Cost-Effectiveness Analysis Of Pegfilgrastim In Patients With Non-Small Cell Lung Cancer Receiving Ramucirumab Plus Docetaxel In Japan

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Abstract

Purpose: The dose-limiting factor of ramucirumab plus docetaxel (RAM+DTX) therapy in patients with non-small cell lung cancer (NSCLC) is febrile neutropenia (FN), which has a higher incidence in Asians. Pegfilgrastim (Peg-G) is routinely used for FN prophylaxis in Japan. This study aimed to evaluate the cost-effectiveness of Peg-G in patients with NSCLC receiving RAM+DTX in Japan.

Methods: We simulated model patients treated with RAM+DTX in Japan and developed a decision-analytical model for patients receiving Peg-G prophylaxis or no primary prophylaxis. The expected cost, quality-adjusted life-year (QALY), and incremental cost-effectiveness ratio (ICER) of each treatment were calculated from the perspective of a Japanese healthcare payer. The willingness-to-pay (WTP) threshold was set at 45,867 United States dollars (USD) (5 million Japanese yen) per QALY gained. The probabilities, utility values, and other costs were obtained from published sources. Deterministic sensitivity analysis (DSA) and probabilistic sensitivity analysis (PSA) were conducted to evaluate the effect of each parameter on the results and robustness of the base-case results.

Results: The expected cost and QALYs gained were 4,394 USD and 0.603 for Peg-G prophylaxis, and 2,242 USD and 0.578 for no primary prophylaxis, respectively. The ICER was calculated to be 83,147 USD per QALY gained. The results of DSA were most sensitive to FN risk with Peg-G. PSA revealed a 23.7% probability that primary prophylaxis with Peg-G was cost-effective.

Conclusion: Peg-G is not cost-effective in patients with NSCLC receiving RAM+DTX in Japan.

Introduction

Febrile neutropenia (FN) is one of the most serious adverse events in patients undergoing chemotherapy, which can be fatal and should be avoided. Granulocyte colony-stimulating factor (G-CSF) effectively reduces the incidence of infection and risk of FN, and prophylactic administration of G-CSF is recommended in regimens with high-risk of FN. The American Society of Clinical Oncology [1], National Comprehensive Cancer Network [2], and European Society for Medical Oncology guidelines [3] recommend primary prophylaxis with G-CSF in regimens associated with a 20% or greater risk of FN, and the Japanese Society for Clinical Oncology guidelines are similar. Pegfilgrastim (Peg-G) is an N-terminal pegylated form of filgrastim that has a long elimination half-life. A meta-analysis of trials comparing the efficacy of Peg-G and filgrastim suggested that Peg-G is superior and more effective [4]. Peg-G is approved in Japan in a dose of 3.6 mg and is widely used for primary prophylactic administration in regimens associated with a high risk of FN because it requires only a single dose.

In patients with advanced non-small cell lung cancer (NSCLC), ramucirumab (RAM) plus docetaxel (DTX) therapy is effective in patients who are refractory to platinum-based therapy [5-7]. FN is a dose-limiting factor of RAM+DTX. In the global phase III study (REVEL study), the dose of DTX was set at 75 mg/m^2 [5]; however, in a phase II study conducted in Japan [6], the dose of DTX was reduced to 60 mg/m^2 because the incidence of FN was found to be high (43.8%) in East Asian patients in the subgroup analysis [7].

Nevertheless, the FN rate was high in the study (34.2 %). Therefore, primary prophylaxis with Peg-G is widely used in Japan in patients receiving RAM+DTX.

Because G-CSFs are expensive drugs, uniform administration in regimens with a low FN risk is not recommended, and it is better to consider the cost-effectiveness. Peg-G is a highly expensive drug, and its price in Japan is 108,635 Japanese yen (JPY) (1,017 United States dollars [USD]). Recently, there have been several reports on the cost-effectiveness of Peg-G, but the results vary according to the cancer type and study conditions [8-15]. Most of the studies concluding that Peg-G is cost-effective have been reported in potentially curable cancer types such as malignant lymphoma and early stage breast cancer, and these results were based on the condition that G-CSF improves the survival outcomes by maintaining the relative dose intensity. However, few studies have examined the cost-effectiveness of Peg-G in palliative chemotherapy in patients with advanced or recurrent disease. FN prophylaxis with G-CSF is very important in high FN risk regimens, such as RAM + DTX, but it should be used with consideration of cost-effectiveness. Therefore, we conducted this study to evaluate the cost-effectiveness of Peg-G in patients with NSCLC receiving RAM+DTX in Japan.

Methods

1. Model overview

The economic model was constructed using TreeAgePro2020 (TreeAge Software, Inc., MA, USA) to evaluate the cost-effectiveness of Peg-G. The model patients were NSCLC patients who became refractory to platinum-based therapy and received RAM+DTX as an outpatient therapy. The expected costs and quality-adjusted life years (QALYs) of the two treatment strategies, primary prophylaxis of FN with Peg-G and no primary prophylaxis, were calculated. The rationale for choosing no primary prophylaxis for comparison was that, in Japan, most RAM+DTX therapy is administered as an outpatient treatment, and there are few opportunities to use daily G-CSF.

2. Model structure

We constructed a decision analytic model (Fig. 1). Patients initially received four cycles of RAM+DTX, which is the median number of cycles completed in the JVCG trial [6]. The JVCG study is a phase II trial conducted in Japan. The main eligibility criteria were patients who became refractory to platinum-based therapy, did not receive prior epidermal growth factor receptor tyrosine kinase inhibitor monotherapy, aged ≥20 years, and Eastern Cooperative Oncology Group performance status 0 or 1. The dose of RAM+DTX comprised 10 mg/kg of RAM and 60 mg/m^2 of DTX, and one cycle was 21 days. Peg-G primary prophylaxis or no primary prophylaxis were selected in the first branch of the decision analytic model. Each had a certain probability of developing FN, and patients who developed FN had a certain possibility of developing FN-related mortality. Patients who survived each cycle moved on to the next cycle, and after up to four cycles, they were considered to survive in the progressive state for one year. The rationale for choosing one year was that the median overall survival (OS) of patients receiving RAM+DTX in the JVCG

and REVEL studies was 15.15 months and 15.44 months, respectively [5, 6], and the survival time after four courses of RAM+DTX therapy was expected to be about one year.

3. Probabilities

The probabilities included in the model were the probability of FN with Peg-G and no primary prophylaxis, and FN-related mortality (Table 1). The probability of FN with no primary prophylaxis was 34.2% (26/76) based on the JVCG study [6]. The incidence of FN with Peg-G use was set at 5.0% (1/20) based on a phase II study conducted in Japan [16]. The definition of FN differs slightly among countries and guidelines, but based on the Japanese Society of Medical Oncology definition, these studies defined FN as an absolute neutrophil count of <500 neutrophils/μL or anticipated decline to ≤500 neutrophils/μL within the next 48 hours, accompanied by an axial temperature of ≥37.5 °C (or oral temperature of ≥38.0 °C). The FN-related mortality rate was set at 2.4% for both the Peg-G primary prophylaxis and no primary prophylaxis groups based on a report by Chan et al. that showed a mortality of 2.4% in patients with solid tumors and lymphoma when G-CSF was administered therapeutically for the treatment of FN [17]. Even in the absence of primary prophylaxis, G-CSF is expected to be administered therapeutically for the treatment of FN; therefore, the value of FN-related mortality was set when G-CSF was administered therapeutically in both groups.

4. Cost

The costs included in the model were the drug costs of Peg-G and treatment costs of FN. The cost of chemotherapy, supportive care other than Peg-G, and cost of the progressive state after chemotherapy were not included because they were considered equal in both groups. The cost of Peg-G is based on the National Health Insurance Drug Price Standard listed in 2021. The cost of FN treatment was assumed to be 22,150 JPY per day based on the Diagnostic Procedure Combination (DPC) electronic score sheet in Japan, and multiplied by the average hospitalization period of 8 days to arrive at 177,200 JPY. The DPC electronic score sheet was based on the clinical data collected by Japan's Ministry of Health, Labor, and Welfare. This allowed us to check the medical costs per day for insurance-covered diseases and the average number of days of hospitalization. The costs calculated in JPY were converted to USD using the exchange rate reported by the Organization for Economic Cooperation and Development in 2020 (1 USD = 106.78 JPY) [18].

5. Utility values

The baseline utility value was set at 0.727, based on a report by Pérol et al. [19], which assessed the quality of life (QOL) in the REVEL study, because no study has directly evaluated the QOL in the Japanese population. Pérol et al. assessed the patients' QOL using the Lung Cancer Symptom Scale (LCSS). The LCSS includes six symptoms and three global items measured on a 0-100 mm scale; higher scores represent a greater symptom burden. The mean (standard deviation [SD]) value of the baseline total LCSS score was 27.3 mm (17.08) mm for RAM+DTX. The decrease in the utility values during FN and the progressive state was based on a report by Nafees et al. [20, 21]. The decrease in the utility value from the

baseline during FN and the progressive state was set at 0.470 and 0.180, respectively. Nafees et al. calculated the impact of health state utilities and treatment-related adverse events on the QOL of patients with NSCLC based on interviews with oncologists and oncology specialist nurses.

6. Cost-effectiveness analysis

6.1. Base-case analysis

The incremental cost-effectiveness ratio (ICER) was calculated to evaluate the cost-effectiveness of Peg-G. The ICER was calculated using the following formula:

ICER (USD per QALY gained) = (expected cost with Peg-G – expected cost without primary prophylaxis) / (expected QALYs gained with Peg-G – expected QALYs gained without primary prophylaxis).

The willingness-to-pay (WTP) threshold was set at 45,867 USD (5 million JPY) per QALY gained, as defined by Shiroiwa et al. [22]. No discount was applied since the study lasted for only about a year. A cost-utility analysis was performed from the perspective of a Japanese healthcare payer.

6.2. Deterministic sensitivity analysis

In the deterministic (one-way) sensitivity analysis (DSA), each parameter was varied within a set range, and the effect of each parameter on the results was evaluated. The range of parameter variation was determined using 95% confidence intervals (95% CIs), SDs, and ranges obtained from published literature.

The number of treatment cycles varied between two and eight due to a lack of statistical information to calculate the 95% CI. The cost of Peg-G varied from 70% to 100%. The rationale for this range was that although no biosimilars of Peg-G have been approved in Japan, generic biosimilars in Japan are generally set at approximately 70% of the price of the branded ones. The cost of FN treatment and length of hospital stay for FN varied by ±20% due to a lack of statistical information to calculate the 95% CI. The maximum decrease in the utility score during FN was set at 0.50, which was based on the results of a study in the United Kingdom (UK) that reported the largest decrease in the utility score by Nafees et al. [21]. The minimum decrease in the utility score was set at 0.05, which was the lower limit of the range of variation reported by Lathia et al. [13]. For the baseline utility values, decrease in the utility value in the progressive state, and FN probability, the 95% CIs were calculated based on previous reports [6, 16, 19, 20]. For the FN-related mortality rate, the minimum value was set at 0, and the maximum value was set at 0.08 based on a report by Kuderer et al. [23]. For parameters in which the ICER was below the WTP threshold in the DSA setting range, a threshold analysis was conducted to calculate the value at which the ICER equals the WTP threshold.

6.3. Probabilistic sensitivity analysis

In the probabilistic sensitivity analysis (PSA), each parameter was varied under the conditions listed in Table 1 to evaluate the robustness of the base-case analysis. For the range of variation and probability

distributions of the parameters, we consulted the published literature or considered reasonable values when the CI was not given. A Monte Carlo simulation was conducted for 1,000 iterations of each comparison.

Results

1. Base-case analysis

The expected costs were 4,394 USD for Peg-G and 2,242 USD for no primary prophylaxis, and the expected QALYs gained were 0.603 and 0.578 for Peg-G and no G-CSF, respectively. The incremental cost of Peg-G for no primary prophylaxis was 2,152 USD, with incremental QALYs of 0.025, while the ICER was calculated as 83,147 USD per QALY gained. This value was above the WTP threshold. Consequently, in the base-case analysis, primary prophylaxis with Peg-G was less cost-effective than no primary prophylaxis.

2. Deterministic sensitivity analysis

A tornado diagram based on DSA is shown in Fig. 2. It is arranged in order of the degree of influence on the ICER. The most influential parameter for ICER was the FN risk with Peg-G, followed by FN-related mortality, FN risk with no primary prophylaxis, disutility due to FN, cost of Peg-G, length of hospital stay for FN, FN hospitalization cost per day, number of treatment cycles of RAM+DTX, disutility in the progressive state, and baseline utility. The parameters within the range of variation of DSA that were below the WTP threshold were the FN-related mortality rate, FN risk with no primary prophylaxis, and cost of Peg-G. The FN-related mortality rate was > 0.064, FN risk with no primary prophylaxis was > 0.435, and cost of Peg-G was less than 775 USD, which was below the WTP threshold, indicating that Peg-G was cost-effective under these conditions.

3. Probabilistic sensitivity analysis

The PSA results are shown in a scatter plot (Fig. 3). According to the scatter plot, Peg-G is more cost-effective than no primary prophylaxis, and the incremental QALYs are positive below the WTP line (45,867 USD per QALY gained) for the points obtained by random sampling. Probabilistic sensitivity analysis revealed a 23.7% probability that Peg-G was cost-effective compared to no primary prophylaxis. Bases on the cost-acceptability curve (Fig. 4), the cost-effectiveness of Peg-G and no primary prophylaxis were equal when the WTP threshold was set at 72,056 USD.

Discussion

To the best of our knowledge, this is the first report to evaluate the cost-effectiveness of Peg-G in NSCLC patients receiving RAM+DTX. In the base-case analysis, the ICER of Peg-G for no primary prophylaxis was higher than the set WTP threshold (45,867 USD per QALY gained), indicating that primary prophylaxis with Peg-G may be less cost-effective than no primary prophylaxis in Japanese NSCLC patients treated

with RAM+DTX. Some previous reports that evaluated the cost-effectiveness of Peg-G did not assess the FN-related mortality [12, 13]. However, since many studies have recently reported that primary G-CSF prophylaxis reduces infection-related mortality, we included the effect of FN-related mortality in our model [23-25]. In a meta-analysis by Clark et al., which included 13 studies involving 1,518 patients, a clear reduction in infection-related mortality (odds ratio [OR], 0.51; 95% CI, 0.26–1.00) was observed with the prophylactic use of G-CSFs [24]. In a systematic review of 17 randomized trials including 3,493 patients with solid tumors and lymphoma, primary prophylaxis with G-CSF reduced the risk of infection-related mortality (relative risk [RR], 0.55; 95% CI, 0.33–0.90) and early death during chemotherapy (RR, 0.60; 95% CI, 0.43–0.83) [23]. Based on these results, we believe that the inclusion of FN-related mortality in our model is reasonable. If FN-related mortality was not included in the model, the ICER of the base-case analysis would be even larger. Therefore, not including the effect of FN-related mortality in the model increases the robustness of the conclusion that Peg-G is not cost effective.

In DSA, the FN risk with Peg-G was the most influential parameter for ICER, and FN risk with no primary prophylaxis also had a significant impact on ICER. This indicates that the extent to which the absolute FN risk is reduced significantly impacts the ICER. Threshold analysis showed that FN risk in patients without primary prophylaxis was 0.435 or higher, which is below the WTP threshold, indicating that if the absolute FN risk can be reduced by approximately 40%, it may be cost-effective even at the current Peg-G drug price. Furthermore, the results showed that Peg-G is cost-effective if its cost is less than 775 USD, which is less than the WTP threshold. Although Peg-G biosimilars have not been approved in Japan, several Peg-G biosimilars have been approved by the Food and Drug Administration (FDA). Peg-G-jmdb, Peg-G-cbqv, and Peg-G-bmez have been shown to exhibit pharmacokinetic and pharmacodynamic properties comparable to those of the original products, and to be equivalent in safety and equivalence [26-32]. In Japan, the price of biosimilars is approximately 70% of that of the original product. Therefore, if a Peg-G biosimilar is approved, it is expected to cost less than 775 USD, making Peg-G cost-effective. If a Peg-G biosimilar is approved in Japan, its use should be recommended from a cost-effectiveness perspective.

In PSA, the probability of exceeding the WTP threshold was 23.7%, indicating the robustness of the results. The WTP threshold at which the cost-acceptability curves for Peg-G and no prophylaxis intersected was 72,056 USD. It is difficult to define the WTP threshold uniformly because it is affected by each country's economic situation and insurance system. The WTP threshold in the U.S. is generally set at 50,000 USD per QALY gained [33]. The National Institute for Health and Care Excellence (NICE) in the UK has set the WTP threshold for use in the national insurance system at £20,000 - 30,000, with some drugs such as cancer drugs set at £50,000 [34, 35]. In Japan, it is believed that the WTP threshold should be set at 7.5 million JPY per QALY gained for rare diseases and anticancer drugs [36]. In addition, since Peg-G is used in various regimens, it is necessary to comprehensively evaluate its cost-effectiveness for multiple diseases and regimens.

This study has some limitations. First, the utility values were not based on studies of Japanese patients receiving RAM+DTX. The utility value has been reported to vary by country. Nafees et al. reported that the disutility due to FN was -0.47 globally, -0.36 in Taiwan, and -0.50 in the UK [21]. As there are no

appropriate QOL-related studies in Japanese NSCLC patients, we adopted the global value for the base-case analysis. However, since the ICER was higher than the WTP threshold even at -0.05, the smallest disutility in DSA, the adoption of the global value as the utility value had little impact on the results. Similarly, disutility in the progressive state was estimated based on interviews with oncologists and oncology specialist nurses in the UK, and may differ from the utility value in the Japanese [20]. However, the impact of disutility in the progressive state on the ICER was the smallest among all DSA parameters. Therefore, using the utility value of the progressive state in the UK also had a small impact on ICER. Second, because the analysis was conducted from the standpoint of the healthcare payer, it does not consider indirect costs such as lost productivity and lost wages of the patients and their supporting family members. Since Peg-G, which does not require daily hospital visits, is a drug with a significant benefit related to indirect costs, it is possible that the cost-effectiveness of Peg-G was underestimated. In the future, it is necessary to evaluate such indirect costs.

Finally, although this study showed that Peg-G is not cost-effective in Japanese patients with NSCLC receiving RAM+DTX, it is clear that Peg-G has significant benefits in those receiving high FN risk regimens. The use of Peg-G should not be limited based on the results of this study. We hope that the price of Peg-G will be reviewed in the future so that its use can be recommended from a cost-effectiveness perspective.

Declarations

Compliance with Ethical Standards

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Availability of data and material: The authors have full control of the data, which are available upon request.

Code availability: Analyses were performed with TreeAge® Pro 2020 (TreeAge Software Inc. Williamstown, MA, USA).

Author contributions: All authors were involved in the design of the study. YK and HT coordinated this study. YK, TT, and HT drafted the manuscript. YK, TS, JK, JA, TM, and YM performed the data analyses. All authors critically revised, read, and approved the final manuscript.

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Table

Table 1. Variables, DSA range, and distribution type for PSA in the model

Parameters	Base case (DSA range)	Distribution type for PSA	Reference
Utility weight			
Base line utility	0.727 (0.712 – 0.742)	Beta (SE = 0.171)	Pérol et al. [19]
Disutility due to FN	0.470 (0.050 - 0.500)	Beta (SE = 20% of base-case)	Nafees et al. [21] Lathia et al. [13]
Disutility in the progressive state	0.180 (0.138 – 0.223)	Beta (SE = 0.022)	Nafees et al. [20]
Probabilities			
FN risk with no primary prophylaxis	0.342 (0.237 – 0.460)	Beta (α = 26, ß = 50)	Yoh et al. [6]
FN risk with Peg-G	0.050 (0.001 – 0.249)	Beta (α = 1, ß = 19)	Kasahara et al. [16]
FN related mortality risk	0.024 (0 – 0.080)	Triangular (Minimum = 0, Most likely = 0.024, Maximum = 0.080)	Fust et al. [10] Kuderer et al. [23]
Costs (USD)			
Pegfilgrastim 3.6 mg	1017 (712 - 1017)	Did not vary	NHI price list
FN hospitalization cost (per day)	207 (166 – 249)	Triangular (Minimum = 166, Most likely = 207, Maximum = 249)	DPC electronic score sheet
Others			
Treatment cycles of RAM+DTX	4.0 (2.0 – 8.0)	Triangular (Minimum = 8.0, Most likely = 4.0, Maximum = 2.0)	Yoh et al. [6]
Length of stay in hospital for FN (days)	8.0 (6.4 – 9.6)	Triangular (Minimum = 6.4, Most likely = 8.0, Maximum = 9.6)	DPC electronic score sheet

DPC: diagnostic procedure combination, DSA: deterministic sensitivity analysis, DTX: docetaxel, FN: febrile neutropenia, NHI: National Health Insurance, PSA: probabilistic sensitivity analysis, Peg-G: pegfilgrastim, RAM: ramucirumab, SE: standard error

Figures

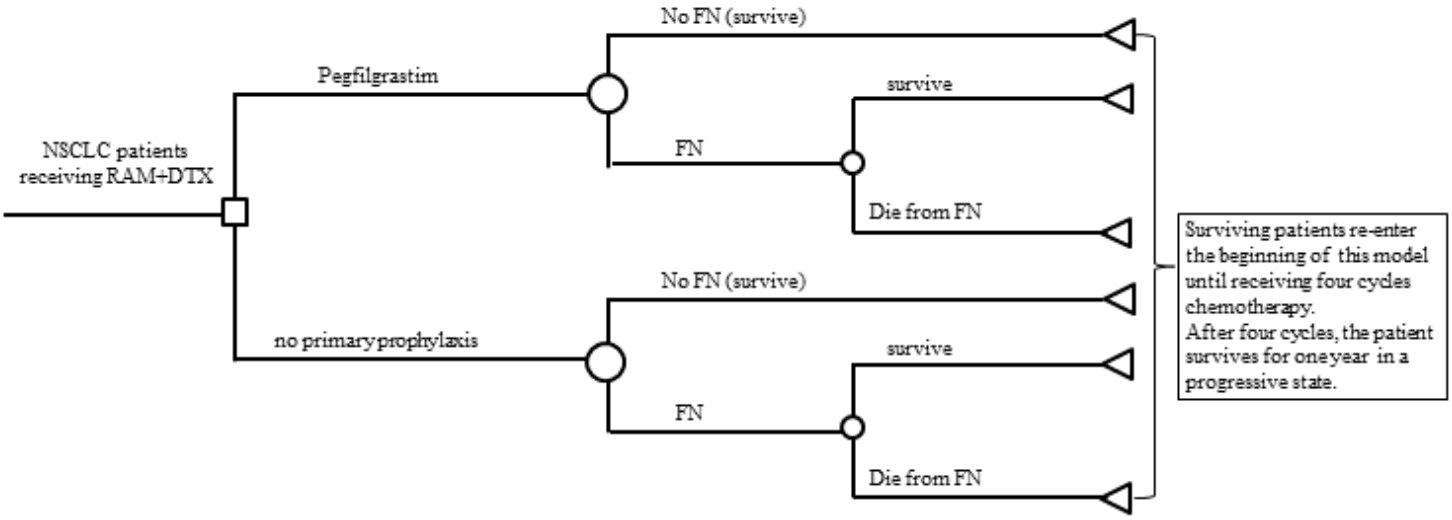

Figure 1

Decision-analytic model for cost-utility analysis

DTX, docetaxel; FN, febrile neutropenia; NSCLC, non-small cell lung cancer; RAM, ramucirumab

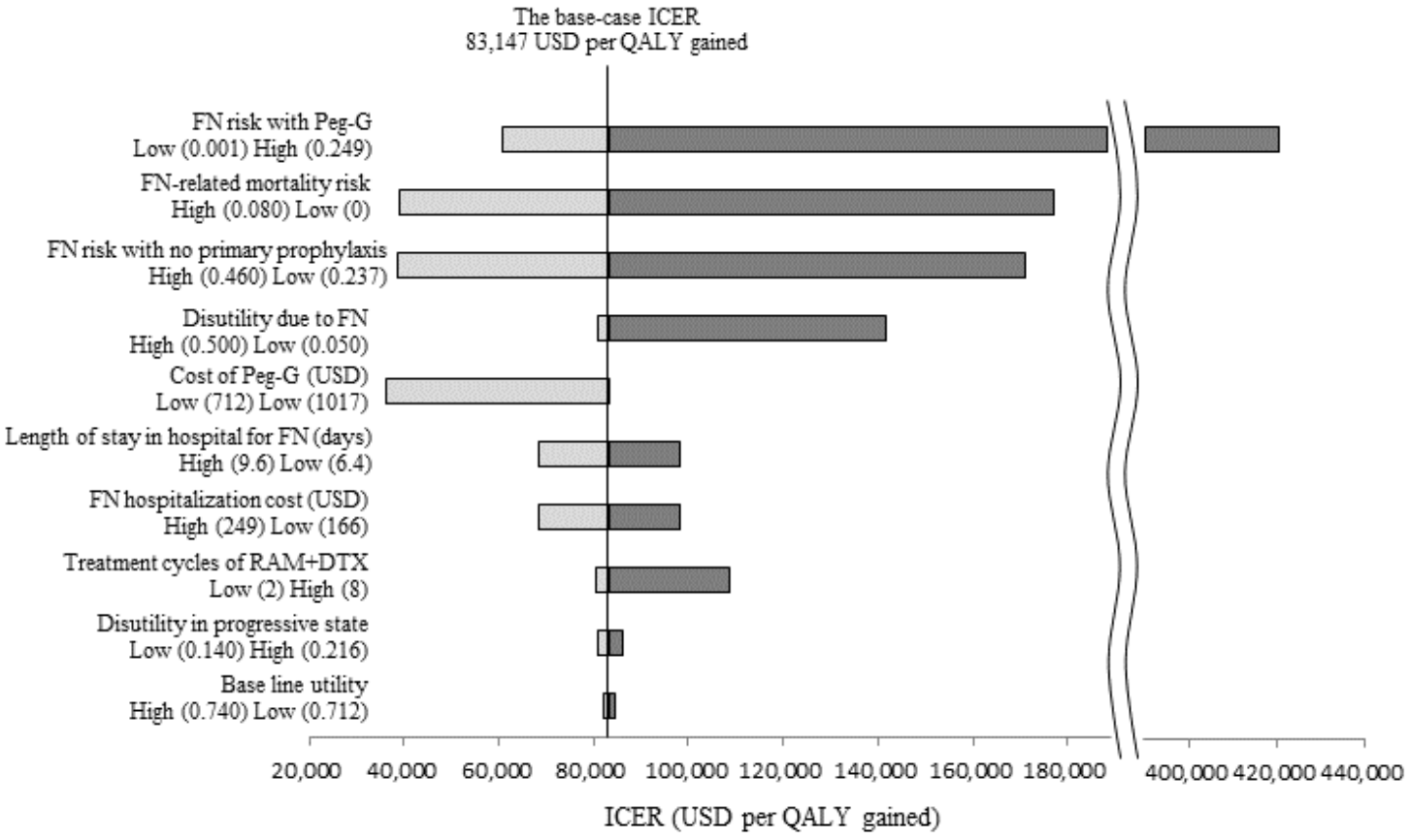

Figure 2

Results of deterministic sensitivity analysis

DTX, docetaxel; FN, febrile neutropenia; ICER, incremental cost-effectiveness ratio; Peg-G, pegfilgrastim; QALY, quality-adjusted life year; RAM, ramucirumab; WTP, willingness to pay. The vertical axis represents the base-case ICER, horizontal bars represent the difference between the base-case ICER and ICER generated when the model was run using the high and low values of the plausible range, and the entire length of each horizontal bar represents the magnitude of variation in the cost-effectiveness results.

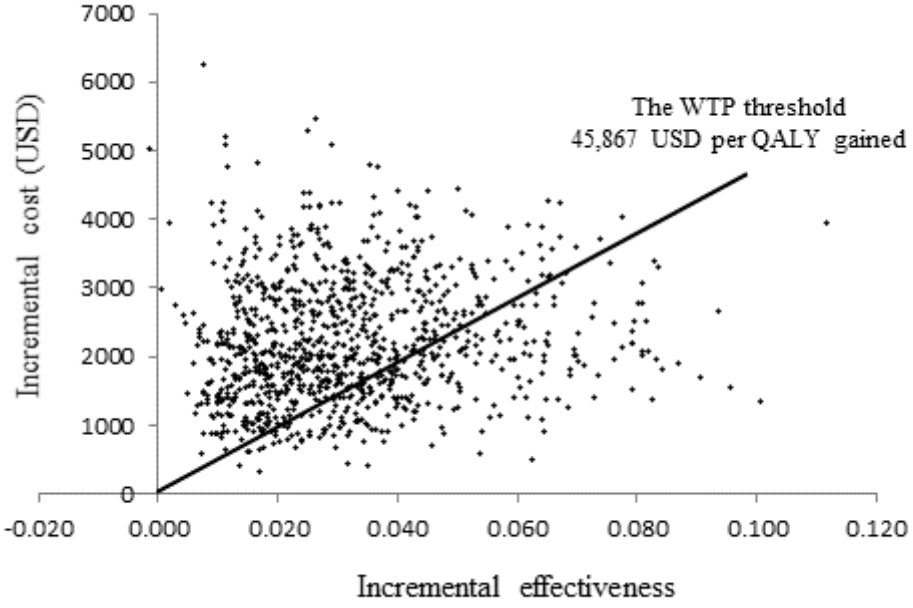

Figure 3

Scatter plot showing results of probabilistic analysis

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; WTP, willingness to pay

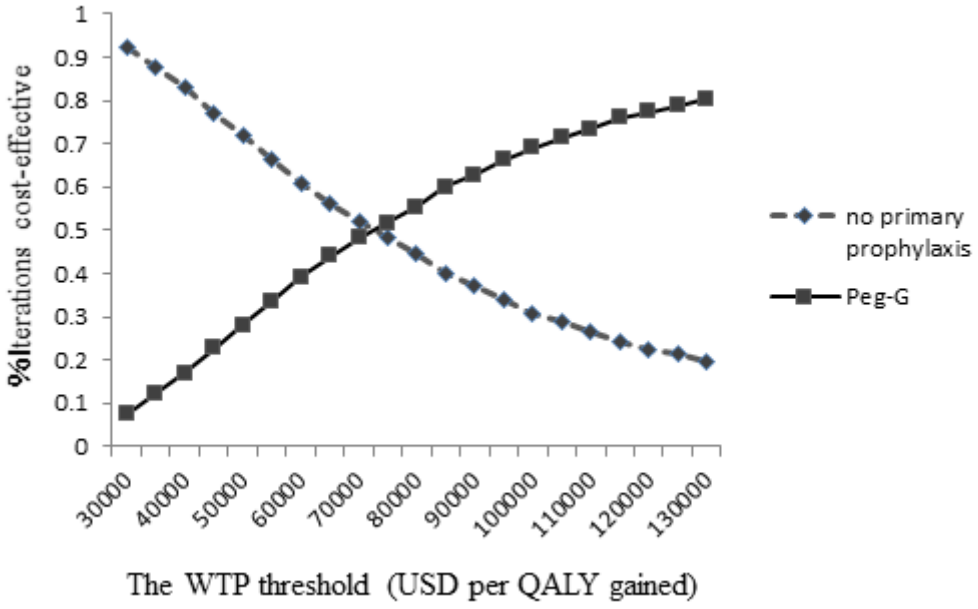

Figure 4

Cost-effectiveness acceptability curve

QALY, quality-adjusted life year; WTP, willingness-to-pay