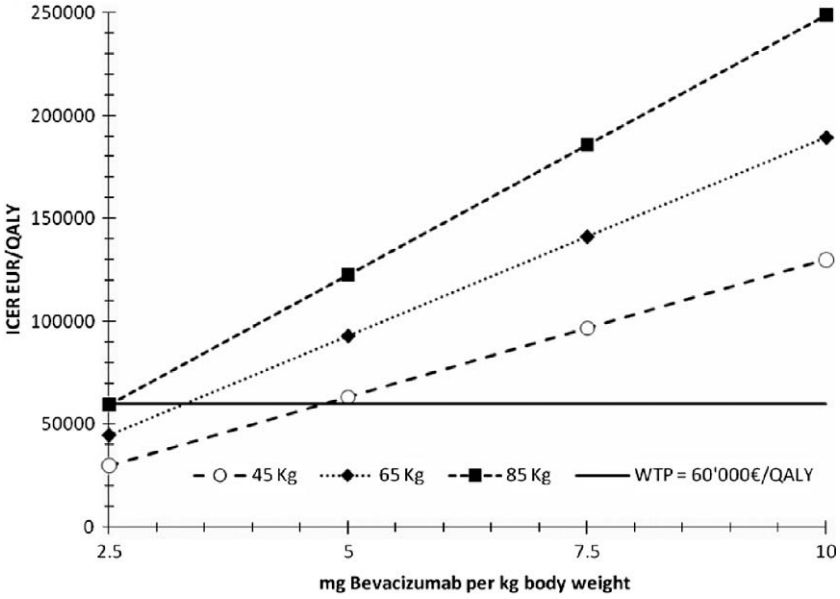

Fig. 4 – Effect of reducing Bev dosage on the ICER for women with different body weights.

sulted in 0% of the cases meeting the 60,000 €/QUALY willingness-to-pay threshold (Fig. 2). Fixing the median times to event for the Pac arm resulted in a narrowing of the range of ICERs seen (see Table 5).

3.4. *Additional scenarios*

3.4.1. *Sub-group analysis*

The results for different age groups are shown in Table 6. Although younger patients incurred the highest costs they also showed the greatest difference in effect (QALYs gained), resulting in an improved ICER (152,894 €/QALY). The highest age group showed a very high ICER (1,226,615 €/QALY) due to a minimal gain in QALYs.

3.4.2. *Assumption of no difference in time from progression to death*

The alternative model assuming the same time from progression to death in both arms decreased the base case ICER (all ages) to 150,369 €/QALY (incremental effect, 0.30 QALYs; incremental cost, € 45,274), with 0% of the cases in the probabilistic sensitivity analysis meeting the willingness-to-pay threshold.

3.4.3. *Effect of body weight and dosage*

Body weight and thereby the amount of Bev given per administration resulted in ICER value ranging from 130,001 €/QALY for women with a weight of 45 kg to 248,853 €/QALY for women with a weight of 85 kg. Reducing dosages to 7.5, 5 and 2.5 mg/kg body weight had a strong influence on the ICER as shown in Fig. 4. Very low dosages may result in ICER values below the WTP threshold of 60,000 €/QALY.

4. Discussion

The addition of Bev to Pac alone as primary treatment of HER-2 negative metastatic breast cancer, based on the E2100 trial, results in a gain of 0.21 QALYs or 2.5 quality-adjusted life months according to our model. This survival advantage is associated with monthly additional costs of approximately €5000 for Bev compared to the cost of Pac alone. Given the favourable side-effect profile of Bev, costs for treatment of side-effects are negligible in the combination treatment (Fig. 2). Overall, however, the resulting ICER of 189,500 € per QALY gained is high and above the commonly accepted thresholds for new health care interventions. The ICER is higher than that of trastuzumab treatment for metastatic breast cancer 63,137 € to 162,417 € reported by Norum et al.[23] Trastuzumab has been introduced into the routine clinical practice in developed countries despite the high costs. Cost-effectiveness analyses on Bev in breast cancer have not yet been published, but for the treatment of advanced non-small cell lung cancer Grusenmeyer and Gralla have concluded that combination treatment with Bev is not cost-effective given the cost-effectiveness of 350,000 USD per life year gained.[24]

In the probabilistic sensitivity analysis, the willingness-to-pay threshold of 60,000 € was never met (Fig. 3). The most influential parameters in univariate sensitivity analysis were the clinical end-points in terms of progression-free survival and post progression survival. In the E2100 trial, patients in the Bev arm were significantly longer progression-free than those in the Pac alone arm. Survival post progression, however, was unexpectedly poorer in the combination arm so that the overall survival remained equal in both arms. So far no convincing explanation is available for this fact, except that Bev pre-treated patients may respond less to second-line palliative chemotherapy. An effect of different second-line therapies or a crossover effect, where patients in the control arm would have received Bev as second-line chemotherapy, cannot be excluded. However, according to the E2100 trial publication, patients assigned to Pac monotherapy could not receive Bev at any time.[4] Furthermore, during the time of the E2100 trial, Bev use was not approved for metastatic breast cancer. In sensitivity analysis, we neutralised the find-

ing of a poorer post progression survival, by assuming equal post progression survival for both arms (Fig. 3), and this still resulted in a cost-utility ratio above €60,000 per QALY gained.

Younger patients showed a non-significant trend towards a better response to Bev treatment than older patients. On the basis of the age group-specific results of the E2100 study, the ICER improved for patients <50 years to 153,000 € per QALY but rose to 1,200,000 € per QALY in patients >65 years. From a clinical point of view, the underlying difference in response to Bev is not understood. Further research may elucidate if age or menopausal status are predictive of response to Bev treatment which would be of clinical as well as pharmaco-economic interest.

In the E2100 trial, Bev was administered at a dosage of 10 mg per kg of body weight q2w. Bev in combination with capecitabine for pre-treated metastatic breast cancer patients was administered at a dosage of 15 mg per kg of body weight q3w and in the ongoing trial studying Bev in combination with docetaxel, there is an arm with 7.5 mg and another with 15 mg per kg body weight q3w. In both arms there were no significant differences in disease free survival in interim analysis (Table 1). In contrast, in a phase II trial of Bev for metastatic colorectal cancer the low-dose regimen 5 mg/kg q2w seemed to be to be more efficient than the high-dose 10 mg/kg q2w.[25] In general, the optimal Bev dosage is still not clear for different cancer types as well as for breast cancer.[26,27] Therefore, we also examined how different Bev drug dosages influenced the ICER. Assuming equal efficacy we found that a dosage of around 3 mg per kg q2w might be cost-effective.

There are some limitations that need to be addressed regarding the present study. First of all the study is based on the efficacy and safety data of one single randomised trial and such results usually differ from what is seen in routine clinical practice. Further phase III trials with bevacizumab in breast cancer are underway studying other combination treatments (e.g. docetaxel and anthracyclines) but could not be included in this study as efficacy data are still immature. However, the interim results do not show any hints that assumptions and results of this study would go in a wrong direction. The quality of life data available from the E2100 trial were affected by missing values and the finding of no quality of life differences between the study arms, for patients in stable disease, may be of limited validity. Some input data (e.g. quality of life and costs) had to be extracted from the available literature or had to be based on assumptions, an approach that is very common in cost-effectiveness analyses but leads to limitations that must be understood. The sensitivity analyses performed aimed at quantifying the potential impact of these limitations and the resulting degree of variation did not affect the main conclusion.

In conclusion, the present study based on the E2100 trial and examining Bev in combination with Pac for primary treatment of metastatic breast cancer shows that this regimen is expensive if compared with common willingness-to-pay thresholds. However, this analysis is based on a single randomised trial with a limited amount of available detail. Therefore further pharmaco-economic studies are needed to fully assess the cost-effectiveness of Bev for metastatic breast cancer. If clinical trials can show that the administration of lower dosages of Bev results in equal efficacy, more cost-effective treatment strategies including Bev may emerge. Restriction of Bev use to patient subgroups with an above-average benefit (e.g. those <50 years) may also improve the cost-effectiveness of Bev in combination with Pac.

Conflict of interest statement

None declared.

Acknowledgements

The authors thank Kathy D. Miller, Indianapolis, and Molin Wang, Boston, for kindly supporting us in collecting clinical data.

REFERENCES

1. Hudis CA. Trastuzumab-mechanism of action and use in clinical practice. *New Engl J Med* 2007;**357**:39–51.
2. Banerjee S, Dowsett M, Ashworth A, Martin LA. Mechanisms of disease: angiogenesis and the management of breast cancer. *Nat Clin Pract Oncol* 2007;**4**:536–50.
3. Miller KD, Chap LI, Holmes FA, et al. Randomized phase III trial of capecitabine compared with bevacizumab plus capecitabine in patients with previously treated metastatic breast cancer. *J Clin Oncol* 2005;**23**:792–9.
4. Miller K, Wang M, Gralow J, et al. Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. *New Engl J Med* 2007;**357**:2666–76.
5. Miles D, Chan A, Romieu G, et al. Randomized, double-blind, placebo-controlled, phase III study of bevacizumab with docetaxel or docetaxel with placebo as first-line therapy for patients with locally recurrent or metastatic breast cancer (mBC): AVADO. *J Clin Oncol* 2008;**26**:LBA1011.
6. Meropol NJ, Schulman KA. Cost of cancer care: issues and implications. *J Clin Oncol* 2007;**25**:180–6.
7. Orsi C, Bartolozzi B, Messori A, Bosi A. Event-free survival and cost-effectiveness in adult acute lymphoblastic leukaemia in first remission treated with allogeneic transplantation. *Bone Marrow Transplant* 2007;**40**:643–9.
8. Hirth RA, Chernew ME, Miller E, Fendrick AM, Weissert WG. Willingness to pay for a quality-adjusted life year: in search of a standard. *Med Decis Making* 2000;**20**:332–42.
9. Tengs TO. Cost-effectiveness versus cost-utility analysis of interventions for cancer: does adjusting for health-related quality of life really matter? *Value Health* 2004;**7**:70–8.
10. Ubel PA, Hirth RA, Chernew ME, Fendrick AM. What is the price of life and why doesn't it increase at the rate of inflation? *Arch Intern Med* 2003;**163**:1637–41.
11. Schwenkglenks M, Lippuner K. Simulation-based cost-utility analysis of population screening-based alendronate use in Switzerland. *Osteoporosis Int* 2007;**18**:1481–91.
12. Seidman AD, Berry D, Cirrincione C, et al. Randomized phase III trial of weekly compared with every-3-weeks paclitaxel for metastatic breast cancer, with trastuzumab for all HER-2 overexpressors and random assignment to trastuzumab or not in HER-2 nonoverexpressors: final results of cancer and leukemia group B protocol 9840. *J Clin Oncol* 2008;**26**:1642–9.
13. Martikainen JA, Kivioja A, Hallinen T, Vihinen P. Economic evaluation of temozolomide in the treatment of recurrent glioblastoma multiforme. *Pharmacoeconomics* 2005;**23**:803–15.

14. Miller DK, Homan SM. Determining transition probabilities: confusion and suggestions. *Med Decis Making* 1994;**14**:52–8.
15. Leung PP, Tannock IF, Oza AM, Puodziunas A, Dranitsaris G. Cost-utility analysis of chemotherapy using paclitaxel, docetaxel, or vinorelbine for patients with anthracycline-resistant breast cancer. *J Clin Oncol* 1999;**17**:3082–90.
16. Dedes KJ, Szucs TD, Imesch P, Fedier A, Fehr MK, Fink D. Cost-effectiveness of trastuzumab in the adjuvant treatment of early breast cancer: a model-based analysis of the HERA and FinHer trial. *Ann Oncol* 2007;**18**:1493–9.
17. Bundesamt für Statistik. Schweizerischerische Gesundheitsbefragung, Bern, Switzerland; 2002.
18. Schweizerisches Arztneimittelkompendium. www.documed.ch [accessed on September 2008].
19. Swiss National Tariff Catalogue. www.tarmed.ch [accessed on September 2008].
20. Bundesamt für Gesundheit. Analysenliste. http://www.bag.admin.ch/themen/krankenversicherung/02874/index.html?lang=de#sprungmarke0_37 [accessed on September 2008].
21. Berkowitz N, Gupta S, Silberman G. Estimates of the lifetime direct costs of treatment for metastatic breast cancer. *Value Health* 2000;**3**:23–30.
22. Remak E, Brazil L. Cost of managing women presenting with stage IV breast cancer in the United Kingdom. *Brit J Cancer* 2004;**91**:77–83.
23. Norum J, Risberg T, Olsen JA. A monoclonal antibody against HER-2 (trastuzumab) for metastatic breast cancer: a model-based cost-effectiveness analysis. *Ann Oncol* 2005;**16**:909–14.
24. Grusenmeyer PA, Gralla RJ. Examining the cost and cost-effectiveness of adding bevacizumab to carboplatin and paclitaxel in advanced non-small cell lung cancer. *J Clin Oncol* 2006;**24**:6057.
25. Kabbinavar F, Hurwitz HI, Fehrenbacher L, et al. Phase II, randomized trial comparing bevacizumab plus fluorouracil (FU)/leucovorin (LV) with FU/LV alone in patients with metastatic colorectal cancer. *J Clin Oncol* 2003;**21**:60–5.
26. Haines IE, Miklos GL. Paclitaxel plus bevacizumab for metastatic breast cancer. *New Engl J Med* 2008;**358**:1637 [author reply 1637–1638].
27. Kerr DJ. Targeting angiogenesis in cancer: clinical development of bevacizumab. *Nat Clin Pract Oncol* 2004;**1**:39–43.
28. Levy E, Gabriel S, Dinet J. The comparative medical costs of atherothrombotic disease in European countries. *Pharmacoeconomics* 2003;**21**:651–9.