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Cost-effectiveness of Pembrolizumab as Second-line Therapy for the Treatment of Locally Advanced or Metastatic Urothelial Carcinoma in Sweden

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Abstract

Background: Urothelial carcinoma (UC) is the most common subtype of bladder cancer. The randomized phase 3 KEYNOTE-045 trial showed that pembrolizumab, used as second-line therapy significantly prolonged overall survival with fewer treatment-related adverse events than chemotherapy for advanced UC. Pembrolizumab has been approved by the European Medicines Agency for the treatment of locally advanced or metastatic UC in adults who have received platinum-containing chemotherapy. Many European countries use cost-effectiveness analysis to inform reimbursement decisions.

Objective: To assess the cost-effectiveness of pembrolizumab as second-line therapy for the treatment of advanced UC from a Swedish health care perspective.

Design, setting, and participants: We developed a partitioned-survival model to assess the costs and effectiveness of pembrolizumab compared with vinflunine (base case), paclitaxel, or docetaxel monotherapy in patients with advanced UC over a 15-yr time horizon. We obtained Kaplan-Meier estimates for survival endpoints, adverse events, and utility data from KEYNOTE-045.

Outcome measurements and statistical analysis: We performed parametric extrapolations to estimate overall and progression-free survival beyond the clinical trial period. Swedish costs and utility weights were used to estimate total costs, quality-adjusted life years (QALYs), and incremental cost-effectiveness ratios (ICERs). We performed deterministic and probabilistic sensitivity analyses to assess the robustness of the model results.

Results and limitations: In the base-case analysis, pembrolizumab resulted in a mean survival gain of 1.66 years (1.38 QALYs) at an incremental cost of €69 852 and an ICER of €50 529/QALY gained versus vinflunine monotherapy. ICERs for other chemotherapies were €81 356/QALY for pembrolizumab versus paclitaxel or docetaxel monotherapy, and €71 924/QALY for pembrolizumab versus paclitaxel, docetaxel, or vinflunine monotherapy. Long-term follow-up from KEYNOTE-045 and real-world data are needed to validate the extrapolations.

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Conclusions: The results indicate that pembrolizumab improves survival, increases QALYs, and is cost-effective as second-line therapy at a willingness-to-pay threshold of €100 000/QALY for the treatment of advanced UC.

Patient summary: To date, pembrolizumab is the only treatment associated with a significant overall survival benefit compared with chemotherapy in a randomized controlled trial as second-line therapy for advanced urothelial carcinoma. Our trial-based cost-effectiveness analysis suggests that pembrolizumab is a cost-effective option over chemotherapy in patients with advanced urothelial carcinoma after platinum-based therapy in Sweden.

1. Introduction

Bladder cancer (BC) is the ninth most common cancer worldwide [1] and results in significant mortality, morbidity, and costs [2,3]. The vast majority of BC cases (90%) are urothelial carcinoma and occur in developed countries, with the highest incidence in North America and Europe [1,4]. In 2015, the incidence in Sweden was approximately 2700 patients with a median age of 73 yr [5,6]. In 2012, the total estimated cost of BC was €4.9 billion in Europe, with €2.9 billion in direct costs and €2.0 billion in indirect costs associated with productivity losses due to mortality and morbidity [7,8]. In Sweden, BC accounted for €136.61 million in total costs in 2012 [7]. Intense follow-up, high recurrence rates, and preoperative and postoperative complications were the key contributors to this economic burden [7].

In patients with locally advanced or metastatic urothelial carcinoma, platinum-based combination therapies are recommended as the first-line standard of care (SoC) [9]. Most patients experience relapse following first-line therapy (40–70%) and historically were faced with a choice between receiving second-line toxic chemotherapies with limited efficacy (vinflunine or a taxane) or palliative symptom relief with noncurative intent [10]. Pembrolizumab, a monoclonal antibody against PD-1, is the first immunotherapy to demonstrate superior overall survival (OS) compared with chemotherapy in patients with advanced urothelial carcinoma after failure of platinum-based therapy [11]. The clinical efficacy of pembrolizumab in advanced urothelial carcinoma after failure of platinum-based therapy was established in KEYNOTE-045 (NCT02256436), a phase 3 multicenter global randomized clinical trial with chemotherapy comparators that included paclitaxel, docetaxel, and vinflunine monotherapy. The trial demonstrated improvements in median OS when compared to chemotherapy (10.3 mo in the pembrolizumab arm compared with 7.4 mo in the chemotherapy arm) [11]. On the basis of KEYNOTE-045 data, pembrolizumab was approved in Europe for the treatment of locally advanced or metastatic urothelial carcinoma in adults who have previously received platinum-containing chemotherapy [12].

In many European countries, cost-effectiveness evaluations play a critical role in the decision to reimburse health care providers for pharmaceuticals. In the Swedish health care system, the Dental and Pharmaceutical Benefits Agency and the New Therapies Council recently recommended pembrolizumab for patients with advanced urothelial carcinoma who have previously received platinum-containing chemotherapy on the basis of ethical considerations and health economics evaluation of this treatment [13].

The objective of the current analysis was to evaluate the cost-effectiveness of pembrolizumab compared with chemotherapy as second-line therapy for the treatment of locally-advanced or metastatic urothelial carcinoma at a willingness-to-pay threshold of €100 000 per quality-adjusted life year (QALY) from a Swedish health care perspective [14].

2. Patients and methods

2.1. Patient population

The target population was patients with advanced urothelial carcinoma who had received platinum-based chemotherapy and experienced disease progression during or following that chemotherapy [11].

2.2. Comparators

For the base-case analysis, costs and effects for pembrolizumab were compared with those for vinflunine, the only therapy recommended as second-line treatment for advanced urothelial carcinoma according to Swedish guidelines. Two additional analyses were considered: pembrolizumab compared with taxanes (paclitaxel or docetaxel monotherapy), and pembrolizumab compared with paclitaxel, docetaxel, or vinflunine monotherapy (the control arm in KEYNOTE-045). The dose and frequency considered were as for KEYNOTE-045: pembrolizumab, 200 mg; vinflunine, 320 mg/m^2; paclitaxel, 175 mg/m^2; and docetaxel, 75 mg/m^2; each treatment was administered intravenously once every 3 week.

Costs and effectiveness were evaluated for pembrolizumab and comparators in the target patient population using data from KEYNOTE-045. Patient characteristics in the pembrolizumab and comparator arms were comparable.

2.3. Model structure

A partitioned-survival model was developed in Excel 2010 (Microsoft, Redmond, WA, USA) to project the costs and effects for each regimen in the target population [15]. The model includes three health states (Fig. 1): progression-free, progressive disease, and death. The progression-free health state includes patients who have progressed on first-line treatment with platinum-based chemotherapy and have begun second-line treatment.

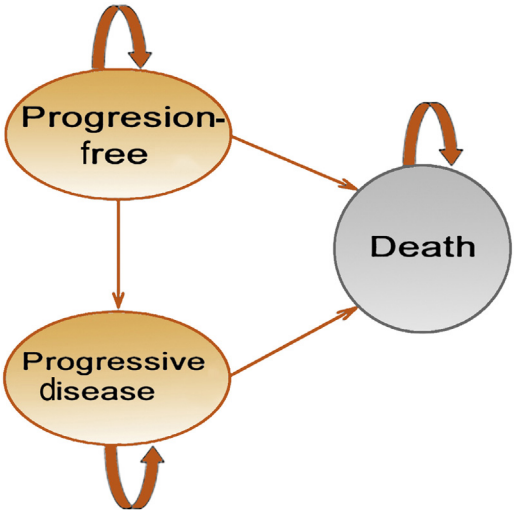

Fig. 1 – Diagram of transitions in the partitioned survival model used to estimate health economics outcomes.

Transition to the progressive disease health state occurs once they experience disease progression. Progression is defined in line with KEYNOTE-045 and assessed by blinded independent central review in accordance with Response Evaluation Criteria in Solid Tumors v1.1. Patients may also die in either the progression-free or progressive disease health state (transition to the death state).

The model estimates the probability of being in each of the three health states at the end of each week. Survival estimates from the progression-free survival (PFS) curve provide the probability a patient is in the progression-free health state. The survival estimates from the OS distribution represent the patient's likelihood of being dead or alive at each particular time point. Finally, the difference between the OS and PFS curves yields the probability that the patient is in the progressive disease health state. Kaplan-Meier survival curves based on clinical trial endpoints in KEYNOTE-045 were used for time points during the trial period, while parametric survival functions were developed to project PFS and OS beyond the trial period (Table 1). Life expectancy data from Swedish life tables were also considered to account for age-specific all-cause mortality. The model assumed that the cost and health benefits accrued at weekly-spaced discrete time points over the time horizon of 15 yr.

2.4. Clinical and utility inputs

Clinical inputs such as adverse event (AE) incidence rates, weight, body surface-area distributions, and utility inputs were drawn from KEYNOTE-045 with a cutoff date of January 18, 2017. We used utility values for the progression-free and progressive disease health states, and the disutility associated with grade ≥3 AEs using EQ-5D survey responses from KEYNOTE-045 and Swedish utility weights [16,17].

2.5. Cost inputs

The costs for resources utilized by patients were expressed in 2018 euros (€) [18]. We obtained drug acquisition costs from Pharmacy Heart (Apotek Hjärtat), a national Swedish pharmacy. We also considered drug administration and diagnostic tests in our model [19]. We modeled the cost for subsequent therapy on the Swedish clinical input whereby 10% of patients in the vinflunine arm were subsequently administered gemcitabine and carboplatin for an average of 20 week [19]. We included in our analysis the disease management costs incurred while in the progression-free and progressive disease health states, hospice and other costs associated with the last month before death, and AE-related costs (Table 1).

2.6. Statistical analysis

Kaplan-Meier survival curves for PFS, OS, and time-on-treatment (ToT) were obtained from KEYNOTE-045. Because 13.3% of the patients in the vinflunine arm received immunotherapy after discontinuation, it is likely that OS was overestimated in the control arm [20]. To adjust for this bias, we used the prespecified rank-preserving structural-failure time (RPSFT)

Table 1 – Model inputs.

	Pembrolizumab	Vinflunine	Data source
Patient characteristics			
Mean body weight, kg (SD)	73.58 (17.23)	73.58 (17.23)	KEYNOTE-045
Mean BSA, m^2 (SD)	1.85 (0.25)	1.85 (0.25)	KEYNOTE-045
Cost inputs			
Drug cost (€)			
50-mg vial	1688	257	[27]
250-mg vial		1252	
Administration (€/administration)	269	269	[18]
Disease management			
PF (€/week)	92	92	Weekly HCRU and unit costs
Progressive disease (€/week)	215	215	Weekly HCRU and unit costs
Subsequent treatment (€/week)	0	714	[19]
Terminal care (month before death)	7356	7356	[28]

Utilities	Mean EQ-5D utility (95% confidence interval) [a]			Data source
	Pembrolizumab	Vinflunine	Pooled	
PF with grade ≥3 AE	0.798 (0.772–0.823)	0.822 (0.796–0.848)	0.806 (0.787–0.825)	KEYNOTE-045
PF without grade ≥3 AE	0.865 (0.857–0.874)	0.830 (0.812–0.848)	0.859 (0.851–0.866)	KEYNOTE-045
Disutility due to grade ≥3 AE (by subtraction)	0.067	0.008	0.053	KEYNOTE-045
Progressive disease	0.821 (0.808–0.834)	0.764 (0.736–0.792)	0.813 (0.801–0.824)	KEYNOTE-045

AE = adverse event; BSA = body surface area; HCRU = health care resource utilization; PF = progression-free; SD = standard deviation.
[a] EQ-5D utility based on all treated patients as per the Swedish algorithm.

method in the base-case analysis [21]. Two-stage adjustment was not feasible for the base-case comparator owing to the small sample size. Two-stage adjustment was applied as a better method in addressing the OS bias than the RPSFT method for comparison of pembrolizumab with paclitaxel/docetaxel/vinflunine and with paclitaxel/docetaxel in the sensitivity analysis [21].

Survival projections beyond the trial period were developed to estimate long-term OS and PFS in accordance with National Institute for Health and Care Excellence (NICE) guidelines [22]. We applied a piecewise extrapolation technique to account for structural differences observed in the initial parts of the Kaplan-Meier curves from KEYNOTE-045. We divided the time horizon into two parts, with the cutoff point determined according to the statistical method recommended by NICE, for both treatment arms [22]. The first part uses the Kaplan-Meier estimates for OS and PFS, while the subsequent part provides extrapolation based on the best fit among exponential, Weibull, Gompertz, log-logistic, log-normal, and generalized gamma parametric distributions. We used visual inspection of the Kaplan-Meier curves, goodness-of-fit statistics, and clinical plausibility to determine the parametric distribution with the best fit.

Similar to the approach for OS and PFS, ToTs for pembrolizumab and comparator arms were explicitly modeled as an outcome and estimated on the basis of KEYNOTE-045 data. We extrapolated and modeled ToT data using one-piece parametric curves (Supplementary material).

2.7. Outputs

We estimated the proportion of patients in each health state for each cycle over 15 yr by modeling OS and PFS. Costs and utility weights were subsequently assigned to the health states. We summed the costs and utilities over the cycles to estimate the projected direct medical costs, total costs, life years, and QALYs for pembrolizumab and the selected comparator. The incremental costs and QALYs were then used to estimate the incremental cost-effectiveness ratio (ICER; incremental cost per QALY gained). We used an annual discount rate of 3% to determine the present value of costs and health outcomes in this economic evaluation.

We depicted one-way sensitivity analyses using a tornado diagram to examine the impact of changes in each of the input parameters on the results. We conducted a probabilistic sensitivity analysis using a second-order Monte Carlo simulation with 1000 iterations to examine the robustness of the model outputs and the uncertainty of all parameters taken together.

3. Results

3.1. Base-case results

We considered Kaplan-Meier curves before week 15 for PFS and week 32 for OS and used the best-fitting parametric distributions, which were a log-logistic distribution for the pembrolizumab arm and an exponential distribution for the vinflunine arm, for time after these points (Fig. 2). For ToT, Weibull and exponential distributions gave the best fit for the pembrolizumab and vinflunine arms, respectively.

Results for the base case are presented in Table 2. The projected discounted direct-treatment costs/per patient were €98 354 and €28 501 in the pembrolizumab and vinflunine arms, respectively. We further estimated that patients treated with pembrolizumab and vinflunine would experience a mean-discounted life expectancy of 2.40 and 0.73 yr, respectively. Pembrolizumab-treated patients had a discounted QALY gain of 1.38 QALYs when compared with vinflunine (1.99 vs 0.61 QALYs).

Cost-effectiveness analysis revealed an overall ICER of €50 529/QALY gained with pembrolizumab over vinflunine. ICERs of €81 356/QALY and €71 924/QALY were attained for pembrolizumab compared with taxanes (paclitaxel or docetaxel monotherapy) and with the pooled treatment with paclitaxel, docetaxel, or vinflunine monotherapy.

3.2. Sensitivity analyses

The one-way sensitivity analysis results are presented in Figure 3. The dose intensity of pembrolizumab, extrapolation of OS for pembrolizumab, and the discount rate for health outcomes had the greatest impact on ICER values, while the costs for AEs, terminal care, and subsequent treatment had the least impact.

Probabilistic sensitivity analysis gave an expected ICER of €50 845/QALY, suggesting that pembrolizumab has a 99% chance of being cost-effective compared to vinflunine at a willingness-to-pay threshold of €100 000/QALY [14] (Supplementary material).

4. Discussion

Treatment of advanced urothelial carcinoma poses significant clinical and economic burdens on health care systems [2]. Despite the availability of platinum-based chemotherapy for advanced urothelial carcinoma, the majority of patients experience disease progression [23]. Until recently, no globally accepted SoC was available in the second-line setting. In KEYNOTE-045, pembrolizumab was superior to chemotherapy in terms of OS, safety, and quality of life [11,24]. Thus, pembrolizumab received approval from global regulatory agencies for the treatment of patients with locally advanced or metastatic urothelial carcinoma who have previously received platinum-containing chemotherapy. Our model-based analysis showed that pembrolizumab is projected to be cost-effective compared with vinflunine among patients in Sweden when evaluated at a cost-effectiveness threshold of €100 000/QALY from a Swedish health care perspective [14]. Pembrolizumab was also cost-effective when compared with paclitaxel or docetaxel monotherapy, or the pooled arm for paclitaxel, docetaxel, or vinflunine monotherapy. In both scenarios, pembrolizumab had better LYs and QALYs.

Medical costs associated with pembrolizumab were primarily driven by drug acquisition and disease management costs. The total drug acquisition costs for pembrolizumab were sensitive to the pembrolizumab treatment duration. AE-related costs only account for approximately 2% of the non–drug costs for pembrolizumab, compared with 18% for vinflunine.

An analysis based on Kaplan-Meier curves without RPSFT adjustment for patients receiving subsequent therapy in the vinflunine arm revealed a slight increase in the ICER, but pembrolizumab was still considered cost-effective (Table 2).

Sarfaty et al. [25] recently reported on the cost-effectiveness of pembrolizumab as second-line therapy for advanced urothelial carcinoma. However, their study

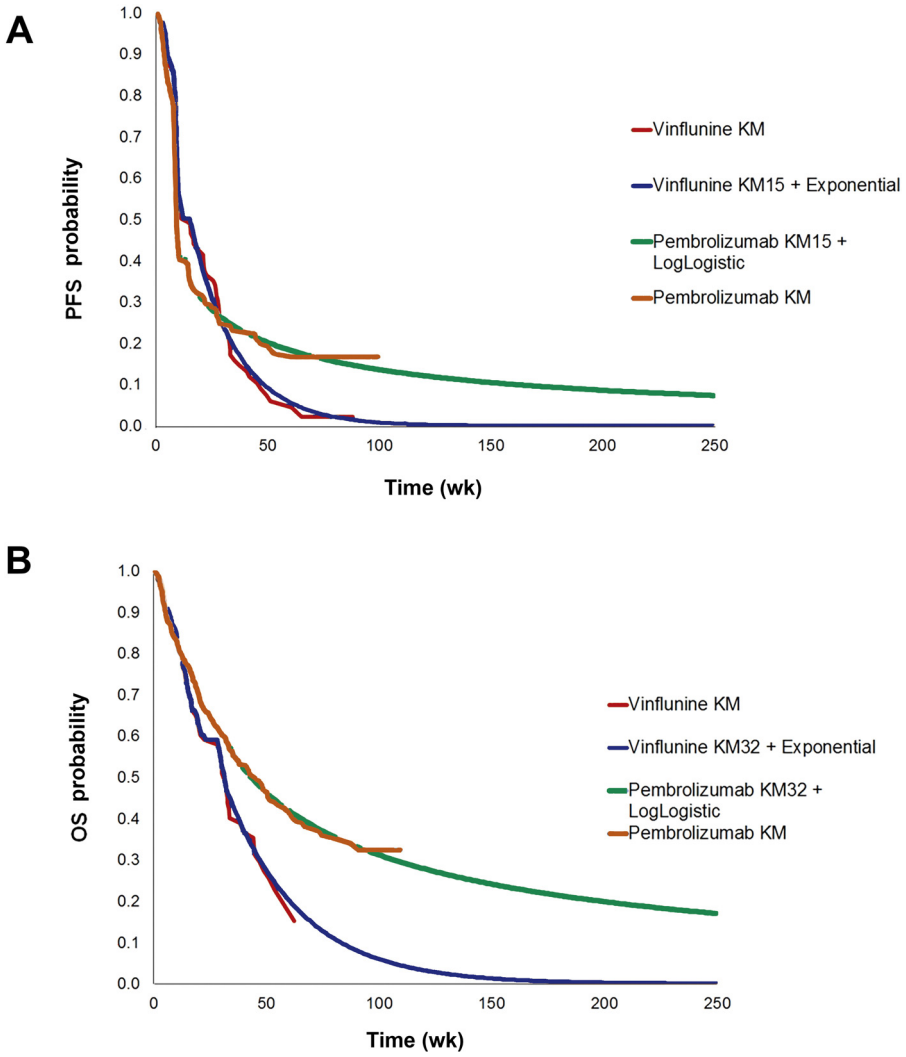

Fig. 2 – Estimation of overall survival (OS) and progression-free survival (PFS). KM = Kaplan-Meier; KM15 + LogLogistic = KM up to 15 week and log-logistic model thereafter; KM15 + Exponential = KM up to 15 week and exponential model thereafter; KM32 + LogLogistic = KM up to 32 week and log-logistic model thereafter; KM32 + Exponential = KM up to 32 week and exponential model thereafter. OS for vinflunine was adjusted using the rank-preserving structural-failure time method.

Table 2 – Discounted results for the cost-effectiveness of pembrolizumab compared to chemotherapy.

Comparator	Total			Incremental			ICER
	Costs (€)	LYs	QALYs	Costs (€)	LYs	QALYs	(€/QALY)
Base case: Pembro vs vinflunine (with RPSFT adjustment)							
Vinflunine	28 501	0.73	0.61				
Pembrolizumab	98 354	2.40	1.99	69 852	1.66	1.38	50 529
Pembro vs vinflunine (no adjustment)							
Vinflunine	28 844	0.76	0.63				
Pembro	98 354	2.40	1.99	69 510	1.63	1.36	51 215
Pembro vs paclitaxel/docetaxel/vinflunine (with two-stage adjustment) [a]							
P/D/V	25 054	1.18	0.97				
Pembro	98 208	2.40	1.99	73 154	1.22	1.02	71 924
Pembro vs paclitaxel/docetaxel (with two-stage adjustment) [a]							
P/D	25 182	1.33	1.09				
Pembro	98 348	2.40	1.99	73 166	1.07	0.90	81 356

ICER = incremental cost-effectiveness ratio; RPSFT = rank-preserving structural failure time; LY = life years; QALY = quality-adjusted life years; P/D/ = paclitaxel/docetaxel; P/D/V = paclitaxel/docetaxel/vinflunine.

[a] For the P/D/V and P/D control arms, two-stage adjustment and a log-logistic distribution for fitting of overall survival was the most appropriate technique according to statistical analysis of the KEYNOTE-045 data. The RPSFT adjustment method was the second best method in this scenario.

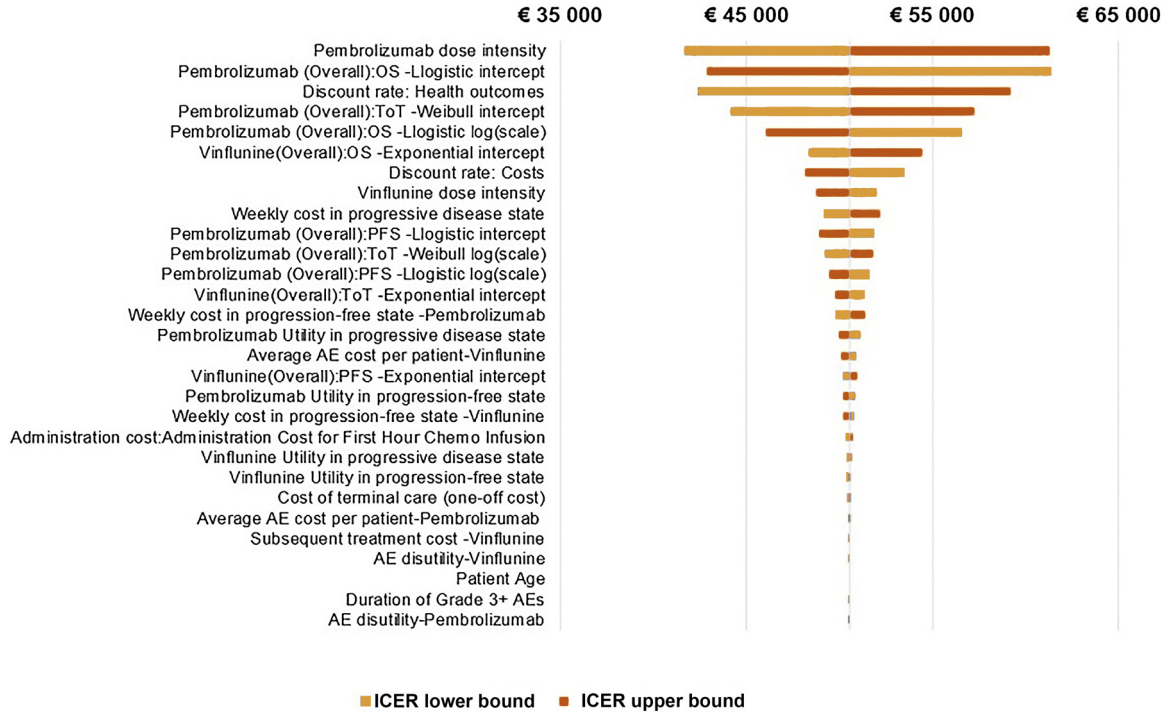

Fig. 3 – Tornado diagram showing the impact of changes in each of the input parameters on the incremental cost-effectiveness ratio (ICER) results. AE = adverse event; RPSFT = rank-preserving structural failure time; OS = overall survival; PFS = progression-free survival; ToT = time on treatment; Llogistic = log-logistic. The intercept and log(scale) are estimated parameters for the respective parametric survival models.

was subject to limitations of data availability and suboptimal modeling methods for survival, utility, and costs [20,25]. Our analysis has several strengths that explain the difference in results. We modeled OS and PFS using a partitioned survival approach that directly uses trial results to model survival and is commonly applied when evaluating cost-effectiveness in advanced oncology indications [15]. A piecewise approach was used for extrapolation, and survival was adjusted for patients in the control arm who received immunotherapy after chemotherapy. These analyses allowed more accurate prediction of OS. We also adopted a time horizon long enough to capture long-term health outcomes and costs. This was essential, as the treatment effect of immunotherapy may last even after discontinuation and lead to long-term survival gains [26]. Our model uses EQ-5D utility values estimated by health state directly from KEYNOTE-045 trial. In addition to drug costs, administration costs, and AE costs as used by Sarfaty et al. [25], we modeled disease management costs by health state as well as terminal care costs. Our comparators include vinflunine, taxanes (paclitaxel and docetaxel), and the entire KEYNOTE-045 control arm, thus providing a comprehensive evaluation of the cost-effectiveness of pembrolizumab in comparison to different comparators as second-line therapy for advanced urothelial carcinoma after platinum-based chemotherapy.

Overall, pembrolizumab remained cost-effective compared with vinflunine, taxanes (paclitaxel or docetaxel monotherapy), and with the pooled treatment (paclitaxel, docetaxel, or vinflunine monotherapy) over several input parameters as second-line therapy for patients with advanced urothelial carcinoma who had received platinum-based chemotherapy, and experienced disease progression during or following that chemotherapy. The evidence for the cost-effectiveness of pembrolizumab for advanced urothelial carcinoma as observed for Sweden in our analysis is generally representative of several European countries with similar health care systems.

4.1. Limitations

Owing to the lack of long-term PFS and OS data, extrapolations performed in the model make the results sensitive to distributional assumptions. The model used statistical methodology and objective criteria recommended by NICE to extrapolate Kaplan-Meier data for OS and PFS over the time horizon of the model [22]. However, actual survival rates may differ and long-term follow-up from clinical trials or real-world data is needed to validate the results. A sensitivity analysis showed that the model results are robust to input variations. In addition, the ICER results are only interpretable for the health system evaluated in this study or for countries with similar resource utilization, treatment costs, and AE management costs. However, the modeling framework and methods used in this study are generalizable to the other countries.

5. Conclusions

The model results suggest that pembrolizumab improves survival, increases QALYs, and is cost-effective as second-line therapy compared with vinflunine for the treatment of locally

advanced metastatic urothelial carcinoma in Swedish adults who have received prior platinum-containing chemotherapy at a willingness-to-pay threshold of 100 000 €/QALY gained. Pembrolizumab is also cost-effective when compared with paclitaxel or docetaxel monotherapy, and with paclitaxel, docetaxel, or vinflunine monotherapy.

Author contributions: Yichen Zhong had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Li, Mamtani, Pellissier, Perini, Prabhu, Srivastava.
Acquisition of data: Prabhu, Srivastava, Zarabi.
Analysis and interpretation of data: Li, Mamtani, Pellissier, Perini, Prabhu, de Wit, Srivastava, Xu, Zarabi, Zhong.
Drafting of the manuscript: Prabhu, Srivastava, Zhong.
Critical revision of the manuscript for important intellectual content: Li, Mamtani, Pellissier, Perini, Prabhu, de Wit, Srivastava, Xu, Zarabi, Zhong.
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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.euo.2018.09.012.

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