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Cost-effectiveness of maintenance pemetrexed in patients with advanced nonsquamous-cell lung cancer from the perspective of the Swiss health care system

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Abstract: OBJECTIVES: A recent randomized study showed switch maintenance with pemetrexed after nonpemetrexed-containing first-line chemotherapy in patients with advanced nonsmall-cell lung cancer to prolong overall survival by 2.8 months. We examined the cost-effectiveness of pemetrexed in this indication, from the perspective of the Swiss health care system, and assessed the influence of the costs of best supportive care (BSC) on overall cost-effectiveness. METHODS: A Markov model was constructed based on the pemetrexed maintenance study, and the incremental cost-effectiveness ratio (ICER) of adding pemetrexed until disease progression was calculated as cost per quality-adjusted life-year gained. Uncertainties concerning the costs of BSC on the ICER were addressed. RESULTS: The base case ICER for maintenance therapy with pemetrexed plus BSC compared to BSC alone was €106,202 per quality-adjusted life-year gained. Varying the costs for BSC had a marked effect. Assuming a reduction of the costs for BSC by 25% in the pemetrexed arm resulted in an ICER of €47,531 per quality-adjusted life-year, which is below predefined criteria for cost effectiveness in Switzerland. CONCLUSIONS: Switch maintenance with pemetrexed in patients with advanced nonsquamous-cell lung cancer after standard first-line chemotherapy is not cost-effective. Uncertainties on the resource use and costs for BSC have a large influence on the cost-effectiveness calculation and should be reported in more detail.

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Cost effectiveness of maintenance pemetrexed in patients with advanced non squamous-cell lung cancer from the perspective of the Swiss health care system

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Keywords: lung cancer, pemetrexed, maintenance treatment, cost effectiveness, best supportive care, health economics

Running title: Cost effectiveness of pemetrexed in advanced NSCLC

ABSTRACT [First-level Header]

Objectives: A recent randomized study showed switch maintenance with pemetrexed after non-pemetrexed-containing first-line chemotherapy in patients with advanced non-small-cell lung cancer to prolong overall survival by 2.8 months. We examined the cost-effectiveness of pemetrexed in this indication, from the perspective of the Swiss health care system, and assessed the influence of the costs of best supportive care (BSC) on overall cost effectiveness.

Methods: A Markov model was constructed based on the pemetrexed maintenance study, and the incremental cost-effectiveness ratio (ICER) of adding pemetrexed until disease progression was calculated as cost per quality-adjusted life-year gained. Uncertainties concerning the costs of BSC on the ICER were addressed.

Results: The base case ICER for maintenance therapy with pemetrexed plus BSC compared to BSC alone was €106,202/QALY gained. Varying the costs for BSC had a marked impact. Assuming a reduction of the costs for BSC by 25% in the pemetrexed arm resulted in an ICER of €47,531/QALY, which is below predefined criteria for cost effectiveness in Switzerland.

Conclusions: Switch maintenance with pemetrexed in patients with advanced non-squamous-cell lung cancer after standard first-line chemotherapy is not cost effective. Uncertainties on the resource use and costs for BSC have a large impact on the cost-effectiveness calculation and should be reported in more detail.

Introduction [First-level Header]

Non-small-cell lung cancer (NSCLC) is the leading cause of cancer-related deaths worldwide, with more than 161,000 people in the United States dying of the disease in 2007 [1]. The majority of patients present with advanced disease, and the five-year age- and area-adjusted relative survival of all lung cancer patients in Europe continues to be barely 11% [2]. Current guidelines recommend platinum-based combination chemotherapy [2-4], as they have shown a modest improvement of overall survival (OAS) in several clinical studies [3-7]. Over time, improving on standard platinum-based doublets has proven difficult and median OAS of patients with advanced NSCLC remains between 10 and 12 months, with no substantial improvements in the last decade. More recently, molecularly-targeted drugs have been added upfront to improve the efficacy of first-line chemotherapy in advanced NSCLC patients. Many of these drugs, however, have not proven to be very useful in prolonging OAS (erlotinib and gefitinib [8,9] , cetuximab [10]) or toxicity problems limit their use (bevacizumab [11,12]). Additionally, prolonged first-line treatment has not been shown to be beneficial [13-15], and most patients are unable to tolerate long-term combination treatment after first induction [16,17]. Therefore, present guidelines recommend four to six cycles of platinum-based chemotherapy for advanced NSCLC, followed by a treatment-free interval until disease progression [2,4].

Pemetrexed is an antifolate antineoplastic agent that exerts its action by disrupting folate-dependent metabolism [18]. Pemetrexed is approved in combination with cisplatin for first-line treatment of malignant pleural mesothelioma [19], as a single agent for second-line treatment of advanced NSCLC [20], and in combination with cisplatin for the first-line treatment of advanced non squamous-cell NSCLC [21]. Because of the efficacy of pemetrexed in second-line NSCLC [20], its favorable safety profile and ease of administration (infusion over 10 minutes, given once every 3 weeks), a recent phase-III clinical study examined pemetrexed as maintenance therapy in patients who had not progressed following one of six non-pemetrexed-containing induction regimens [22]. The authors showed that pemetrexed treatment until progression prolongs progression-free survival by 1.7 months and OAS by 2.8 months [22]. This comes at the cost of substantially higher drug expenses. While the trial by Ciuleanu and colleagues [22] used a non pemetrexed-containing, platinum-based first-line chemotherapy irrespective of the tumor histotype, the platinum-pemetrexed doublet has become standard first-line treatment in patients with advanced non squamous-cell lung cancer based on the study by Scagliotti et al. [21]. As a consequence, a new Spanish-led clinical trial will assess the benefit of pemetrexed maintenance treatment after first-line cisplatin-pemetrexed induction chemotherapy in patients with advanced non squamous-cell lung cancer [23].

The objective of the present study was to examine the cost-effectiveness of pemetrexed maintenance treatment following standard platinum-based chemotherapy in advanced, inoperable stage IIIB or IV non squamous-cell NSCLC from the perspective of the Swiss health care system, and to compare it with different willingness-to-pay (WTP) thresholds between €72,000 [24,25] (Swiss federal court decision, November 23, 2010) and €150,000 [26] per QALY gained. Secondly, the influence of the costs of best supportive care (BSC) on overall cost effectiveness was assessed.

Materials and methods [First-level Header]

A Markov model was constructed to assess the cost-effectiveness of maintenance therapy with pemetrexed plus best supportive care (BSC), and compared to BSC alone in patients with advanced non squamous-cell lung cancer, based on the results of one phase III, placebo-controlled randomized study by Ciuleanu and colleagues [22], as no other trials with a similar setting were available. The model adopted a life-long time horizon. Costs were assessed from a Swiss health care system perspective. Direct medical costs included pemetrexed therapy, costs for BSC, treatment of major adverse events, 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 2010 Swiss prices, and are reported in Euros (€). An exchange rate of €0.72 per CHF (average exchange rate January 2010– December 2010 [27]) was used. Utilities for the health states represented in the model were obtained from the literature. Costs and benefits were not discounted given the short life expectancy of the patient population studied. Inclusion criteria and details of the study treatment were previously published [22]. In brief, 663 patients with stage IIIB or IV disease who had not progressed during four cycles of non pemetrexed-containing doublet chemotherapy were randomly assigned in a 2:1 ratio. Patients received pemetrexed at a dose of 500 mg/m² or placebo on day 1 of a 3-weekly cycle until disease progression or unacceptable toxicity. All patients received additional BSC. The primary endpoint of the study was progression-free survival (PFS) and the secondary endpoint OAS. The maximum length of survivor follow-up was 41.5 months. For the health economics analysis, only data for the non squamous-cell lung cancer patients (n=481, based on independently central reviewed scans of patients who had a baseline and at least one follow-up scan), were used, as pemetrexed has been approved for maintenance therapy in this subgroup of patients. The primary endpoint of this analysis was the incremental cost-effectiveness ratio of pemetrexed maintenance therapy plus best supportive care, and compared to BSC alone, expressed as cost per QALY gained. Results were compared with WTP thresholds of €72,000/QALY and €150,000/QALY. One-way sensitivity analyses and probabilistic sensitivity analyses (Monte Carlo simulation) were used to assess the robustness of the results. Markov cohort and Monte Carlo analyses were performed using TreeAge Pro Suite 2009® (TreeAge Software Inc., Williamstown, MA, USA).

Structure of the Markov model and clinical model inputs [Second-level Header]

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. Markov cycle length was 3 weeks, to match the duration of the pemetrexed cycles. Preference-based utility scores for stable and progressive disease were derived from the literature. The utility assumed for stable disease was 0.61 and was calculated as the mean utility over all utilities for stable disease reported in the review by Carlson et al. [28]. These included utilities for stable patients on oral or i.v. therapy and for stable patients who partially had several adverse reactions like neutropenia, neuropathy, nausea etc. The utility of 0.61 for stable disease, with a range for sensitivity analysis of 0.24 –0.73, was used for both the control and treatment arm, as pemetrexed therapy was not expected to impact on quality-of-life. For time in progression, a utility of 0.47 (range 0.19 –0.58) (28) was used. Effectiveness data used in the model were inferred from the data on progression free survival (PFS) and overall survival reported in the original publication. 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:

$$hazard\ rate = \frac{-\ln(0.5)}{median\ time\ in\ state}$$

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). Median time from treatment failure to death and the corresponding HR were estimated to fit the reported median OAS in each treatment arm, as they were not detailed in the original publication. With regard to treatment-associated toxicity, the only economically relevant differences in the occurrence of grade 3-4 adverse events were reported for febrile neutropenia. Therefore, only the cost of febrile neutropenia but no other adverse event costs were taken into account in the modelling.

Use of medical resources and unit costs[Second-level Header]

Medical resource use estimates were based on the study by Ciuleanu and colleagues [22]. Pemetrexed costs were calculated for a body surface area (BSA) of 1.77 m^2, the mean observed in an earlier Swiss lung cancer study [29]. As there were no data on resource use for BSC given in the Ciuleanu study, we adopted costs for BSC from a Dutch study by Pompen et al. [30] (see Table 1), after adjustment for the cycle length of our model and accounting for purchasing power differences between the Netherlands and Switzerland, and inflation (2005 -> 2010). Claims-based US data indicated BSC costs for stable disease to be around 30% of the BSC costs for progressive disease [31]. This proportion was applied, while keeping weighted average BSC costs constant at the value derived from the Dutch study, which provided no such information. Costs for administration, monitoring, and minor side-effect, were assumed to be included in BSC costs. Management of febrile neutropenia was discounted separately (see Table 1). Follow-up treatments were implemented in the model as observed in the Ciuleanu study (see Table 2). Swiss public prices were used for pemetrexed and anticancer drugs used post progression [32]. The exact individual amount of drug was used for the costing, 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 so for small ones.

Sensitivity analysis [Second-level Header]

To assess the impact of statistical uncertainty on key model parameters, a series of univariate and probabilistic sensitivity analyses were performed. In the univariate sensitivity analysis, median progression free and overall survival with corresponding HR, utility parameters, weighted average costs for BSC per cycle, proportional BSC costs in cycles spent in stable versus progressive disease, percentage of patients with febrile neutropenia and percentage of patients with chemotherapy treatment post progression were varied as described in Table 3.

Probabilistic sensitivity analysis (second-order Monte Carlo simulation) was based on corresponding distributions (Table 3). Two separate analyses were performed. In the first, the cost of BSC per unit of time was based on the study by Pompen et al. [30] as in the base case analysis. This estimate is believed to be the best approximation of the Swiss situation that is currently available. In a second

analysis, the value for BSC cost per unit of time was reduced by a factor 10, to illustrate the potential impact of low BSC costs as described in a health technology assessment report for the UK by Greenhalgh et al. [33]. This wide range reflects a knowledge gap with respect to the cost of BSC [34]. A multiplier for the BSC cost per unit of time in the pemetrexed arm versus the BSC arm was additionally included to cover the possibility of differences in BSC-related resource use between strategies. The probability of being cost effective was calculated for thresholds of €72,000 [24], and €150,000 [26]. Each sensitivity analysis was based on 1000 sets of randomly drawn input parameters.

Additional scenarios [Second-level Header]

In the Ciuleanu study, patients received 1-55 cycles of pemetrexed (median 5 cycles) [22] but the optimal duration of pemetrexed treatment is unknown. In order to approximate a hypothetical situation of restricted duration of use but equal clinical effectiveness, an additional scenario analysis assumed a maximum of 6 cycles with pemetrexed administration. In the absence of real cost information for BSC in Switzerland for patients in stable or progressive disease we also performed an analysis in which BSC costs were assumed equal in all stages of the disease.

Model validation [Second-level Header]

The model was calibrated to match the original survival data of the Ciuleanu study [22]. Trackers for PFS, OAS and cycle number were included in the model to assess for correct data fit. All model outputs were reviewed for plausibility, and key input parameters were subjected to extreme variation to test for correct behavior of the model.

Results [First-level Header]

The clinical outputs of the Markov model matched the results of the Ciuleanu study satisfactorily. Model-based median PFS and median OAS for the present model (and the original Ciuleanu data) were 1.7 (1.8) months and 10.7 (10.3) months, respectively, in the BSC alone arm. Corresponding results for the treatment arm were 4.5 (4.4) months and 15.6 (15.5) months, respectively. Progression free survival probabilities and overall survival probabilities for both arms as reported in the original paper and estimated by the model are reported in Table 4. The base case model for a patient with a BSA of 1.77 m^2 indicated that maintenance therapy with pemetrexed plus BSC (costs €99,705, effect 0.82 QALY) compared to BSC alone (costs €71,316, effect 0.56 QALY) in patients with advanced non squamous-small-cell lung cancer leads to a gain of 0.27 QALYs per patient at an additional cost of €28,389. The incremental cost effectiveness ratio (ICER) for maintenance therapy with pemetrexed + BSC compared to BSC alone is €106,202/QALY gained for a BSA of 1.77 m^2.

Sensitivity analysis [Second-level Header]

Univariate sensitivity analysis was performed for the base case analysis assuming a BSA of 1.77 m^2 (Fig. 2). Varying the utility for stable disease led to the highest ICER range, but not to an ICER approaching the willingness to pay threshold of €72,000 (Fig. 2). The second most influential parameter was the multiplier for BSC costs in the pemetrexed arm relative to BSC arm. Assuming the

cost of BSC per unit of time in the pemetrexed arm to be 75% of the value for the placebo arm resulted in an ICER €47,531 per QALY below the WTP threshold. None of the other single parameters tested resulted in an ICER below the WTP threshold. Simultaneous assumption of low overall BSC costs and lower BSC costs in the pemetrexed arm resulted in an ICER, of €65,799 per QALY gained.

Reducing the number of pemetrexed cycles to a maximum of 6, assuming no impact on clinical effectiveness, resulted in an ICER of €54,092 per QALY. Keeping costs for BSC equal for stable or progressive disease resulted in an ICER of €143,605 per QALY gained. Generally, sensitivity analyses showed the results to be robust.

Probabilistic sensitivity analysis [Second-level Header]

Substantial uncertainty about the mean cost of BSC led us to use a triangular distributional assumption. In order to assess the influence of this uncertainty, two probabilistic analyses were performed; one with the costs for BSC as adopted from the study by Pompen et al. [30] (Fig. 3), a second by a 10-fold reduction of these costs for BSC. In the former, the probability of an ICER of pemetrexed + BSC compared to BSC alone, of €72,000 per QALY was 23.4% and for the latter the probability increased to 50.6% (Fig. 3). Triangular BSC cost distributions in the main analysis, reflecting increased parameter uncertainty resulted in a wide range of possible ICER outcomes, documenting the importance of studying the resource use and cost implications of BSC, in different situations, in greater detail. The results of the probabilistic sensitivity analyses were put in relation to different willingness to pay (WTP) values. With the highest acceptable WTP of €150,000 per QALY, the probability that the pemetrexed maintenance therapy is cost effective is 84.3%. This probability increases to 99.8% when BSC costs are reduced by a factor of 10.

Discussion [First-level Header]

Improving the outcome of patients with advanced NSCLC has proven to be difficult, and the addition of molecularly-targeted drugs has only led to some marginal improvement of clinical outcome [12]. The approval of pemetrexed as an exceptionally well tolerated drug that is given i.v. at 500 mg/m^2 over 10 minutes every three weeks, however, has opened the doors for prolonged maintenance treatment in patients not refractory to first-line platinum-based treatment. In fact, pemetrexed treatment to progression has been shown to improve PFS and OAS in a recent phase III, placebo-controlled clinical trial [22]. Given the fact that these patients received non pemetrexed-containing, platinum-based first-line chemotherapy, and the fact that pemetrexed is an active drug in the second-line setting of advanced NSCLC, the experimental treatment in the study by Ciuleanu and colleagues might rather be seen as early second-line treatment. Discussion on the value of maintenance or early second-line treatment in patients with advanced NSCLC has additionally been fueled by the additional costs introduced by prolonged treatment. According to the present model, the sequential addition of pemetrexed to standard platinum-based first-line chemotherapy in patients with advanced NSCLC results in an average gain of 0.27 QALYs per patient. This survival advantage is associated with an average additional lifetime cost per patient of €28,389, resulting in an average incremental cost-effectiveness ratio of €106,202/QALY for maintenance therapy with pemetrexed plus BSC as compared to BSC alone. A very recent cost-effectiveness analysis of

pemetrexed as first-line maintenance therapy in this group of patients was performed by Klein and colleagues [31]. According to this study, the ICER per life-year gained was $122,371 for pemetrexed as compared to placebo in patients with non-squamous-cell advanced lung cancer [31]. This is comparable to the €106,202/QALY as found in the present study. A second and very similar cost-effectiveness analysis was performed by the National Institute for Health and Clinical Excellence (NICE) from the perspective of the British health care system [33,35]. In the latter study, the cost of pemetrexed was £800 for a 500 mg vial, accounting for drug costs per patient of approximately £12,076. Again, based on the study results of Ciuleanu and colleagues [22], the ICER for pemetrexed compared with best supportive care in the non-squamous-cell patient population was calculated to be £39,364 per QALY gained, based on an incremental cost of £9,554 and an incremental QALY of 0.24 [33,35]. The ICER of £39,364 per QALY as estimated by the latter study corresponds to €46,449 per QALY, partially as a consequence of lower drug costs. With equal costs for pemetrexed, the ICER estimate would amount to €68,886 per QALY, still seen as cost-effective with regards to a WTP threshold of €72,000.

One disadvantage of this cost-effectiveness analysis is that it is based on data of only one clinical trial, as no other trials with a similar setting were available. Secondly, we had to rely on the summary results provided in the clinical trial publication [22] and had no access to individual patients' histories. This made it impossible to model, e.g., situations where patients stopped pemetrexed treatment while still stable. Although we found no indication of relevant distortions, this may have influenced cost-effectiveness results to a limited extent. Finally, in the present cost-effectiveness analysis, assumptions on the mean costs of BSC per unit of follow-up time had a strong impact on the final ICER, as demonstrated in the probabilistic sensitivity analysis (Fig. 3). As there were no data on the resource use and cost implications of BSC, a base case assumption of equal costs of BSC in both treatment arms was made. However, the assumption of a relatively slight decrease of the costs of BSC by 25% in patients receiving maintenance pemetrexed as compared to patients receiving placebo resulted in an ICER of roughly €47,531 per QALY, below our tentative cost-effectiveness threshold. Data on the costs of BSC in patients with advanced NSCLC are very limited. From an economic evaluation perspective, it is of major interest whether the use of chemotherapy leads to a relative (percentage) decrease of BSC costs compared to patients receiving BSC alone. Various studies suggest a potential for a modest reduction of BSC costs within the range of 12-23%, when standard chemotherapy is administered to patients with advanced NSCLC (cisplatin/navelbine chemotherapy vs. BSC [36], cisplatin/paclitaxel versus BSC [37], gemcitabine vs. BSC[38]). Accordingly, these data provide some limited validation of our cost estimates and assumption of a reduction of BSC costs up to 25% in patients receiving pemetrexed maintenance therapy, which resulted in an ICER per QALY of roughly €47,531. Exact estimates of the real costs for BSC, however, are difficult to obtain. The recent Dutch study by Pompen et al. [30] showed yearly BSC cost of €25,222 (for hospitalisations, outpatient visits, diagnostic and laboratory tests, at 2005 prices) for patients who only received first line therapy, compared to €19,420 for patients also receiving a second line therapy. These costs were assumed to be realistic for the Swiss setting after adjustment for purchasing power differences and inflation. In the absence of confidence intervals for this parameter or other appropriate distributional information, we used a triangular distribution to represent uncertainty around this parameter representing a central tendency. Compared to the true

distributions of most parameters, a triangular distribution of similar width tend to underestimate the central region of the distribution and to overestimate the tales, i.e. they can be assumed to rather overestimate than underestimate the impact of parameter uncertainty. The use of a range of ±50% was necessarily arbitrary. Furthermore it is unclear to what extent the difference in the costs of BSC for stable versus progressive disease described by Klein et al. [31] for the USA represents European or Swiss clinical practice. These issues stress that the lack of rigorous, structured assessment of BSC data in clinical studies is a point of major concern, as has been outlined by leading experts in palliative cancer care in a recent position paper [39]. There might even be some potential for systematic bias or error in clinical trials implementing BSC as part of the study treatment, mainly as a result of lacking standardization of the delivery of BSC. This has some major implications for the assessment of treatment costs, as has been outlined in the present study.

Conclusion [First-level Header]

The addition of maintenance pemetrexed to BSC in patients with advanced NSCLC not progressing on standard first-line chemotherapy is not assumed cost effective from the perspective of the Swiss health care system. Assuming a large reduction of the costs of BSC can be achieved this treatment might become cost-effective. A structured assessment of the costs for BSC is essential for reducing the level of uncertainty with regards to the assessment of cost-effectiveness of anticancer therapy.

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Table 1 Unit costs and resource use

	Unit cost	Resource use per cycle	
		Pemetrexed arm	Best supportive care arm
Best supportive care	2'555€*	per cycle	per cycle
Pemetrexed [29]	2.88€/mg	500 mg/m2, BSA = 1.77	0
Neutropenia	5'400 €	3% of patients once per stage	0
Follow up Chemotherapy	See Table 2	51% of patients	67% of patients

*Adopted from Pompen et al. [30], BSA=body surface area

Table 2 Unit costs of follow up chemotherapies [22]

						Percentage patients (of those receiving further chemo-therapy) receiving a given therapy	
	Price/ mg €*	Dose	Frequency of use	Total dosage per cycle	Price per cycle (BSA=1.77)	Pemetrexed + BSC	BSC alone
Docetaxel	11.23	75 mg/m²	once per cycle	75 mg/m²	€ 1'490.99	22%	29%
Erlotinib	0.64	150 mg	daily	3150 mg	€ 2'021.02	22%	21%
Gefitinib	0.36	250 mg	daily	5250 mg	€ 1'864.80	13%	10%
Vinorelbine	2.59	30 mg/m²	3x in 4 weeks	67.5 mg/m²	€ 309.68	13%	17%
Gemcitabine	0.16	1000 mg/m²	3x in 4 weeks	2250 mg/m²	€ 630.83	9%	14%
Carboplatin	0.43	400 mg/m²	once per cycle	400 mg/m²	€ 305.86	7%	9%
Cisplatin	1.58	50–100 mg/m²	once per cycle	75 mg/m²	€ 210.28	5%	6%
Paclitaxel	1.73	175 mg/m²	once per cycle	175 mg/m²	€ 535.25	4%	6%
Pemetrexed	2.88	500 mg/m2	once per cycle	500 mg/m2	€ 2'548.80	1%	18%
Total Price per chemotherapy follow up cycle						€ 1'191	€ 1'715

* mean price over several manufacturers and packages [32], BSA=body surface area, BSC=best supportive care

Table 3 Ranges of variation and distributional assumptions for sensitivity analysis

	Base case	Values used in univariate sensitivity analysis	Basis of variation	Distribution Type	Study arm
Cost for best supportive care(30)	€ 2'555	€1'277 / €3'833	+/- 50%	Triangular	both arms
Multiplier for costs for BSC in pemetrexed arm relative to BSC arm	1	0.75 / 1.25	+/- 25%	Uniform	Pemetrexed arm
Proportion of BSC costs in stable versus progressive disease	0.3	0.1 -0.5	Low – high*	Triangular	both arms
Utility stable disease (28)	0.61	0.24 / 0.73	Low – high°	Beta	both arms

Utility progressive disease (28)	0.47	0.19 / 0.56	Low – high°	Beta	both arms
HR progression free survival (22)	0.47	0.37 / 0.60	95% CI	Lognormal	
HR overall survival (22)	0.70	0.56 / 0.88	95% CI	Lognormal	
Progression free survival in BSC arm (22)	1.8 Month	1.5 / 2.8	95% CI	Gamma	
Time from progression to death in BSC arm(22)	5.7 Month	4.4 / 7.0	95% CI	Gamma	
% patients with follow up chemotherapy (22)	51%	35.7% / 66.3%	+/- 30%	Beta	BSC arm
	67%	46.9% / 87.1%	+/- 30%	Beta	Pemetrexed arm

° as reported by Carlson [28], * as reported by Klein [31], BSC=best supportive care, HR=hazard ratio

Table 4 Survival probabilities observed in the Ciuleanu [22] study and estimated by the health economic model.

Arm	Progression free survival		Overall survival	
Pemetrexed	Model	Original study (22)	Model	Original study (22)
6 month	0.44	0.41	0.89	0.85
12 month	0.19	0.18	0.67	0.60
18 month	0.08	0.08	0.47	0.47
Placebo				
6 month	0.08	0.11	0.76	0.75
12 month	0.01	0.05	0.47	0.41
18 month	0	0.01	0.28	0.31

Figure 1

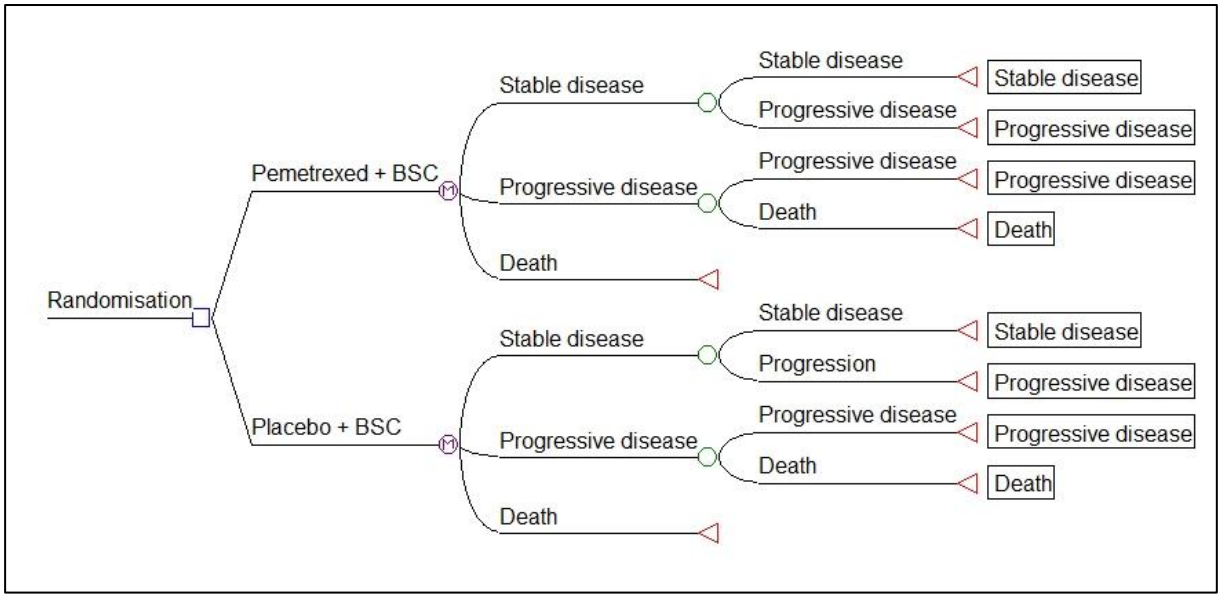


Figure 2

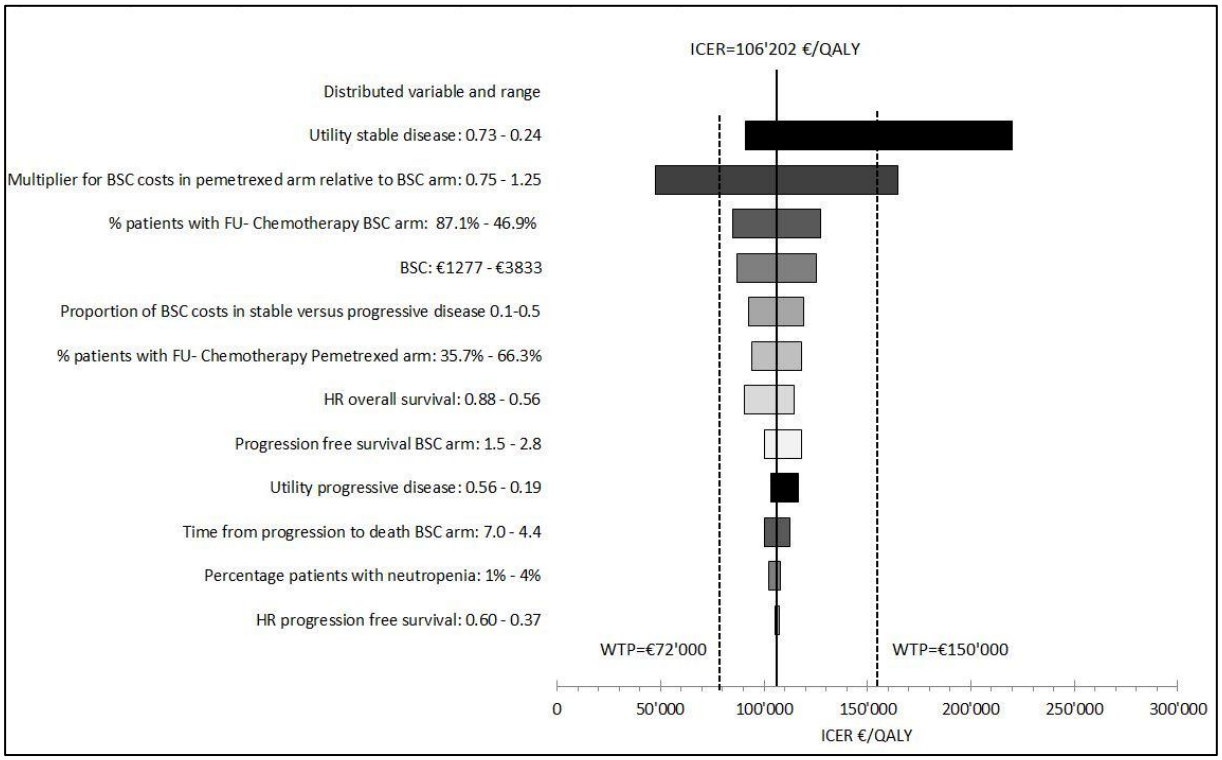
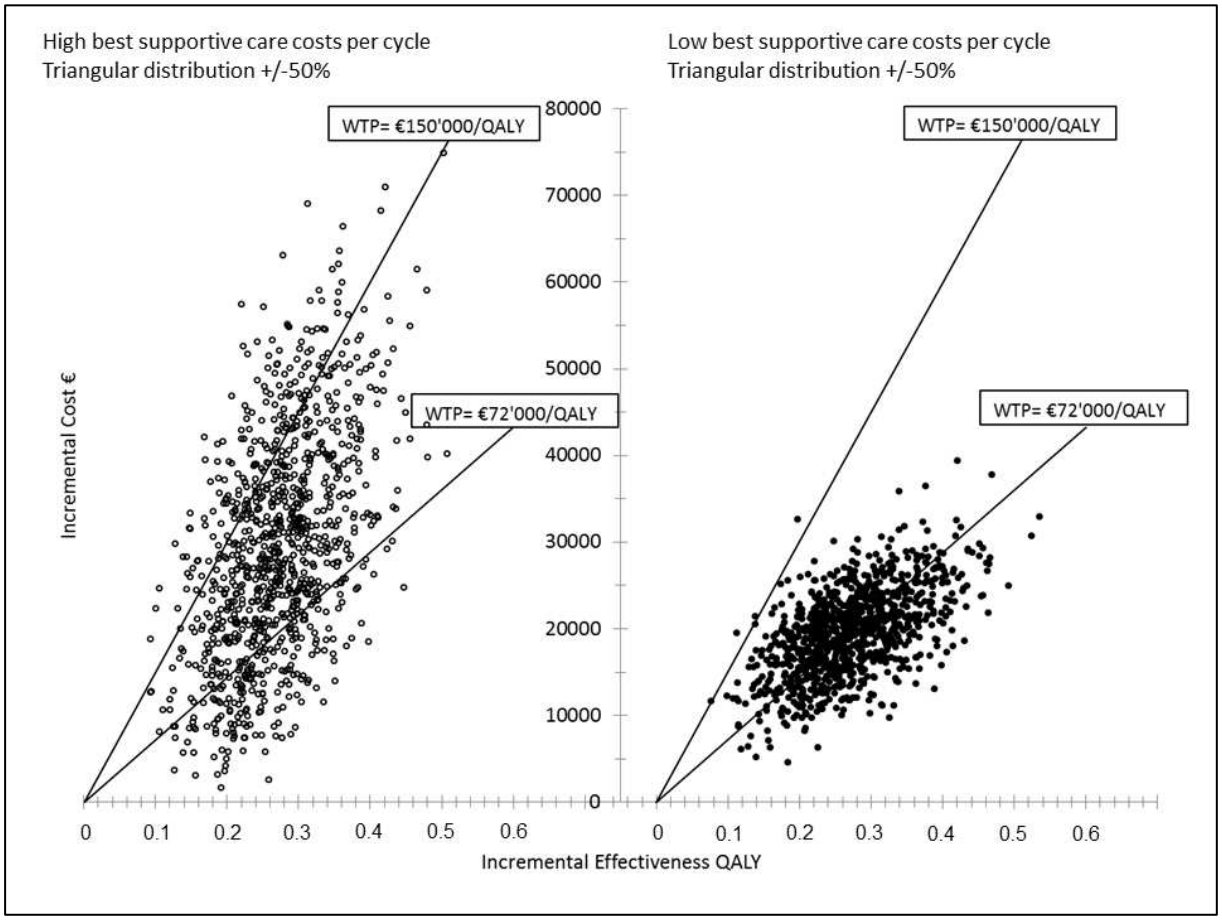


Figure 3


High best supportive care costs per cycle
Triangular distribution +/-50%
Low best supportive care costs per cycle
Triangular distribution +/-50%
WTP= €150'000/QALY
WTP= €72'000/QALY
WTP= €150'000/QALY
WTP= €72'000/QALY
Incremental Cost €
80000
70000
60000
50000
40000
30000
20000
10000
0
0
0.1
0.2
0.3
0.4
0.5
0.6
0
0.1
0.2
0.3
0.4
0.5
0.6
Incremental Effectiveness QALY