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European Association of Urology

Cost-effectiveness of Pembrolizumab for Patients with Advanced, Unresectable, or Metastatic Urothelial Cancer Ineligible for Cisplatin-based Therapy

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Article info

Article history:
Accepted September 19, 2018

Associate Editor:
Ashish Kamat

Keywords:
Cost effectiveness
Pembrolizumab
Urothelial cancer

Abstract

Background: There is an unmet need for effective therapies for patients with advanced or metastatic urothelial cancer who cannot tolerate cisplatin-based chemotherapy. Cisplatin-ineligible patients experience a high frequency of adverse events from the most commonly used standard of care treatment, carboplatin plus gemcitabine, or alternative treatment with gemcitabine monotherapy. Pembrolizumab is a potent, highly selective humanised monoclonal antibody that releases checkpoint inhibition of the immune response system, and provides a new alternative for these patients.

Objective: To assess the cost-effectiveness of pembrolizumab for first-line treatment of urothelial carcinoma ineligible for cisplatin-based therapy in patients with strongly PD-L1–positive tumours in Sweden.

Design, setting, and participants: Parametric survival curves were fitted to overall survival, progression-free survival, and time on treatment data from KEYNOTE-052 to extrapolate clinical outcomes. A simulated treatment comparison and a network meta-analysis were conducted to estimate the comparative efficacy of pembrolizumab versus carboplatin plus gemcitabine and gemcitabine monotherapy. EQ-5D data from KEYNOTE-052 were used to estimate utility, while resource use and cost inputs were estimated using Swedish regional pricing lists and clinician opinion.

Outcome measurements and statistical analysis: The model reported costs, life years, and quality-adjusted life years (QALYs), and results were tested using deterministic and probabilistic sensitivity analysis.

Results and limitations: We estimated that pembrolizumab would improve survival by 2.11 and 2.16 years and increase QALYs by 1.71 and 1.75 compared to carboplatin plus gemcitabine and gemcitabine monotherapy, respectively. Pembrolizumab was associated with a cost increase of €90 520 versus carboplatin plus gemcitabine and €95 055 versus gemcitabine, with corresponding incremental cost-effectiveness ratios of €53 055/QALY and €54 415/QALY.

Conclusions: At a willingness-to-pay threshold of €100 000/QALY, pembrolizumab is a cost-effective treatment versus carboplatin plus gemcitabine and versus gemcitabine.

Patient summary: This is the first analysis to show that pembrolizumab is a cost-effective option for first-line treatment of cisplatin-ineligible patients with locally advanced or metastatic urothelial carcinoma in Sweden.

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https://doi.org/10.1016/j.euo.2018.09.009

1. Introduction

It is estimated that 24 500 people in Sweden are living with urothelial cancer, a disease with an incidence of approximately 2700 cases per year and an average age of onset of 70 yr [1,2]. Several chemotherapies are available for first-line treatment of patients with advanced and metastatic urothelial cancer, both as monotherapies and as combination therapies. Although platinum-based treatments, especially those containing cisplatin, are preferred, these require that patients are fit enough to tolerate such treatments (meeting specific criteria including Eastern Cooperative Oncology Group [ECOG] status 0–1). It has been estimated that approximately half of all treated patients with locally advanced and metastatic urothelial cancer receive therapies other than cisplatin-based regimens [3,4]. With a European incidence rate of 151 297 [5] and assuming that 15% of diagnoses are of stage IV (advanced disease requiring systemic therapy) [6], at least 11 347 cisplatin-ineligible patients across Europe would benefit from new therapies.

Although carboplatin plus gemcitabine is the preferred treatment for cisplatin-ineligible patients [7], and gemcitabine monotherapy could be an alternative option for patients who cannot tolerate combination chemotherapy, currently available chemotherapies still have high frequencies of adverse events (AEs) as they lack tumour tissue specificity. There is therefore an unmet need for systemic therapies that have both high efficacy and tolerability in these patients; this is significant given the lack of major advances in systemic therapy for urothelial cancer in almost 25 years [8].

Pembrolizumab (Keytruda) is a potent and highly selective humanised monoclonal antibody designed to cause dual ligand blockade of the PD-1 protein and release the PD-1 pathway–mediated inhibition of the immune response [9]. The efficacy of pembrolizumab in advanced urothelial cancer was investigated in the KEYNOTE-052 trial. This was a single-arm phase 2 trial of pembrolizumab in patients with locally advanced or metastatic urothelial carcinoma who were not eligible for cisplatin-containing chemotherapy and who had not been previously treated [10]. Trial outcomes were also assessed on the basis of whether patients' tumours were positive or strongly positive for PD-L1 expression. Pembrolizumab has been approved by the European Medicines Agency for the treatment of locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing chemotherapy with strongly PD-L1–positive tumours (express PD-L1 with a combined positive score [CPS] $\geq$10) on the basis of strong phase 2 data [11]. Approximately 30% of cisplatin-ineligible patients are expected to have strongly PD-L1–positive tumours [12]. For patients in countries with a Health Technology Assessment (HTA) system, access to a new innovative treatment depends on a reimbursement decision supported by cost-effectiveness analyses.

This study estimated the cost-effectiveness of pembrolizumab versus current standard of care (SOC) for the treatment of cisplatin-ineligible patients with advanced, unresectable, or metastatic urothelial cancer and strongly PD-L1–positive tumours from a Swedish healthcare perspective.

2. Patients and methods

2.1. Model structure

A partitioned-survival model was used to estimate health outcomes and costs for pembrolizumab and each comparator in the target patient population. The model structure included three mutually exclusive health states (progression-free, progressive disease, and death), as shown in Figure 1.

The proportion of patients in each health state at given time points was calculated using the partitioned-survival approach. Patients remain in the starting progression-free health state until disease progression or death, while the progressive disease health state encompasses patients alive after first progression and before death, which is where they remain until the end of the model.

Outputs from this model include costs, life years, and quality-adjusted life years (QALYs), which inform the incremental cost-effectiveness ratio (ICER). Costs and health outcomes were discounted at a rate of 3% per year, and a time horizon of 15 yr (lifetime) with a weekly model cycle was used for the base case [13].

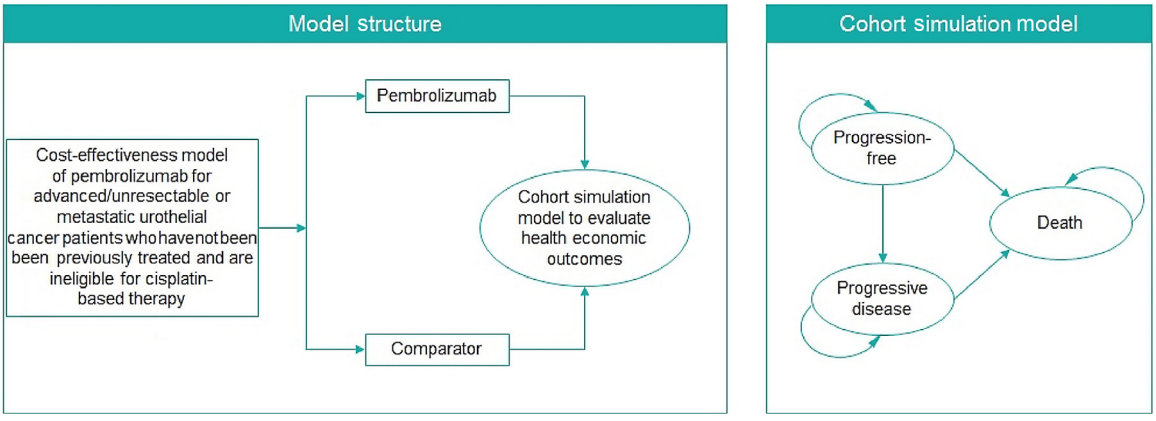

Fig. 1 – Model structure.

2.2. Modelling overall survival, progression-free survival, and time on treatment for pembrolizumab

Parametric survival models were fitted to the KEYNOTE-052 Kaplan-Meier data for patients with strongly PD-L1–positive tumours to model overall survival (OS), progression-free survival (PFS), and time on treatment (ToT). Piecewise extrapolation was used in the PFS and OS survival models by directly applying Kaplan-Meier data before a cutoff point (chosen on the basis of observed structural changes), followed by parametric models fitted to the remaining data. In the base case, 9 and 32 wk were used for PFS and OS cutoff points, respectively. This captures the different shapes and trajectories of individual curves over time, rather than attempting to fit a single curve to a complex-shaped Kaplan-Meier graph. Survival curve fitting was carried out in line with National Institute for Health and Care Excellence (NICE) guidelines [14]. The base-case choice curves fitted for each outcome are presented in Figure 2. The Akaike information criterion and the Bayesian information criterion, combined with visual inspection and the clinical plausibility of extrapolated curves (as advised by a bladder cancer clinician), were used to select the best-fit parametric distributions for the base case. Exponential, log-normal, and Gompertz were selected as the base-case curves for PFS, OS, and ToT, respectively, with alternative Kaplan-Meier cutoff points and extrapolations tested in scenario analyses.

2.3. Modelling OS and PFS for comparators

According to national guidelines and clinical opinion [1], carboplatin plus gemcitabine is provided as current first-line SOC for patients ineligible for cisplatin-containing chemotherapy in Sweden. Although not SOC, gemcitabine monotherapy was identified as another potential treatment option as part of a systematic literature review [15]. Therefore, both treatments were used as comparators in the model.

As KEYNOTE-052 was a single-arm study and none of the comparator trials included a pembrolizumab arm, it was not possible to construct a connected or anchored network meta-analysis (NMA) to estimate a comparative treatment effect for pembrolizumab versus the other treatments. Therefore, a simulated treatment comparison (STC) was performed using patient-level data from KEYNOTE-052 to fit prediction models for pembrolizumab OS and PFS considering a range of relevant patient characteristics of prognostic value, including the proportion of patients with liver and visceral metastases, performance score (ECOG status), and renal function. The fitted prediction model was then applied to estimate the OS and PFS for a simulated pembrolizumab arm for patients with strongly PD-L1–positive tumours in relevant comparator trials identified via systemic review, using reported aggregate patient characteristics [7,15–18]. NMA was then performed using data from KEYNOTE-052 and the comparator trials (including the observed comparator arm and a simulated pembrolizumab arm) to estimate time-constant OS and PFS hazard ratios for the comparator treatments versus pembrolizumab.

For the model base case, the time-constant hazard ratio for OS was 2.78 for carboplatin plus gemcitabine and 2.94 for gemcitabine versus pembrolizumab. For PFS the hazard ratio was 1.64 for both comparators versus pembrolizumab. Pembrolizumab and comparator survival extrapolations (for gemcitabine plus carboplatin only) are presented in Figure 2.

General population mortality was calculated from Swedish life tables [19]. The maximum cycle hazard between general population mortality and extrapolated parametric survival curves was applied for each arm during each model cycle.

2.4. Adverse events

For all treatments, all-cause grade ≥3 AEs that occurred in more than 5% of patients from corresponding clinical trials were included to calculate both costs and utilities (for the SOC comparator arm, AE frequencies were averaged for all four trials included, weighted by the number of patients per trial) [7,15–18].

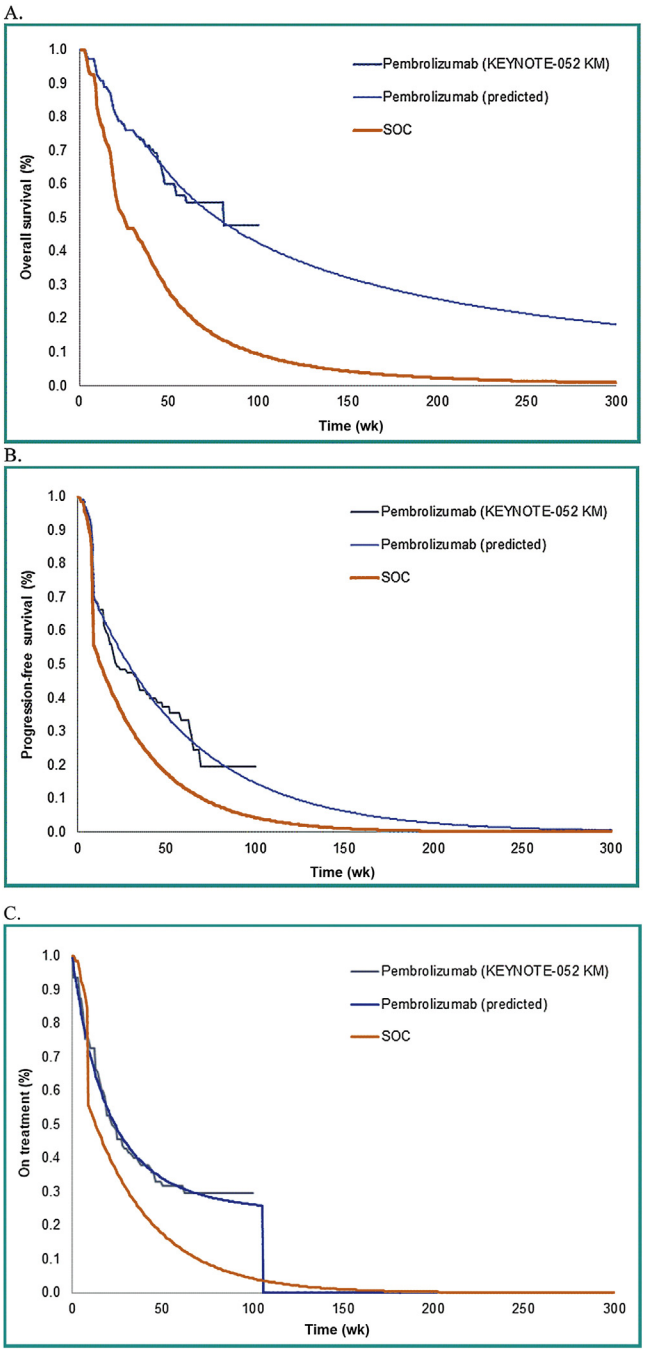

Fig. 2 – Kaplan-Meier (KM) and fitted survival curves. SOC = standard of care (gemcitabine plus carboplatin).

2.5. Health-related quality of life

For each health state, a specific quality-of-life adjustment weight (a utility, where 1 is full health and 0 is death) was assigned to calculate the cumulative QALYs over the time horizon modelled. The base-case utilities were calculated using EQ-5D data for patients with strongly PD-L1–positive tumours in KEYNOTE-052 and using the Swedish scoring algorithm [20]. The average utility was 0.842 for progression-free

patients and 0.800 for patients experiencing disease progression. Utilities based on time-to-death categories were used in another scenario analysis [21]. The same utility values were applied in both the pembrolizumab and comparator arms. An average disutility of 0.041 for any all-cause grade ≥3 AE was estimated using differences between the utility for progression-free patients with and without grade ≥3 AEs. This was then multiplied by the average duration of AEs from KEYNOTE-052 (0.07 yr) and the probability of experiencing any grade ≥3 AE. These QALY decrements were applied once at the start of the model.

2.6. Costs and resource utilisation

Drug costs for pembrolizumab were based on ToT curves combined with the KEYNOTE-052 fixed dosing schedule of 200 mg intravenously every 3 wk (Q3W). A maximum treatment duration of 35 treatment cycles (104 wk) was applied for the pembrolizumab arm, while ToT was assumed to be equal to PFS for the comparators. The dosing schedule for gemcitabine monotherapy was 1000 mg/m^2 intravenously per week for 3 wk, followed by a 1-wk rest. For carboplatin plus gemcitabine combination therapy the schedule was 1000 mg/m^2 intravenous gemcitabine on days 1 and 8, and 512 mg intravenous carboplatin on day 1, every 3 wk [22]. All treatments were assigned an administration cost of €263.90 in accordance with the Swedish regional price list [23]. Subsequent treatment costs were not included in the base case.

To identify one patient with a strongly PD-L1–positive tumour, approximately three patients need to be tested for tumour PD-L1 status (since 30% of patients have strongly PD-L1–positive tumours) [12]. A single PD-L1 test was costed at €102.59 (list price of €5129.40 for a PD-L1 testing kit containing 50 tests) [24].

All-cause grade ≥3 AEs that occurred in more than 5% of patients were assigned management costs from the regional price list [23]. One-off average AE costs were totalled for each treatment arm and applied at the start of the model on the basis of overall AE probabilities and management costs.

Resource utilisation estimates were sourced from a survey of four clinicians, with unit costs from the regional price list [23]. This yielded weekly monitoring costs of €69.54 in the progression-free health state and €94.07 in the disease progression state. The cost of terminal care was applied upon death and was based on the 2014 ipilimumab Tandvårds- och läkemedelsförmånsverket submission (€7226.30) [25].

2.7. Sensitivity analysis

One-way sensitivity analysis was performed by varying each input to its lower and upper bounds and recording the impact on the model result. In addition, a probabilistic sensitivity analysis was run, with all inputs assuming a random value across their individual distributions. Scenario analysis tested model sensitivity to specific parameters, such as survival curve extrapolations, treatment stopping rules, and EQ-5D tariffs. Key model inputs and their distributions are summarised in Supplementary Table 1. The willingness-to-pay threshold was based on the high cost per QALY value published by the Sweden National Board (500 000–1 000 000 kronor/€50 000–100 000) [26], and validated using the cost per QALY for previously accepted treatments in Sweden [27]..

3. Results

The base-case model results reveal that pembrolizumab provides more life years and QALYs than both carboplatin plus gemcitabine and gemcitabine monotherapy, improving survival by 2.11 and 2.16 yr and QALYs by 1.71 and 1.75, respectively (the life years and QALYs are mean estimates over the time horizon modelled). Pembrolizumab is associated with increases in costs of €90 520 versus carboplatin plus gemcitabine and €95 055 versus gemcitabine; the ICER for pembrolizumab is €53 055/QALY versus carboplatin plus gemcitabine and €54 415/QALY versus gemcitabine monotherapy (Table 1). The modelled estimates for patients in the progression-free, progression, and death states for the different treatment arms over the model time horizon are presented in the Supplementary Table 1.

A one-way sensitivity analysis showed that parameters informing pembrolizumab ToT, OS, and dose intensity had the greatest effect on the model results (Fig. 3 and Supplementary Table 1 [owing to the similarity in results, only the results for carboplatin plus gemcitabine are shown here]). Probabilistic sensitivity analysis based on 1000 iterations suggested that pembrolizumab was more cost-effective than carboplatin plus gemcitabine with probability of 87% at a willingness-to-pay threshold of €100 000 (Fig. 4). The ICER was robust to changes in scenario analysis, such as methods for estimating utility (including the use of UK EQ-5D tariffs to calculate utility values) and subsequent treatment assumptions, but scenarios regarding maximum treatment duration and OS extrapolations were highly influential (Supplementary Table 2).

4. Discussion

The model results indicate that pembrolizumab improves life expectancy compared to its comparators. Interpretation of cost-effectiveness always depends on the willingness-to-pay threshold specific to the model perspective and setting, but pembrolizumab provides QALY gains at ICERs that are lower than those for treatments previously approved for reimbursement in Sweden, and within the high cost-per-QALY threshold defined by the National Board of Health and Welfare (€50 000–100 000) [26,27].

Table 1 – Incremental cost-effectiveness results (pairwise comparisons) for the base case

	Cost (€)	LYs	QALYs	Pembrolizumab versus comparator				
				Incremental costs (€)	Incremental LYs	Incremental QALYs	ICER (€/QALY)	ICER (€/LY)
Pembrolizumab	119 366.12	2.93	2.38					
Carbo + Gem	28 845.92	0.82	0.67	90 520.20	2.11	1.71	53 055.42	42 967.32
Gemcitabine	24 311.12	0.77	0.63	95 055.00	2.16	1.75	54 414.78	44 025.65

Carbo + Gem = carboplatin plus gemcitabine (standard of care); ICER, incremental cost-effectiveness ratio (calculated as incremental costs divided by incremental LYs or incremental QALYs); LY = life year (can be interpreted as mean lifetime over the time horizon modelled); QALY = quality-adjusted LY (can be interpreted as mean QALY over the time horizon modelled).

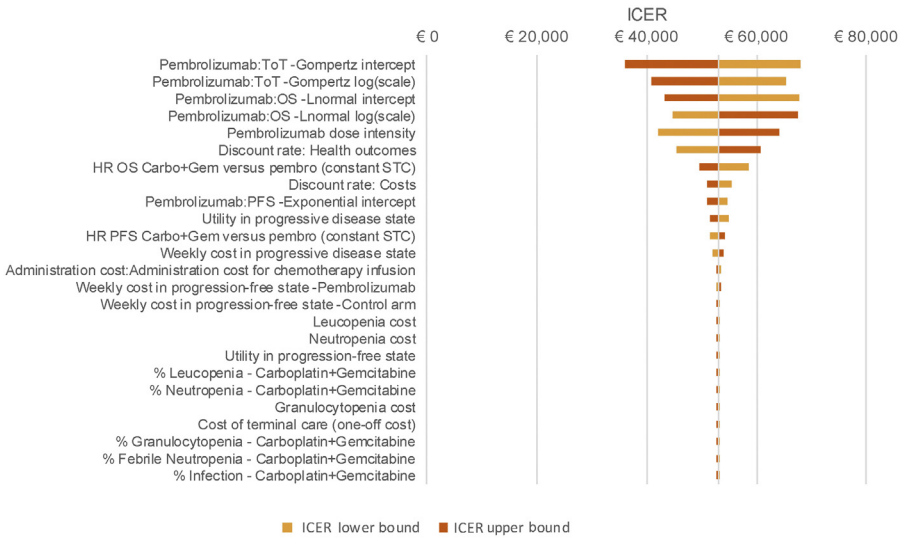

Fig. 3 – One-way sensitivity analysis for pembrolizumab versus standard of care (SOC). AE = adverse event; ICER = incremental cost-effectiveness ratio; KN052 = KEYNOTE-052; Lnormal = log-normal; OS = overall survival; PFS = progression-free survival.

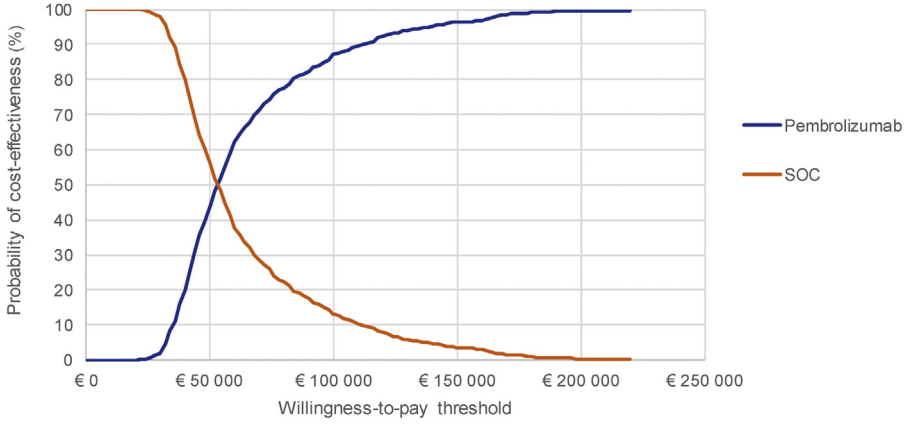

Fig. 4 – Cost-effectiveness acceptability curve. SOC = standard of care (carboplatin plus gemcitabine).

The results of this study are robust to sensitivity analysis, with extrapolation and comparative efficacy methodology validated using health economic experts, and key clinical inputs and assumptions sourced from Swedish clinical experts. Median OS predicted from the model closely matches latest median OS observed from KEYNOTE-052 (PD-L1 CPS $\geq$10 subgroup: 18.4 vs 18.5 mo) [12]. The calculations presented here were based on the health care system and drug pricing in Sweden, but estimates of life years and QALYs gained are likely to be comparable across other European countries. Should resource utilisation, treatment costs, and AE management costs prove to be similar between countries, overall cost-effectiveness results are also likely to be generalisable.

One limitation of the model is the lack of direct comparison of pembrolizumab with the comparators in a randomised controlled trial. As KEYNOTE-052 was a single-arm study, pembrolizumab cannot be directly connected to the evidence network (ie, only an "unanchored" network for pembrolizumab and comparators can be constructed). The comparative efficacy for the comparators versus pembrolizumab was therefore based on an STC in which patient-level data from KEYNOTE-052 were used to fit a prediction model considering a range of patient characteristics. This prediction model was then used to construct a simulated pembrolizumab arm for each comparator trial based on the aggregated patient characteristics reported in each comparator trial. STC is one of the methods recommended by the recent NICE Decision Support Unit guidance on performing population-adjusted indirect comparisons for an "unanchored" network for which patient-level data exist for the intervention trial but only aggregate data are available from the comparator trial. However, there are significant limitations related to the use of an STC or any other currently available method that derives comparative efficacy in an "unanchored" network [28]. In addition, we made a simplifying assumption by using constant hazard ratios in the base case; whether the proportional hazard assumption truly holds over the modelled time horizon is uncertain. Although OS projections and relative comparator

efficacy are key drivers of the model, the results are robust to treatment waning after 5 yr in the scenario analysis. Additional uncertainty is found in the assumed pembrolizumab treatment duration (ie, maximum of 2 yr), as per the KEYNOTE-052 protocol, which may not be consistent with real-life practice.

The phase 2 KEYNOTE-052 trial showed very promising durable efficacy and high tolerability for pembrolizumab, and provided a new treatment option in the first-line setting for cisplatin-unfit patients [29]. Longer follow-up from KEYNOTE-052 can provide more mature OS and ToT data to improve model extrapolations [12], but this will still be in the context of a single-arm phase 2 trial. A future randomised controlled phase 3 trial, KEYNOTE-361 (NCT02853305), is likely to help inform and/or validate modelled results by providing head-to-head data with a relevant comparator [30].

5. Conclusions

The results show that pembrolizumab is a cost-effective option for first-line treatment of locally advanced or metastatic urothelial carcinoma in cisplatin-ineligible patients with strongly PD-L1–positive tumours in Sweden at a willingness-to-pay threshold of €100 000, with potential survival and QALY benefit compared to chemotherapies.

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: Meng, Patterson, Prabhu.
Acquisition of data: Prabhu, Zarabi.
Analysis and interpretation of data: Batteson, Grivas, Keefe, Li, Meng, Patterson, Pellissier, Prabhu, de Wit, Xu, Zarabi, Zhong.
Drafting of the manuscript: Batteson, Meng, Patterson, Prabhu.
Critical revision of the manuscript for important intellectual content: Batteson, Grivas, Keefe, Li, Meng, Patterson, Pellissier, Prabhu, de Wit, Xu, Zarabi, Zhong.
Statistical analysis: None.
Obtaining funding: Zhong.
Administrative, technical, or material support: None.
Supervision: None.
Other: None.

Financial disclosures: Yichen Zhong certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: Karl Patterson, Rachael Batteson, and Yang Meng are employees of BresMed, who received consulting fees for the production of this manuscript from Merck and Co., Inc. Petros Grivas has a consultancy role with Merck, Genentech, Bristol Myers Squibb, AstraZeneca, EMD Serono, Clovis Oncology, Seattle Genetics, Biocept, Foundation Medicine, Driver, Pfizer, and QED Therapeutics. Ronald de Wit has a consultancy role with Merck, Lilly, Sanofi, and Roche, and has received speaker fees from Sanofi and research grants from Sanofi and Bayer. Stephen Keefe, Haojie Li, James Pellissier, Vimalanand Prabhu, Ruifeng Xu, and Yichen Zhong are employees of Merck. Natalie Zarabi is an employee of MSD. Haojie Li, Vimalanand Prabhu, and Yichen Zhong own restricted stock options and/or stocks in Merck.

***Funding/Support and role of the sponsor*:** This study was supported by funding from Merck & Co. Inc. The sponsor was involved in the design and conduct of the study; data collection, management, analysis, and interpretation; and review and approval of the manuscript.

Acknowledgments: The authors would like to acknowledge Jane Liao and Fansen Kong for their contribution to the data analysis.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.euo.2018.09.009.

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