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Clinical-Bladder cancer

Effect of PD-L1 testing on the cost-effectiveness and budget impact of pembrolizumab for advanced urothelial carcinoma of the bladder in the United States

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Abstract

Purpose: Our purpose was to evaluate the effect of PD-L1 testing on the cost-effectiveness of pembrolizumab for second-line treatment of advanced urothelial carcinoma in the bladder from the U.S. societal perspective.

Materials and methods: We developed a microsimulation model to compare 3 treatment strategies: (1) treat all patients with standard-of-care chemotherapy, (2) treat all patients with pembrolizumab, and (3) treat patients with PD-L1-positive tumors at a ≥1% expression threshold with pembrolizumab, and all others with standard-of-care chemotherapy. Additionally, we performed a budget impact analysis based on the projected number of urothelial carcinoma patients eligible for second-line pembrolizumab treatment.

Results: Treating all patients with chemotherapy resulted in a mean cost of $17,232 and mean effect of 0.43 quality-adjusted life-years. The PD-L1 test strategy was the most efficient strategy, with an incremental cost-effectiveness ratio of $122,933/quality-adjusted life-year. Treating all patients with pembrolizumab resulted in an incremental cost-effectiveness ratio of $197,383/quality-adjusted life-year compared to the PD-L1 test strategy. The PD-L1 test strategy would produce an incremental budget impact of $14.9 million in the first year of use compared to chemotherapy, increasing to $16.5 million in the fifth year of use. Treating all patients with pembrolizumab would produce an incremental budget impact of $19.6 million compared to the PD-L1 test strategy in its first year of use, increasing to $20.9 million by year 5.

Conclusions: Pembrolizumab was not cost-effective in either strategy based on a $100,000/quality-adjusted life-year willingness-to-pay threshold. Using PD-L1 testing to select for patients who may have better associated outcomes may improve the affordability of pembrolizumab.

Keywords: Immunotherapy; Cost-effectiveness analysis; Urothelial carcinoma; Bladder cancer; Computer simulation

1. Introduction

Bladder cancer is the sixth most common type of cancer in the United States and is associated with poor late-stage survival [1]. Urothelial carcinoma is the predominant histologic type of bladder cancer [2,3], making it a primary target for new immunotherapy treatments. Five immunotherapy treatments have been approved for the treatment of urothelial carcinoma by the U.S. Food and Drug Administration (FDA), each of them acting as checkpoint inhibitors to activate the immune system against cancer cells. Estimates from the biopharmaceutical industry project that total annual revenues from immunotherapy could reach up to $20 to $30 billion in the coming decade [4]. In an environment with strong financial incentives for pharmaceutical companies to increase drug prices, formal cost-effectiveness analysis can provide important context for public policymakers

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and prescribing physicians on the underlying value of such therapies.

The FDA approved pembrolizumab (*Keytruda*, Merck Sharp & Dohme Corp.) in 2017 to treat locally advanced or metastatic urothelial carcinoma in patients whose cancer progressed during or after first-line chemotherapy [5]. Pembrolizumab is a programmed cell death protein 1 (PD-1) immune-checkpoint–inhibitor antibody that obstructs PD-1–mediated signaling and, thus, restores antitumor T-cell activation [6]. In a randomized, open-label, phase 3 international study (KEYNOTE-045, NCT02256436), overall survival with pembrolizumab was greater than that with the comparator regimen: docetaxel, paclitaxel, or vinflunine (10.3 months vs. 7.4 months, respectively) [6]. Patients receiving pembrolizumab also experienced a lower adverse event rate [6]. Patients whose tumors expressed higher PD-1 ligand (PD-L1) expression had improved survival when on pembrolizumab compared to chemotherapy [6].

Prior analysis by the U.K.'s National Institute for Health and Care Excellence (NICE) concluded that pembrolizumab should not be recommended for treating advanced urothelial carcinoma in the second line because it was not cost-effective at a willingness-to-pay (WTP) threshold of £50,000/quality-adjusted life-year (QALY) [7]. A recently published study by Sarfaty et al. examined the cost-effectiveness of pembrolizumab vs. chemotherapy for second-line treatment of advanced bladder cancer in the U.S.A., U.K., Canada, and Australia, concluding that it was only cost-effective in the United States at a WTP threshold of $150,000/QALY [8]. Neither of these studies considered a strategy in which pembrolizumab treatment was dependent on PD-L1 expression, nor did they assess the potential budget impact of adopting pembrolizumab-based treatment strategies. Based on these conclusions and in light of the growing market for immuno-oncology therapies, an analysis of the cost per QALY trade-off of using pembrolizumab, with or without prior PD-L1 testing, in treating advanced urothelial carcinoma in the United States is warranted.

2 . Materials and methods

2.1 . Simulation model

We developed a microsimulation model to estimate health and economic outcomes of patients presenting with advanced urothelial carcinoma in the bladder who experienced disease progression after first-line platinum-based chemotherapy. We compared 3 strategies in our base case analysis: (1) treat all patients with standard-of-care second-line chemotherapy (50% receiving docetaxel and 50% receiving paclitaxel), (2) treat all patients with pembrolizumab, and (3) treat patients with PD-L1-positive tumors at a ≥1% expression threshold with pembrolizumab, and all others with second-line chemotherapy (Fig. 1). Survival data for patients with PD-L1 positivity at a 10% threshold were published, but require further investigation before conducting a formal cost-effectiveness analysis, as this subgroup exhibited poorer survival in both the pembrolizumab and chemotherapy groups compared to the same groups in the overall intention-to-treat population [6]. The chemotherapy arm in the clinical trial included the investigator's choice of docetaxel, paclitaxel, or vinflunine [6], but because vinflunine is not approved for treatment of advanced urothelial carcinoma in the United States, we excluded vinflunine from the cost of chemotherapy in our analysis. However, progression-free and overall survival times by chemotherapy type were not published, preventing us from excluding

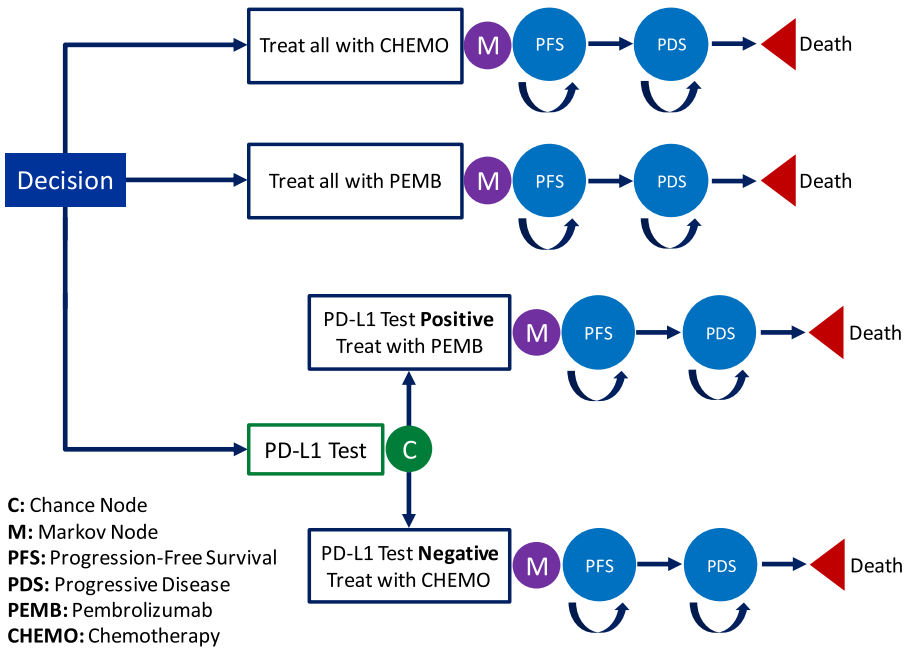

Fig. 1. Microsimulation model schematic for three treatment strategies.

survival data related to vinflunine in our model. As a result, we assumed that median survival times between docetaxel, paclitaxel, and vinflunine regimens did not differ and used the combined chemotherapy survival data published from the study for all patients treated with chemotherapy in the model. Outcomes reported in the literature show that differences between survival times for advanced urothelial carcinoma patients treated with second-line docetaxel, paclitaxel, and vinflunine are minimal [9,10]. While the trial included patients with urothelial carcinoma of the renal pelvis, ureters, and urethra, in addition to the bladder, these patients represented a small minority of the intention-to-treat population [6]. Therefore, we focused our analysis on treatment of urothelial carcinoma in the bladder, as the undersampling of nonbladder cancer patients may cause the results to be poorly generalizable to these patients.

We calculated an incremental cost-effectiveness ratio (ICER) for each strategy, using $100,000/QALY as the WTP threshold [11]. To minimize stochastic variation of the outcomes, 1 million patients were simulated for each strategy and were followed from progression-free survival to progressive disease and finally death—3 mutually exclusive health states (Fig. 1). A model cycle length of 1 month was used, with patients receiving doses of either chemotherapy or pembrolizumab every 3 weeks until disease progression. We used a discount rate of 3% per year for both life-year and cost projections.

2.2 . Costs

We evaluated each strategy from the societal perspective of the U.S. healthcare system, using cost data derived from relevant U.S. sources (Supplementary Table 1) [12–17]. Medical costs considered in the analysis included drug therapy and administration, PD-L1 staining, treatment of major adverse events, surveillance, and supportive care. We determined drug therapy costs using the Centers for Medicare & Medicaid Services 2017 Average Sales Price Drug Pricing Files (October 2017 version updated file) and dosing information from the KEYNOTE-045 trial [6]. For dose size calculations, average body surface area was assumed to be 1.79 m^2 [18]. We considered the costs of treatment for major adverse events that occurred in at least 1% of patients in the KEYNOTE-045 trial, which were obtained from the Agency for Healthcare Research and Quality's Healthcare Cost and Utilization Project using relevant ICD-9 and DRG codes [19]. All costs were adjusted to 2017 U.S. dollars using the Centers for Medicare & Medicaid Services Personal Health Care Price Index [20,21].

2.3 . Survival and health state utility

We elicited median progression-free and overall survival times used to estimate progression rates, as well as PD-L1 test results, from the original clinical trial data for KEYNOTE-045 [6]. Progression-free survival and overall survival hazards were held constant over time. In addition, we used literature sources to inform the quality-adjusted health state utility and disutility of treatment and adverse events (Supplementary Table 2) [35,36,40–45]. Quality of life estimates from the KEYNOTE-045 trial have been published [22]. However, the published quality of life data does not differentiate between quality of life for patients with progressive disease and those without. As a result, we collected a thorough selection of estimates for progression-free and progressive disease utilities from bladder, breast, and nonsmall cell lung cancer patients, and used the average of these estimates in our model (additional detail and literature references in Supplementary Table 2). Because of the lack of analogous data in the published literature and based on the reduced toxicity of immunotherapy treatment, a quality-adjusted utility of 0.80 for patients on pembrolizumab in the progression-free health state was chosen. Supplementary Table 1 provides additional information on the values for the base case input parameters.

2.4 . Sensitivity analyses

We performed 1-way sensitivity analyses on key variables to evaluate the influence of uncertainty in these parameter estimates on the cost-effectiveness of pembrolizumab treatment. We utilized 95% confidence intervals associated with base case parameter estimates as the upper and lower bounds, when available (Table 1). Each variable was tested at the upper and lower limit of their respective ranges.

2.5 . Budget impact analysis

To complete our economic assessment of these treatment strategies, we provide a projection of the maximum additional healthcare expenditure that would be necessary for implementation at a societal level [23]. Our budget impact analysis shows how much more would need to be spent to treat all eligible advanced bladder urothelial carcinoma patients in the United States using the pembrolizumab treatment strategies over the cost of using the standard-of-care chemotherapy method. Eligible patients were those diagnosed with stage IV urothelial carcinoma of the bladder who have received prior chemotherapy. The number of potential patients was approximated by applying the proportion of bladder cancers diagnosed as stage IV urothelial carcinoma from 2000 to 2015, estimated using the Surveillance, Epidemiology, and End Results Program dataset, to the number of new cases in the United States estimated for 2018 by the American Cancer Society [1,24]. This figure was then multiplied by the percentage of stage IV bladder cancer patients who received some form of chemotherapy from 2006 to 2015, according to the National Cancer Data Base [25], to find the total number of eligible patients. To project the potential impact, we assumed that 64% of these eligible patients received treatment according to each strategy, based on the likely proportion of patients who go on to receive second-line treatment [26]. We

Table 1
Parameters used in deterministic sensitivity analysis

Variables	Mean	Lower limit	Upper limit
Utilities			
PFS utility (PEMB)[a]	0.80	0.60	1.00
PFS utility (CHEMO)[a]	0.69	0.51	0.86
PDS utility[a]	0.45	0.33	0.56
Costs			
PEMB price/mg[a]	$47.97	$35.97	$59.96
Cont. care cost[a]	$320.00	$240.00	$400.00
Adverse event cost (CHEMO)[a]	$8,331.54	$6,248.66	$10,414.43
Survival (mo)			
PFS (PEMB)	2.10	2.00	2.20
PFS (PEMB)—1% PD-L1+	2.10	2.00	2.40
PFS (CHEMO)	3.30	2.30	3.50
OS (PEMB)	10.30	8.00	11.8
OS (PEMB)—1% PD-L1+	11.30	7.70	16.00
OS (CHEMO)	7.40	6.10	8.30
Other			
Body SA[a]	1.79	1.35	2.25

AE = adverse event; CHEMO = chemotherapy; Cont. care = continuing care; OS = overall survicval; PDS = progressive disease survival; PEMB = pembrolizumab; PFS = progression-free survival; SA =surface area.

[a] 95% confidence interval not available; range indicates 25% change.

projected undiscounted costs per year for each strategy, then multiplied the mean difference in cost between these strategies for each year of treatment by the number of eligible patients [23]. The time period of our budget impact analysis was 5 years and new eligible patients entered the patient population each year based on estimated incidence.

3. Results

We found that patients in the standard-of-care chemotherapy strategy accumulated a mean cost of $17,232 and mean quality-adjusted survival of 0.43 QALYs, with an estimated life expectancy of 0.83 years. The PD-L1 test strategy was the most efficient in comparison to standard-of-care chemotherapy, with an estimated mean cost of $27,579 and mean quality-adjusted survival of 0.51 QALYs (estimated life expectancy = 1.01 years), resulting in an ICER of $122,933/QALY (Table 2). Treating all patients with pembrolizumab was the least efficient of the 3 methods, with an estimated mean cost of $40,573 and mean quality-adjusted survival of 0.58 QALYs (estimated life expectancy = 1.16 years), resulting in an ICER of $197,383/QALY compared to the PD-L1 test strategy (Table 2).

3.1 . Sensitivity analyses

We found that the cost-effectiveness of each strategy was most sensitive to survival, price per mg of pembrolizumab, and utility scores for progression-free and progressive disease. When comparing the PD-L1 test strategy to standard-of-care chemotherapy, the ICER decreased below the $100,000/QALY WTP threshold in 5 scenarios (Fig. 2). Across all sensitivity analyses, the ICER for treating all patients with pembrolizumab compared to the PD-L1 test strategy remained above the WTP threshold (Fig. 3), strongly suggesting that pembrolizumab is unlikely to be cost-effective when administered to all patients in this setting. A significant price reduction would be necessary to reduce the ICER for the PD-L1 test strategy to below the WTP threshold. The PD-L1 test strategy becomes cost-effective when the price is lowered 15.4% to $40.60 per mg, in comparison to standard-of-care chemotherapy.

3.2 . Budget impact analysis

We estimated the total number of new stage IV urothelial carcinomas of the bladder to be 4,824 for 2018, with 1,586 of those patients being eligible for second-line treatment after receiving first-line chemotherapy [1,24,25]. The total incremental cost of treating these patients using the PD-L1 test strategy compared to chemotherapy was $14.9 million in the first year and increased modestly to $16.5 million by the fifth year. The total incremental cost of treating all patients with pembrolizumab vs. the PD-L1 test strategy amounted to $19.6 million in the first year, increasing to $20.9 million by year 5 (Table 3).

4. Discussion

Pembrolizumab has been approved for treatment of a number of different cancers (i.e., urothelial carcinoma, non-small cell lung cancer, Hodgkin's lymphoma, head and neck cancer, melanoma, and gastric cancer) and its effectiveness in advanced stage cancers has been substantiated by numerous clinical trials [6,27–31]. Using the results of the KEYNOTE-045 clinical trial and other literature

Table 2
Summary results for base-case model

Strategy	Mean cost	Mean LY	Mean QALY	Comparator	Inc. cost	Inc. QALY	ICER
Treatment with CHEMO	$17,232	0.83	0.43	–	–	–	–
PD-L1 Test (1%)	$27,579	1.01	0.51	Treatment with CHEMO	$10,347	0.08	$122,933
Treatment with PEMB	$40,573	1.16	0.58	PD-L1 Test (1%)	$12,994	0.07	$197,383

CHEMO = chemotherapy; ICER, incremental cost-effectiveness ratio; Inc., incremental; LY, life-years; PEMB = pembrolizumab; QALY, quality-adjusted life-years.

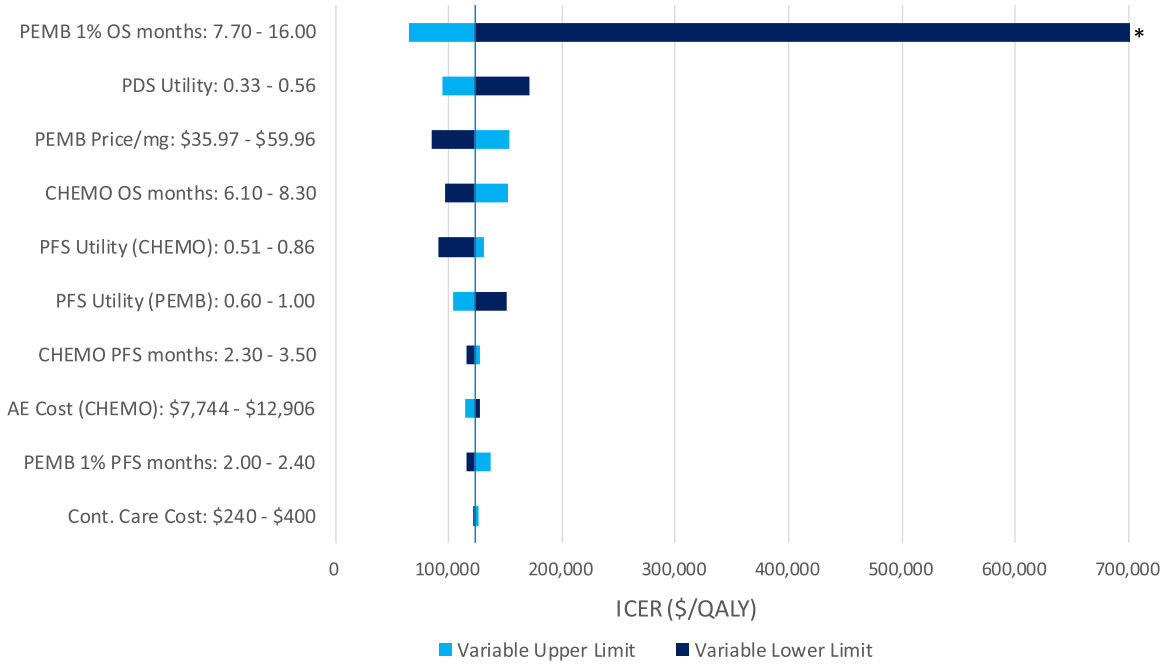

Fig. 2. Sensitivity analysis of key variables for the PD-L1 test strategy vs. standard-of-care chemotherapy.

*Incremental QALYs amounted to only 0.01, causing the ICER to increase to $1.15 million/QALY. Chart is abbreviated for clarity of other variables.

AE = adverse event; CHEMO = chemotherapy; Cont. Care = continuing care; ICER = incremental cost-effectiveness ratio; PDS = progressive disease survival; PEMB = pembrolizumab; PFS = progression-free survival; QALY, quality-adjusted life-year.

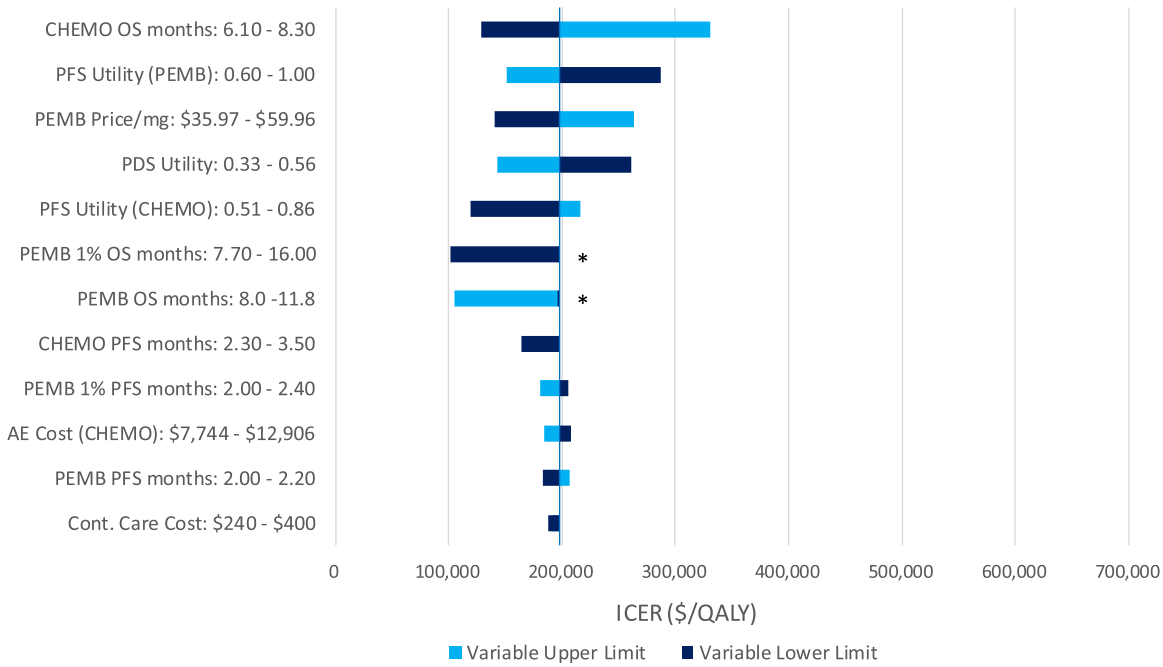

Fig. 3. Sensitivity analysis of key variables for treating all patients with pembrolizumab vs. the PD-L1 test strategy.

* ICER upper limit not meaningful—the pembrolizumab for all patients strategy was dominated by the PD-L1 test strategy.

AE = adverse event; CHEMO = chemotherapy; Cont. Care = continuing care; ICER = incremental cost-effectiveness ratio; PDS = progressive disease survival; PEMB = pembrolizumab; PFS = progression-free survival; QALY = quality-adjusted life-year.

sources, we found that pembrolizumab was not cost-effective in either of the strategies tested against chemotherapy in treating advanced urothelial carcinoma of the bladder at a $100,000/QALY WTP threshold. Using PD-L1 expression to select for patients who may experience better survival on pembrolizumab, the cost-effectiveness of pembrolizumab compared to standard chemotherapy remained above the WTP threshold (ICER = $122,933/QALY).

Table 3
Budget impact analysis by year for (a) PD-L1 test strategy vs. chemotherapy and (b) pembrolizumab for all patients vs. PD-L1 test strategy

(a)

Incremental budget impact: PD-L1 test (1%)—Chemotherapy					
Study population	2018	2019	2020	2021	2022
Diagnosed 2018	14,857,851	607,566	532,643	303,957	161,663
Diagnosed 2019	–	14,857,851	607,566	532,643	303,957
Diagnosed 2020	–	–	14,857,851	607,566	532,643
Diagnosed 2021	–	–	–	14,857,851	607,566
Diagnosed 2022	–	–	–	–	14,857,851
Net budget impact	**14,857,851**	**15,465,417**	**15,998,059**	**16,302,016**	**16,463,679**

(b)

Incremental budget impact: pembrolizumab—PD-L1 test (1%)					
Diagnosed 2018	19,646,815	510,745	400,699	228,322	98,397
Diagnosed 2019	–	19,646,815	510,745	400,699	228,322
Diagnosed 2020	–	–	19,646,815	510,745	400,699
Diagnosed 2021	–	–	–	19,646,815	510,745
Diagnosed 2022	–	–	–	–	19,646,815
Net budget impact	**19,646,815**	**20,157,560**	**20,558,260**	**20,786,581**	**20,884,978**

When all patients were treated with pembrolizumab, the ICER was $197,383/QALY compared to the PD-L1 test strategy. We found that the price of pembrolizumab would need to be lowered substantially (from $47.97 per mg to $40.60 per mg for the PD-L1 test strategy) in order to be cost-effective. Utilizing these pembrolizumab treatment strategies on a national level would add an annual incremental budget cost of $15.8 million on average over 5 years for the PD-L1 test strategy and an additional $20.4 million on average over 5 years if all eligible patients are treated with pembrolizumab.

Two prior studies, by NICE in the U.K. and by Sarfaty et al. in the U.K., U.S.A., Canada, and Australia, have examined the cost-effectiveness of treating all patients with advanced bladder cancer with pembrolizumab in the second-line setting [7,8]. Our results are in agreement with those of the NICE study of pembrolizumab in the U.K., [7] showing that the improvement over chemotherapy in terms of survival for advanced urothelial carcinoma patients has not been significant enough to justify the listed price for pembrolizumab. Sarfaty et al. estimated the ICER between all patients treated with chemotherapy and all patients treated with pembrolizumab in their study, reaching $122,557/QALY [8]. The equivalent ICER calculation using results from our study would have been $155,608/QALY, but considering the PD-L1 test strategy is more cost-effective, the strategy treating all patients with pembrolizumab should not be compared to treating all patients with chemotherapy in our study. This discrepancy is likely explained by differences in our approaches to assigning health state utilities [8]. Despite this discrepancy, both values would not be considered cost-effective at the $100,000/QALY WTP threshold used in this analysis, though support has been shown for the $150,000/QALY WTP threshold used by Sarfaty et al. [8,11].

Our study adds to the literature in several ways. First, we considered a strategy in which patients underwent PD-L1 testing prior to being treated with pembrolizumab. Second, we conducted a budget impact analysis in the United States setting, providing policymakers with a comprehensive economic analysis of pembrolizumab for treatment of advanced bladder cancer in the second line. Third, our results corroborate those of NICE and Sarfaty et al., allowing policymakers to make more robust conclusions about the cost-effectiveness of pembrolizumab from this combination of modeling studies than would be possible from 1 modeling study alone.

Based on the results of our base case analysis and those of our sensitivity analyses, reduction in the price of pembrolizumab will be important for achieving cost-effectiveness. However, a personalized approach to pembrolizumab use, in which patients with a higher likelihood of responding to treatment are identified a priori using PD-L1 expression, represents an alternative method of improving cost-effectiveness. While FDA approval for pembrolizumab in the treatment of advanced urothelial carcinoma does not currently include a provision requiring PD-L1 expression, the FDA has specified PD-L1 expression in tumors as a requirement for use in treating nonsmall cell lung cancer and gastric cancer [32,33]. Our results suggest that using PD-L1 testing, in conjunction with other improvements (namely a price reduction), could move the affordability of pembrolizumab in the right direction. However, it is important to note that PD-L1 testing alone is not enough to bring the use of pembrolizumab into the cost-effective range. Ongoing research into other potentially more accurate biomarkers for patient selection, such as tumor mutational burden [34], could also help to enhance pembrolizumab treatment's cost-benefit tradeoff.

We made several simplifying assumptions in our modeling analysis. First, we used bladder cancer, breast cancer, and non-small cell lung cancer-specific utility estimates elicited from literature sources to inform utility estimates in our model, as has been done in prior bladder cancer cost-effectiveness and treatment analyses [35,36]. Second, as previously mentioned, progression-free and overall survival times by chemotherapy type from the clinical trial were not published. Therefore, we assumed that median progression-free and overall survival were consistent between docetaxel, paclitaxel, and vinflunine treatments. This assumption should not have a significant effect on the results of this study because only marginal differences in survival times for advanced urothelial carcinoma patients receiving docetaxel, paclitaxel, and vinflunine have been reported [9,10]. Third, our model evaluates the use of pembrolizumab in treating urothelial carcinoma of the bladder, rather than all urothelial carcinomas, which can also involve the renal pelvis, ureters, and urethra. The KEYNOTE-045 trial was mostly comprised of patients with primary tumors in the bladder and, therefore, the sample did not include enough patients with primary tumors of the upper urinary tract and urethra to be representative. Finally, the PD-L1 biomarker is dynamically expressed by tumor cells, with multiple antibodies that do not stain consistently [37], making its prognostic reliability less than ideal [34]. Patients with tumors that are PD-L1-negative have also demonstrated complete or partial responses to immunotherapy drugs [38]. Therefore, selecting for patients by PD-L1 expression may not be widely accepted as a treatment option.

Recently, the results from a phase 3 randomized controlled trial for atezolizumab (*Tecentriq*, Genentech/Roche Group) vs. chemotherapy (IMvigor211, NCT02302807) in patients with locally advanced or metastatic urothelial carcinoma who had been previously treated with platinum-based chemotherapy were published [39]. However, these results showed that atezolizumab failed to significantly improve survival over chemotherapy [39], and so, without improvement in effectiveness, atezolizumab is very unlikely to be a cost-effective treatment for advanced urothelial carcinoma and was not included in this analysis.

5. Conclusions

We found that pembrolizumab was not a cost-effective option for the treatment of advanced urothelial carcinoma of the bladder for either of the strategies tested at a WTP threshold of $100,000/QALY. In sensitivity analyses, we determined that significant price reductions would be required to make treating advanced urothelial carcinoma with pembrolizumab an acceptable strategy from a health system perspective. As other immunotherapies approved for treatment of advanced urothelial carcinoma publish results of comparative phase 3 trials, additional analyses should be performed to assess the cost-effectiveness of each approved treatment. Further research must also be focused on ideal patient selection strategies for immunotherapy treatment, as there is promise for more efficient use of these drugs in the improved results for PD-L1-positive patients. Incorporation of other useful biomarkers could also potentially lead to enhanced cost-effectiveness for immunotherapy treatment strategies. Optimal strategies that synthesize use of biomarkers and patient-specific performance status could maximize the value of advanced yet costly immunotherapy treatments.

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Disclosure

The authors have declared no conflicts of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.1016/j.urolonc.2018.11.016.

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