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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.

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

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### Introduction

Nonsmall-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 5-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 past decade. More recently, molecularly targeted drugs have been added upfront to improve the efficacy of first-line chemotherapy in patients with advanced NSCLC. Many of these drugs, however, have not proven to be very useful in prolonging OAS (erlotinib and gefitinib [8,9], and cetuximab [10]) or toxicity problems limit their use (bevacizumab [11,12]). In addition, 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, current 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 nonsquamous-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. Although the trial by Ciuleanu et al. [22] used a nonpemetrexed-containing, platinum-based first-line chemotherapy irrespective of the tumor histotype, the platinum-pemetrexed doublet has become standard first-line treatment in patients

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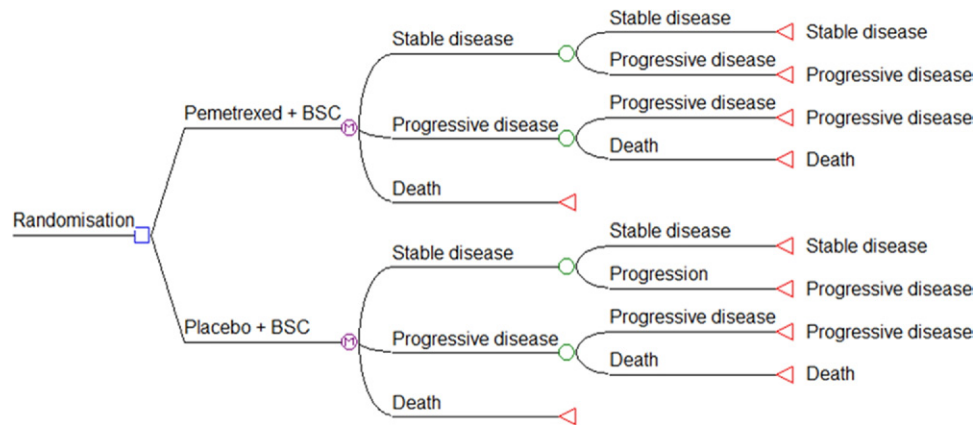


Fig. 1 – Markov model. Model input data for transition probabilities. See Table 3.

with advanced nonsquamous-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 nonsquamous-cell lung cancer [23].

The objective of our study was to examine the cost-effectiveness of pemetrexed maintenance treatment following standard platinum-based chemotherapy in advanced, inoperable stage IIIb or IV nonsquamous-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

A Markov model was constructed to assess the cost-effectiveness of maintenance therapy with pemetrexed plus BSC, compared to BSC alone, in patients with advanced nonsquamous-cell lung cancer, based on the results of one phase III, placebo-controlled randomized study by Ciuleanu et al. [22], because no other trials with a similar setting were available. The model adopted a lifelong 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 because 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 Swiss franc (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 nonpemetrexed-containing doublet chemotherapy were randomly assigned in a 2:1 ratio. Patients received pemetrexed at a dose of 500 mg/m<sup>2</sup> or placebo on day 1 of a thrice-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 was OAS. The maximum length of survivor follow-up was 41.5 months. For the health economic analysis, only data for the nonsquamous-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 because 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 BSC, compared to BSC alone, expressed as cost per quality-adjusted life-year (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 (2009, TreeAge Software Inc., Williamstown, MA).

## Structure of the Markov model and clinical model inputs

The structure of the Markov model is shown in Figure 1. The model comprises three mutually exclusive health states; that is, stable/responsive disease (entry state); disease progression; and death, with state transitions at the end of each treatment cycle. Markov

Table 1 – Unit costs and resource use.

	Unit cost	Resource use per cycle	
		Pemetrexed arm	Best supportive care arm
Best supportive care	€2555*	per cycle	per cycle
Pemetrexed [40]	€2.88/mg	500 mg/m <sup>2</sup> , BSA = 1.77	0
Neutropenia [41,42]	€5400	3% of patients once per stage	0
Follow-up Chemotherapy	See Table 2	51% of patients	67% of patients

BSA, body surface area.

\* Adapted from Pompen et al. [30].

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