original article

Annals of Oncology 22: 567–574, 2011
doi:10.1093/annonc/mdq431
Published online 13 September 2010

Addition of cetuximab to first-line chemotherapy in patients with advanced non-small-cell lung cancer: a cost–utility analysis

M. Joerger[1]*, K. Matter-Walstra[2], M. Früh[1], U. Kühnel[3], T. Szucs[2], B. Pestalozzi[4] & M. Schwenkglenks[2]

[1]*Department of Oncology and Hematology, Cantonal Hospital, St Gallen;* [2]*Institute of Pharmaceutical Medicine, University of Basel, Basel;* [3]*Swiss Group for Clinical Cancer Research, Bern;* [4]*Department of Medical Oncology, University Hospital, Zurich, Switzerland*

Received 13 May 2010; revised 1 July 2010; accepted 5 July 2010

Background: Adding cetuximab to standard chemotherapy results in a moderate increase of overall survival in patients with advanced non-small-cell lung cancer (NSCLC), but the cost-effectiveness is unknown.

Materials and methods: A Markov model was constructed based on the results of the First-Line ErbituX in lung cancer randomized trial, adding cetuximab to cisplatin–vinorelbine first-line chemotherapy in patients with advanced NSCLC. The primary outcome was the incremental cost-effectiveness ratio (ICER) of adding cetuximab, expressed as cost per quality-adjusted life year (QALY) gained, and relative to a willingness-to-pay threshold of €60 000/QALY. The impact of cetuximab intermittent dosing schedules on the ICER was also evaluated.

Results: Adding cetuximab to standard chemotherapy leads to a gain of 0.07 QALYs per patient at an additional cost of €26 088. The ICER for adding cetuximab to chemotherapy was €376 205 per QALY gained. Intermittent cetuximab dosing schedules resulted in ICERs per QALY gained between €31 300 and €83 100, under the assumption of equal efficacy.

Conclusions: From a health economic perspective, the addition of cetuximab to standard first-line chemotherapy in patients with epidermal growth factor receptor-expressing advanced NSCLC cannot be recommended to date, due to a high ICER compared with other health care interventions. Treatment schedules resulting in more favorable cost–utility ratios should be evaluated.

Key words: cetuximab, chemoimmunotherapy, cost-effectiveness, non-small-cell lung cancer, qualy

introduction

Stages IIIB and IV non-small-cell lung cancer (NSCLC) account for ∼46% of newly diagnosed cases of this disease, and the 5-year overall survival (OS) rate for M1 distant disease is still very poor [1]. Cetuximab (Erbitux®; Merck KgA) is an IgG1 subclass chimeric mouse–human antibody that binds to the extracellular portion of epidermal growth factor receptor (EGFR), competing with its natural ligands and preventing activation of the receptor, and potentially inducing destruction of the receptor [2]. At present, cetuximab is approved for the treatment of locally advanced squamous cell carcinoma of the head and neck (SCCHN) in combination with radiotherapy [3], for recurrent or metastatic SCCHN after platinum-based therapy [4], and for EGFR-expressing, KRAS wild-type, metastatic colorectal cancer either alone [5] or in combination with irinotecan after standard chemotherapy [6]. Recently, the addition of cetuximab to standard platinum-based chemotherapy has been shown to result in a significant but moderate increase of the OS in patients with EGFR-overexpressing wet stage IIIB or stage IV NSCLC of 1.2 months (from 10.1 to 11.3 months) in a large randomized open-label study [7]. Cetuximab is given with a loading dose of 400 mg/m^2, followed by a weekly dose of 250 mg/m^2 until disease progression [3–7]. However, the issue of optimal dosing of anti-EGFR-targeted treatment is far from being resolved, and intermittent dosing might be more effective than continuous treatment, especially when given concurrently with chemotherapy [8, 9].

In 2009, the Committee for Medicinal Products for Human Use, part of the European Medicines Agency (EMEA), issued a negative opinion on the use of cetuximab in NSCLC, suggesting that benefits of using the drug to treat the disease did not outweigh its risks. However, the cost-effectiveness of adding cetuximab to standard platinum-based chemotherapy in the first-line treatment of advanced NSCLC has not been examined so far. At the same time, a recent study demonstrated cost-effectiveness of evidence-based treatment guidelines (including adjuvant and first-line chemotherapy treatment) of NSCLC in a community setting, and across a plausible range of

Correspondence to: Dr Markus Joerger, Department of Oncology and Hematology, Cantonal Hospital, Rorschacherstrasse 95, 9007 St Gallen, Switzerland.
Tel: +41-71-4941111; Fax: +41-71-4942563; E-mail: markus.joerger@kssg.ch

willingness-to-pay thresholds [10–12]. The objective of the present study is to assess the cost-effectiveness of adding cetuximab to standard platinum-containing chemotherapy in advanced, EGFR-overexpressing (by immunohistochemistry), inoperable wet stages IIIB or IV non-small-cell lung cancer, from the perspective of the Swiss health care system, and to compare it with a willingness-to-pay threshold of €60 000 per quality-adjusted life-year (QALY) gained.

materials and methods

We constructed a Markov model to assess the cost-effectiveness of adding cetuximab to cisplatin-vinorelbine first-line chemotherapy in patients with EGFR-expressing advanced NSCLC, based on the results of the First-Line ErbituX in lung cancer (FLEX) phase III, randomized open-label clinical trial [7]. The model adopted a life-long time horizon. Costs were assessed from a Swiss health care system perspective. Direct medical costs included chemotherapy, treatment of major adverse events, laboratory tests and follow-up treatment for progressive disease. Indirect costs were not considered as they are irrelevant for the chosen perspective. Costs were based on average 2009 Swiss prices and reported in Euros (€). An exchange rate of CHF1.52 per € was used. Utilities for the health states represented in the model were obtained from the literature [13]. Costs and benefits were not discounted given the short life expectancy of the patient population studied. Inclusion criteria and study treatment of the FLEX study have been published previously [7]. Cetuximab was combined with standard chemotherapy and given at a loading dose of 400 mg/m^2 i.v. over 2 h on day 1, followed by weekly infusions at a dose of 250 mg/m^2. Patients received the assigned therapy until disease progression or unacceptable toxicity. The primary study outcome was the incremental cost-effectiveness ratio (ICER) of adding cetuximab to chemotherapy, expressed as cost per QALY gained. Results were compared with a willingness-to-pay threshold of €60 000/QALY [10–12]. One-way sensitivity analyses and probabilistic sensitivity analyses (Monte Carlo simulation) were used to assess robustness of the results. Markov cohort and Monte Carlo analyses were carried out using TreeAge Pro Suite 2009® (TreeAge Software Inc., Williamstown, MA).

structure of the Markov model

The structure of the Markov model is shown in Figure 1. The model comprises three mutually exclusive health states, i.e. stable/responsive disease (entry state), disease progression and death, with state transitions at the end of each treatment cycle. Cycle length was 3 weeks, to match the duration of chemotherapy cycles. Preference-based utility scores for stable and progressive disease were derived from the literature [13]. The utility assumed for stable disease was 0.65 (range for sensitivity analysis, 0.26–0.78) and was both used for the control and treatment arm, as no difference in quality of life was expected for adding cetuximab to chemotherapy. For time in progression, a utility of 0.47 (range 0.19–0.58) was used [13]. Effectiveness data used in the model were inferred from the data on time to treatment failure (TTF) and OS reported in the original FLEX publication [7]. Hazards were assumed to be constant over time. Median time spent in each stage was used to estimate hazard rates for the control arm, based on the following formula:

$$\text{Hazard rate} = -\ln(0.5)/\text{median time in state} \qquad (1)$$

Hazard rates were converted into Markov state transition probabilities, taking into account the cycle length of 3 weeks. In order to model survival in the treatment arm, hazard rates in the control arm were multiplied with applicable hazard ratios (HR) [7]. Median time from treatment failure to death and the corresponding HR were estimated to fit the reported median OS in each treatment arm, as they were not detailed in the original publication [7]. With regard to treatment-associated toxicity, the only economically relevant differences in the occurrence of grades 3–4 adverse events were reported for febrile neutropenia. Therefore, only the cost of febrile neutropenia was taken into account in the modeling.

use of medical resources and unit costs

Medical resource use estimates were based on the FLEX study [7] and included study medication (including prescription, preparation, and administration), laboratory tests, costs for second-line treatment with drugs or radiotherapy, and management of side-effects such as febrile neutropenia (Table 1). Costs for cetuximab, cisplatin, and vinorelbine were calculated for a body surface area (BSA) of 1.77 m^2 (minimum 1.45 m^2, maximum 2.31 m^2), as observed in an earlier Swiss lung cancer study [14]. Swiss public prices were used for cisplatin (Cisplatin-Mepha®), vinorelbine (Vinorelbin Actavis®), cetuximab (Erbitux® 5 mg/ml), and anticancer drugs for progressing disease [15]. National tariffs were applied for diagnostic tests, routine procedures and other treatments [16, 17]. The exact individual amount of drug was used for cost analysis, assuming the situation where surplus medication is used for another patient, eliminating the need to correct for waste. This is reasonable for any larger oncology ward but might not be for small ones. The use of different second-line treatments was also implemented in the model, based on the data from the FLEX study [7].

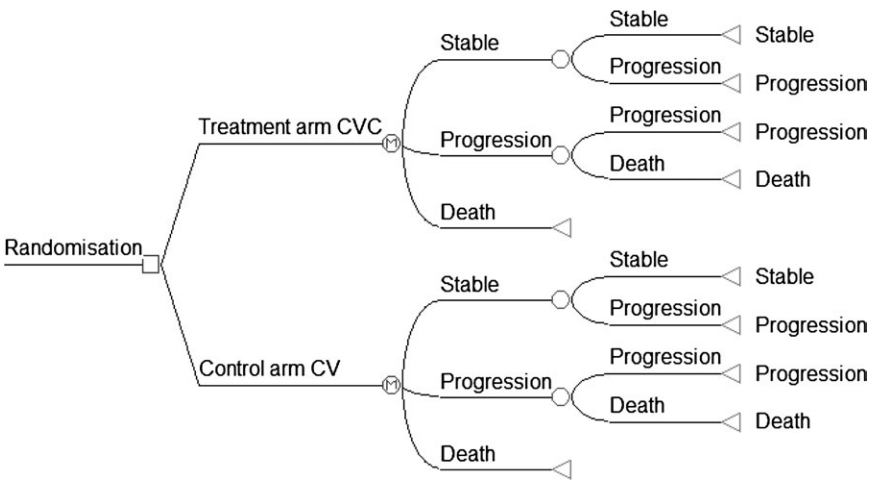

Figure 1. Model structure.

Table 1. Unit costs

Medication on study	€	€/mg	mg/cycle/m^2	€/cycle/m^2
Cetuximab per 100 mg [15]	235.46	2.35	900.00[a]	2119.14
			750.00[b]	1765.95[b]
Cisplatin 1 vial a 50 mg [14]	54.87	1.10	80.00	87.79
Vinorelbine 1 ampulle a 50 mg [14]	83.27	1.67	50.00	83.27
Medication second line	**€**	**€/mg**	**mg/cycle/m^2**	**€/cycle/m^2**
Docetaxel 1 Amp à 80 mg [14]	857.89	10.72	75.00	804.28
Pemetrexed 1 Amp à 500 mg [14]	1406.58	2.81	500.00	1406.58
Erlotinib 1 tablet à 150 mg [14]	77.17	0.51	3150.00 mg/cycle	
General	**€**			
Preparation of chemotherapy [16]	25.15			
Administration of chemotherapy [16]	52.20			
Blood count [16]	88.07			
CT-scan [16]	135.79			
Hospitalization (/day) [16]	878.29			
Treatment for febrile neutropenia [18, 19]	5400.00			
Radiotherapy (single dose) [16]	329.00			

[a]Only first cycle.
[b]Second- and further treatment cycles.
Amp, ampoules; CT, computer tomography.

sensitivity analysis

To assess the impact of statistical uncertainty on key model inputs, a series of univariate and probabilistic sensitivity analyses were carried out. In the univariate sensitivity analysis, median OS with corresponding HR, utility parameters, number of days in hospital, percentage of patients receiving computer tomography, and the percentage of patients with febrile neutropenia were varied as described in Table 2. Probabilistic sensitivity analysis (second-order Monte Carlo simulation) was based on corresponding distributions (Table 3). The probability of being cost-effective was calculated for a threshold of €60 000. Sensitivity analysis was based on 5000 sets of randomly drawn input parameters.

Additional analyses were carried out for a minimal (1.45 m^2) and maximal (2.31 m^2) BSA, using previously described BSA of advanced lung cancer patients in Switzerland [14]. In addition, the impact of the following cetuximab intermittent dosing schedules on ICER was evaluated, assuming no change in clinical effectiveness as compared with weekly dosing of cetuximab according to the FLEX study:

1. one cetuximab cycle with a loading dose of 400 mg/m^2 on day 1 and two doses of 250 mg/m^2 on days 8 and 15 (total dose, 900 mg/m^2);
2. two similar cetuximab cycles with a total dose of 900 mg/m^2 per cycle, concurrently given with the first and fourth chemotherapy cycle; and
3. three similar cetuximab cycles with a total dose of 900 mg/m^2 per cycle, given during the first, fourth and seventh cycle.

The rationale for these alternative dosage schedules is that several studies have suggested intermittent anti-EGFR-targeted treatment to be superior to continuous treatment, especially when given concurrently with chemotherapy [8, 9].

model validation

The model was calibrated to match the original survival data of the FLEX study. Trackers for TTF, OS and cycle number were included in the model to assess for correct data fit. Additionally, all model estimates were reviewed for plausibility, and key input parameters were subjected to extreme variation to test for correct behavior of the model.

results

Output of the Markov model matched the results of the FLEX study satisfactorily, as shown in (Table 4). This resulted in a median TTF and median OS for the present model (and the original FLEX data) of 3.8 (3.7) months and 10.0 (10.1) months, respectively, in the control arm. Corresponding results for the treatment arm were 4.5 (4.2) months and 11.4 (11.3) months, respectively. The base case model for a patient with a BSA of 1.77 m^2 indicated that adding cetuximab to standard cisplatin/vinorelbine chemotherapy in patients with EGFR-expressing advanced NSCLC leads to a gain of 0.07 QALYs per patient at an additional cost of €26 088. As drug costs are BSA dependent, a patient with the minimum BSA of 1.43 m^2 yielded an additional cost of €21 384, while a patient with a maximal BSA of 2.31 m^2 accrued an additional €34 024 for gaining 0.07 QALYs. The ICER for adding cetuximab to cisplatin/vinorelbine chemotherapy was €376 205 per QALY gained for a BSA of 1.77 m^2. There was a wide range from €308 384 per QALY gained to €490 651/QALY gained, for the lowest and highest BSA, respectively (Table 5).

sensitivity analysis

Univariate sensitivity analysis was carried out for the base case analysis assuming a BSA of 1.77 m^2 (Figure 2). Varying the HR for time from treatment failure to death had the highest impact on the ICER but did not lead to an ICER approaching the willingness-to-pay threshold of €60 000 (Figure 3). The second most influential parameter was the HR for TTF. None of the parameters tested resulted in an ICER below the willingness-to-pay threshold of €60 000 per QALY. Correspondingly, probabilistic sensitivity analysis resulted in a zero probability of meeting this threshold. Generally, sensitivity analyses showed the results to be robust.

Intermittent cetuximab dosing schedules indicated that decreasing cetuximab to one single cycle with a total cetuximab dose of 900 mg/m^2 might result in an ICER of €31 300 per QALY gained and increased the probability of being cost-effective to 99% (Figure 4). Two cycles of cetuximab at 900 mg/m^2 per cycle resulted in an ICER of €62 500 per QALY gained and a probability of being cost-effective of 43%. Three cycles of cetuximab at 900 mg/m^2 per cycle resulted in an ICER of €83 100 per QALY gained and a probability of being cost-effective of 7%. These estimates were made under the assumption of equal effectiveness of intermittent cetuximab dosing schedules as compared with the original weekly dosing schedule studied in FLEX.

Table 2. Use of medical resources

Item	Treatment arm	Control arm
Preparation of chemotherapy	3× per cycle as long as cetuximab is given	2× per cycle as long as cisplatin + vinorelbine is given
Administration of chemotherapy	3× per cycle as long as cetuximab is given	2× per cycle as long as cisplatin + vinorelbine is given
Blood count	3× per cycle as long as cisplatin + vinorelbine is given	3× per cycle as long as cisplatin + vinorelbine is given
CT scan	Every second cycle, 50% of patients	Every second cycle, 50% of patients
Hospitalization (per day)	2 days per cycle as long as cisplatin + vinorelbine is given	2 days per cycle as long as cisplatin + vinorelbine is given
Treatment for febrile neutropenia	22% of patients	15% of patients
Follow-up	**Treatment arm**	**Control arm**
Erlotinib [7]	17% of patients [6]	27% of patients [7]
Docetaxel or pemetrexed (in a ratio of 1 : 1) [20] for six cycles	43% of patients [6]	40% of patients [7]
Radiotherapy (single dose)	Once 15 days in follow-up, 21% of patients	Once 15 days in follow-up, 23% of patients
Chemo preparation	1× per cycle as long as docetaxel or pemetrexed is given	
Chemo administration	1× per cycle as long as docetaxel or pemetrexed is given	
Blood count	3× per cycle as long as docetaxel or pemetrexed is given	

Most Swiss institutes apply cisplatin during a 2-day inpatient stay.
CT, computer tomography.

Table 3. Ranges of variation used in sensitivity analysis

Variable	Base case value	Range of variation in deterministic sensitivity analysis	Distribution type in probabilistic sensitivity analysis
% Patients with CT	50%	20%–80%	Triangular
% Patients with febrile neutropenia CVC arm	22.00%	15.4%–28.6% (±30%)	Triangular
% Patients with febrile neutropenia CV arm	15.00%	10.5%–19.5% (±30%)	Triangular
Hazard ratio time from treatment failure to death	0.871	0.762–0.996 (95% CI)	Lognormal
Hazard ratio time to treatment failure	0.86	0.76–0.97 (95% CI)	Lognormal
Days in hospital per cycle	2	1–5 (min–max)	Triangular
Time (months) from treatment failure to death control arm	6.1	5.2–7.1 (95% CI)	Gamma
Time to treatment failure control arm month	3.7	3.1–4.2 (95% CI)	Gamma
Utility during stable disease	0.65	0.26–0.87 (min–max)	Beta
Utility during progression	0.47	0.19–0.46 (min–max)	Beta

CT, computed tomography; CVC, cetuximab-vinorelbine-cisplatin; CV, cisplatin-vinorelbine; min, minimum; max, maximum.

Table 4. Median time to progression and overall survival in model and original data

		Model (month)	Original data (month)
Time to progression (median)	Control	3.81	3.7
	Treatment	4.5	4.2
Overall survival (median)	Control	10.04	10.1
	Treatment	11.42	11.3

discussion

The high cost of some recently developed cancer therapeutics such as the monoclonal antibodies is under increasing scrutiny. Discussion is also fueled by the fact that adding such drugs to standard chemotherapy frequently achieves small benefits, sometimes at the cost of increased toxicity. Platinum-based chemotherapy is a long-standing standard for the first-line treatment of patients with advanced NSCLC [21] and has been shown to be cost-effective [22, 23]. Still, the prognosis of advanced NSCLC remains poor, with a 5-year OS rate for M1 distant disease of 1% [1], and more effective treatment is urgently needed. The addition of anti-VEGF (bevacizumab) and anti-EGFR (cetuximab) antibodies to first-line chemotherapy results in a moderate increase in OS of 2.0 [24] and 1.2 months [7], respectively. After the EMEA issued a negative opinion on the use of cetuximab in NSCLC in 2009, the discussion continues on the cost–benefit implications of adding these monoclonal antibodies to the upfront treatment of advanced NSCLC. According to the present model, the addition of cetuximab to standard chemotherapy with cisplatin

Table 5. Base case incremental cost-effectiveness results

BSA	Strategy	Costs (mean)	Incremental costs	Effectiveness (mean)	Incremental effectiveness	ICER	Probability cost-effective[a]
1.77 m^2	Control	€23 917	€26 088	11.89 month	1.53 month	17 051 €/month 204 612	
	Treatment	€50 004		13.42 month		€/year	
	Control	€23 917	€26 088	0.547 QALY	0.069 QALY	376 205 €/QALY	0%
	Treatment	€50 004		0.617 QALY			
1.45 m^2	Control	€22 943	€21 385	0.547 QALY	0.069 QALY	308 384 €/QALY	0%
	Treatment	€44 327		0.617 QALY			
2.31 m^2	Control	€25 560	€34 024	0.547 QALY	0.069 QALY	490 651 €/QALY	0%
	Treatment	€59 584		0.617 QALY			

[a]Based on probabilistic sensitivity analysis.

BSA, body surface area; ICER, incremental cost-effectiveness ratio.

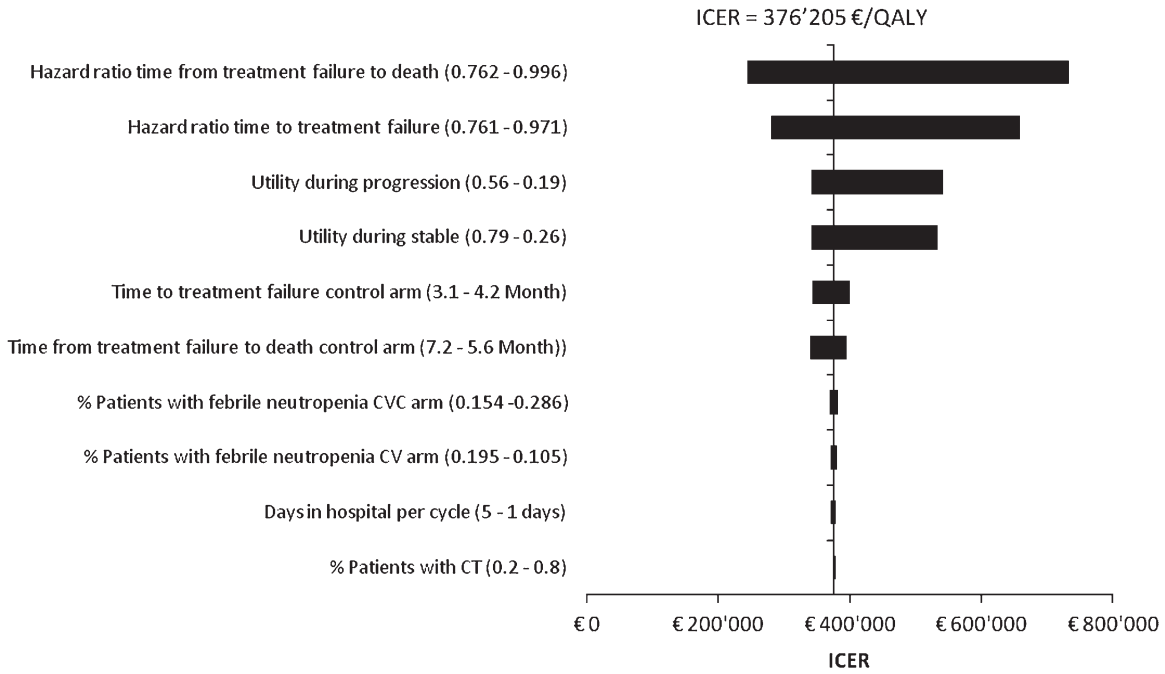

Figure 2. Tornado plot univariate sensitivity analysis.

and vinorelbin in patients with EGFR-expressing advanced NSCLC results in a gain of 0.07 QALYs. This survival advantage is associated with an average additional lifetime cost of €26 088, resulting in an average incremental cost-effectiveness ratio of €376 205/QALY gained (range €308 384–€490 651/QALY depending on patient BSA). The additional costs associated with the combination treatment are mainly the acquisition costs of cetuximab, whereas the cost of administration and treatment of side-effects is negligible. Fojo et al. have recently addressed the same topic from a USA perspective. They estimated an average incremental cost of $80 000 for 18 weeks of cetuximab treatment of patients with advanced NSCLC, translating into an expenditure of US-$800 000 per life-year gained [25]. This figure corresponds to roughly €550 000, which is moderately higher than the €376 205/QALY in the present study. However, the authors did not carry a proper cost–utility analysis and did not include the costs of chemotherapy, supportive therapy, toxicity management or second-line treatment. Higher costs and even more unfavorable cost-effectiveness in the United States may be mainly explained by a higher purchasing cost of cetuximab. A price of US-$11/mg cetuximab in the United States compares with €3.29/mg cetuximab in Europe.

Our results also require comparison with cost-effectiveness data for two registered molecularly targeted drugs in advanced NSCLC, namely erlotinib and bevacizumab. Dutch [26] and Canadian studies [27] considered the cost-effectiveness of erlotinib relative to best supportive care. They showed erlotinib to be associated with incremental costs per QALY gained of €50 000 and Can-$100 000, respectively. To our knowledge, no cost-effectiveness data are currently available for bevacizumab in the first-line treatment of patients with advanced NSCLC. Based on an estimate by Fojo and Grady [25], total bevacizumab treatment costs per patient are higher than for cetuximab (U.S.-$90 816 versus U.S.-$80 352, respectively) and go along with a marginally higher improvement in OS (2 months [24] versus 1.2 months in [7], respectively).

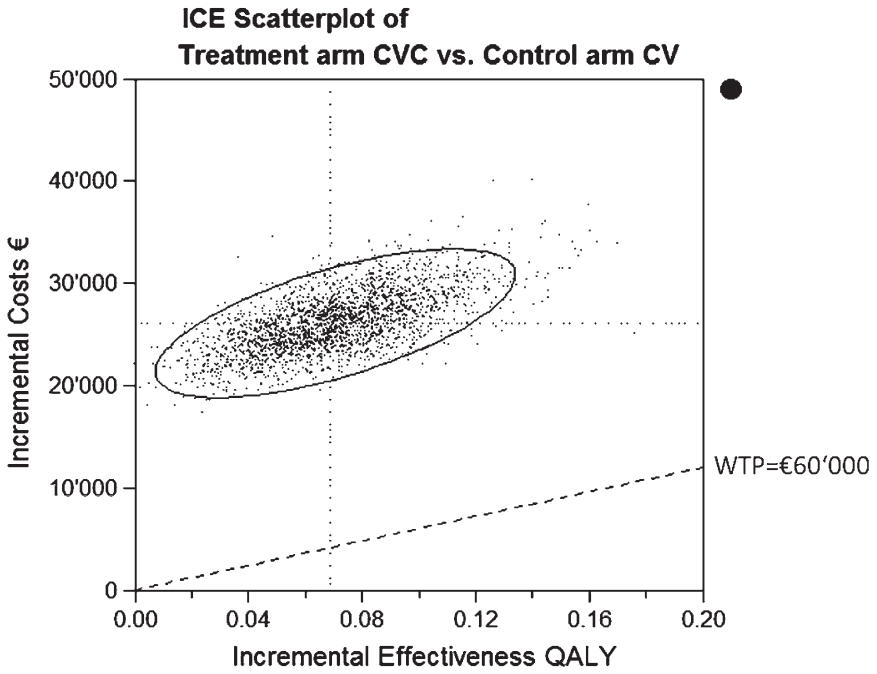

Figure 3. Probabilistic sensitivity analysis.

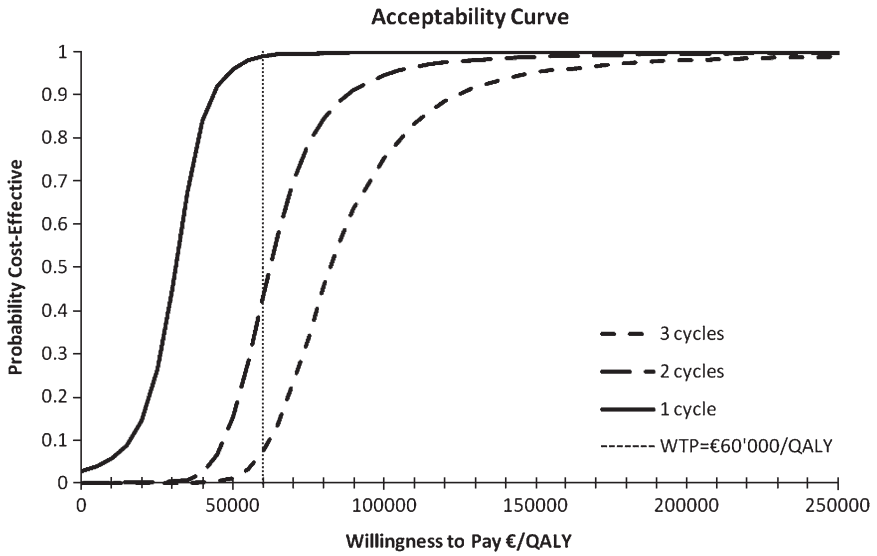

Figure 4. Effect of using 1, 2 or 3 cetuximab cyles (cycles 1, 4 and 7, 900 mg/m^2 per cycle) on incremental cost-effectiveness ratio (assuming no change in clinical effectiveness compared with the schedule studied in the FLEX trial).

In colorectal cancer, cetuximab has been shown to be cost-effective when given in combination with irinotecan and compared with noncetuximab containing care in Belgium, resulting in a maximum ICER of €59 000 per QALY gained for a 12-week cetuximab treatment period [28]. However, a British study found cetuximab/irinotecan treatment to be associated with an incremental cost per QALY gained of £57 608 or €66 249 (£/€ = 1.15) [29], that is usually not seen as cost-effective according to UK standards [30]. Cost-effectiveness analyses were also carried out in patients with locally advanced head and neck cancer receiving cetuximab in combination with radiotherapy in five different European countries [31]. The incremental cost per QALY compared with radiotherapy alone was in the range of €7 538–€10 836 and suggested favorable cost-effectiveness. Higher intrinsic activity of cetuximab in colorectal and head and neck cancer might not be the only reason for a higher cost-effectiveness compared with the NSCLC setting. There are some rather convincing data on a negative effect of continuous inhibition of the EGFR with the concurrent use of chemotherapy in lung cancer. Most notably, the addition of the anti-EGFR tyrosine kinase inhibitor erlotinib to standard first-line chemotherapy in two large randomized phase III studies has not improved clinical outcome but added some relevant toxicity [32, 33]. More

recent nonrandomized clinical data suggest intermittent anti-EGFR-directed treatment given before chemotherapy to result in high response rates and OS [9]. Therefore, we also analyzed the cost-effectiveness of intermittent cetuximab dosing schedules. These showed a reasonably favorable cost–utility relationship, e.g. an ICER of €62 500 per QALY gained for the addition of two cycles of cetuximab at 900 mg/m^2 per cycle and a probability of being cost-effective of 43%. These results are, however, based on the assumption of equal clinical activity of intermittent cetuximab dosing as compared with continuous dosing. Further studies of intermittent dosing of cetuximab in NSCLC are justified from a pharmacological and pharmaco-economic viewpoint.

When implications of cost-effectiveness and cost–utility results for reimbursement are discussed, ICERs for different interventions are usually compared or reference to cost-effectiveness thresholds (based on societal willingness to pay) is made. However, no such thresholds have formally been defined in Switzerland and most other countries. In the United States, a threshold of $50 000–100 000 per QALY gained is usually seen as acceptable [12, 34]. Taking into account differences in purchasing power, this range is roughly equivalent to €32 900–65 800 per QALY gained for Switzerland [35]. This threshold also corresponds to 0.9–1.8 times the Swiss 'per capita' gross domestic product. In the UK, a threshold of £20 000–£30 000 for accepting cost-effectiveness has tentatively been used by the National Institute of Clinical Evidence [30].

In conclusion and from a cost-effectiveness perspective, the addition of cetuximab to standard first-line chemotherapy in patients with EGFR-expressing advanced NSCLC cannot be recommended to date, due to a high ICER compared with other health care interventions. Treatment schedules resulting in more favorable cost–utility ratios should be evaluated.

disclosure

The authors declare no conflict of interest.

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