Cost-effectiveness of Pembrolizumab in Second-line Advanced Bladder Cancer

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Michal Sarfaty[1,2], Peter S. Hall[3], Kelvin K.W. Chan[4,5], Kiran Virik[6,7], Moshe Leshno[8], Noa Gordon[1], Assaf Moore[1], Victoria Neiman[1,2], Eli Rosenbaum[1,2], Daniel A. Goldstein[1,]

[1] Institute of Oncology, Davidoff Cancer Center, Rabin Medical Center, Petach Tikva, Israel
[2]Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel
[3]Edinburgh Cancer Research Centre, University of Edinburgh, United Kingdom
[4]Odette Cancer Centre, Sunnybrook Health Sciences Centre, Toronto, Canada
[5]Canadian Centre for Applied Research in Cancer Control, Canada
[6] Cancer Centre of Southeastern Ontario, Kingston Health Sciences Centre, Kingston, Ontario, Canada
[7] Department of Oncology, Queen's University, Kingston, Ontario Canada
[8]Coller School of Management, Tel Aviv University, Tel Aviv, Israel

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Corresponding Author:

Michal Sarfaty, MD

Davidoff Cancer Center

Rabin Medical Center

Petach Tikva, Israel 49100

Tel/Fax: +972 (0)3 9378047

michalchen1@gmail.com

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Abstract

Background: Immune-modulating drugs have recently been introduced to the second line setting of advanced bladder cancer. Pembrolizumab increases overall survival and is associated with less toxicity compared to chemotherapy in this setting based on the Keynote 045 study. The high cost of immunotherapy necessitates an assessment of its value by considering both efficacy and cost.

Objective: To estimate the cost-effectiveness of pembrolizumab for the second-line treatment of advanced bladder cancer from the perspective of payers in multiple countries.

Design, Setting, and Participants: We developed a Markov model to compare the costs and effectiveness of pembrolizumab with those of chemotherapy in the second-line treatment of advanced bladder cancer based on the Keynote 045 study. Drug costs were acquired for the following countries: U.S., U.K., Canada and Australia. All costs were converted from local currency to U.S. dollars at the exchange rates in September 2017.

Outcome Measurements and Statistical Analysis: Health outcomes were measured in quality-adjusted life-years (QALYs).

Results and Limitation: Pembrolizumab generated a gain of 0.36-0.37 QALYs compared to chemotherapy. Our analysis established the following incremental cost-effectiveness ratios (ICERs) for pembrolizumab versus chemotherapy in second-line advanced bladder cancer treatment - U.S. $122,557/QALY, U.K. $91,995/QALY, Canada $90,099/QALY, and Australia $99,966/QALY. The willingness-to-pay (WTP) thresholds per QALY are considered to be around 100,000-150,000 US dollars for the U.S., 20,000-50,000 pounds for the U.K. [US$25,000-65,000], 20,000-100,000

CAD for Canada [US$16,000-80,000] and 40,000-75,000 AUD for Australia [US$32,000-60,000].

Conclusions: Cost-effectiveness and WTP thresholds vary between countries. Compared to the other countries examined, U.S. drug prices were found to be highest, leading to the highest ICER. With standard willingness-to-pay thresholds, pembrolizumab may be considered cost-effective in the U.S., but not in the other countries examined.

Patient summary: This article assessed the cost-effectiveness of pembrolizumab for treatment of patients with metastatic bladder cancer who have previously failed one treatment regimen. It would cost $122,557 in the U.S., $91,995 in the U.K., $90,099 in Canada and $99,966 in Australia to gain one quality-adjusted life-year with pembrolizumab versus chemotherapy in these patients, which may be considered cost-effective only in the U.S. because of differences in willingness-to-pay thresholds.

Introduction

Metastatic bladder cancer is a lethal disease, with only 5% of patients surviving 5 years[1]. Platinum-based chemotherapy is the standard of care for patients with advanced disease. Unfortunately, after disease progression; second-line chemotherapy yields a response rate of only around 10% with considerable toxicities[2]. Recently, immunotherapy has shown activity in advanced bladder cancer, with 5 checkpoint inhibitors gaining FDA approval for second-line therapy (pembrolizumab, nivolumab, atezolizumab, avelumab, durvalumab)[3]. Pembrolizumab is the only FDA approved checkpoint inhibitor that has so far shown an overall survival benefit in this indication, based on the Keynote 045 study[4]. This pivotal phase III study demonstrated a 2.9 month improved median overall survival with pembrolizumab compared to chemotherapy (10.3 vs. 7.4 months, hazard ratio 0.73). Responding patients on pembrolizumab tended to have longer responses, and the flattening of the survival curve for pembrolizumab hints towards durable survival in some patients. The toxicity profile was also improved, with patients typically suffering from asthenia and infrequently from immune-mediated side effects.

The growing cost of cancer care in the era of immunotherapy is of great concern for public and private payers and for individual patients around the world. This concern triggered both the American[5] and European[6] oncology societies to develop value frameworks for cancer drugs. A standard, well validated method to examine a drug's value is by a cost-effectiveness analysis (CEA), which considers both cost and efficacy in its specific indication. As drug prices and willingness to pay thresholds vary around the world[7], the CEA estimates the value in a specific setting and is not exchangeable between countries. The objective of this study was to estimate the cost-

67 effectiveness of pembrolizumab for second-line treatment of advanced bladder cancer
68 from the perspective of payers in multiple countries, specifically the U.S., U.K.,
69 Canada and Australia.
70

Methods

Model Structure

The Markov model involved an initial treatment decision with either pembrolizumab or chemotherapy (Fig. 1). Patients then transitioned through different health states: stable/responsive (progression free) disease, progressive disease, and death. Each model cycle represented 1 month over a 5-year time horizon. All patients started with stable, progression-free disease and either remained at that stage or transitioned to progressive disease or death. Once in the progressive stage, patients could remain in that stage or transition to death.

The primary outputs of the model were cost and Quality Adjusted Life Years (QALYs), which were used to calculate the incremental cost effectiveness ratio (ICER). The Markov model was implemented in TreeAgePro 2016 software (TreeAge Software Inc., Williamstown, MA, USA), and statistical analyses were performed in Matlab 2016-B software (MathWorks Inc., Natick, MA, USA).

Mortality estimates

The probability for transition from a progression-free state to a post-progression state was derived from the Progression-Free Survival (PFS) curves in the Keynote 045 trial. The probability for transition from any state to the death state was derived from the overall survival (OS) curves in the Keynote 045 trial. For the pembrolizumab and chemotherapy arms we used Plot Digitizer software (version 2.1; http://plotdigitizer.sourceforge.net) to extract the data points from each PFS and OS plot from the Keynote 045 trial, and these data points were then used to fit parametric models.

Weibull distribution was used as it provided the best fit for all curves. (See supplemental material)

Utility estimates

To compute the total quality adjusted life years (QALYs) in the Markov models, survival time was adjusted by the health-related quality of life (HRQL). The health utility score was based on quality-of life data collected in the Keynote 045. In the trial, quality-of life[8] was assessed with the European Organization for Research and Treatment of Cancer quality-of life questionnaire C30 (EORTC QLQ-C30) questionnaire. EORTC QLQ-C30 score was assessed at cycles 1–4, then every 2 cycles for up to 1 year. In the model, based on the trial, we incorporated a baseline utility of 0.6 for all patients for weeks 1-14 and a utility of 0.61 for the pembrolizumab arm and 0.52 for the chemotherapy arm from week 15 until death. We used ±10% as the boundaries of the range in sensitivity analyses.

Cost estimates

Only direct medical costs were considered including drug, administration, and adverse event (AE) costs. The cost of pembrolizumab administration was calculated for intravenous treatment at a dose of 200mg every 3 weeks until disease progression for a maximum of 2 years. The cost of chemotherapy administration was calculated as the mean cost of docetaxel 75mg/m^2 (including dexamethasone 8 mg PO bid for 3 days) and paclitaxel 175mg/m^2, administration intravenously every 3 weeks until disease progression. The cost of vinflunine was not accounted for, as it is not FDA approved and is not used for this indication in the U.S.. To calculate doses, we used a mean body surface area (BSA) of 1.86 m^2.[9]

We included in the model grade 3 to 4 AEs that had significantly different rates between the arms of the Keynote 045 trial[4], which were anemia, neutropenia and febrile neutropenia. The treatment of AEs was estimated based on clinical experience, similar to a previous study[10]. We assumed that an episode of febrile neutropenia would be managed with a 5-day hospitalization. We assumed that grade 3/4 anemia would be managed with one outpatient visit and transfusion of two units of red blood cells (RBC). All costs and health outcomes were discounted by 3% annually for the U.S., U.K. and Australia[11], and 1.5% for Canada[12]. We adjusted all cost estimates for each individual country, similar to a previous study[11]. We used prices that, to the best of our knowledge, account for non-confidential discounts and rebates. However we were unable to account for any country specific confidential discounts. Details of drug costs are available in Table 1 and in the supplemental material.

Sensitivity analysis

A series of sensitivity analyses was performed to evaluate the robustness of the model and to address the uncertainty in the estimation of variables. Utilities incorporated a ±10% range as described above. Drug costs varied within ±20% of their baseline values to account for alternative public and private payers that may pay less or more respectively, as in a similar study[13]. In univariate sensitivity analyses, we varied the value of one parameter at a time over its defined range and examined the effect on the ICER. In probabilistic sensitivity analyses (PSA), we ran the model 10,000 times, each time randomly varying all parameters simultaneously according to the sampling distributions.

Structural sensitivity analysis

We performed two structural sensitivity analyses, one incorporating the price of vinflunine to the U.K. model, and the other comparing pembrolizumab to best supportive care (assuming no survival benefit with taxanes).

Net Benefit Calculation

Net Health Benefit (NHB) expresses the ICER on a single scale in units of QALYs. It requires pre-specification of a fixed monetary value of a QALY, which can be considered to be the opportunity cost of losing one QALY from a health system[14,15]. This is equivalent to a back-calculated cost-effectiveness threshold. Using this, we calculated the country-specific value of pembrolizumab, subject to local pricing, using the value-metric of incremental NHB per person treated (expressed in QALYs where higher values represent higher value).

Results

Base Case Results

Pembrolizumab generated a gain of 0.36 QALYs over chemotherapy for the U.S., U.K. and Australia, and 0.37 QALY for Canada (due to different discounting rates). In the U.S., U.K., Canada, and Australia, in comparison with the base case results, the ICER, meaning the additional cost of pembrolizumab versus chemotherapy was $122,557, $91,995, $90,099, and $99,966 per QALY gained, respectively. Table 2 demonstrates these base case results.

Sensitivity Analyses

The results of univariate sensitivity analyses are presented in the tornado diagram (in supplemental material). The parameters with the greatest influence on the ICER were those of the overall survival extrapolation. The effects of other parameters were negligible. The results of the probabilistic sensitivity analyses are shown in the cost-effectiveness acceptability curves (Fig 2). These curves show the probability that pembrolizumab is cost-effective across increasing willingness-to-pay (WTP) thresholds. These results demonstrated 100% probability in all countries analyzed that pembrolizumab is cost-effective compared to chemotherapy at WTP thresholds of $150,000 per QALY.

Country-Specific Value Estimates

Expressed as NHB, the country specific estimates of the value of pembrolizumab versus chemotherapy are as follows: U.S. -1.46 to -0.74 QALYs; U.K. -1.42 to -1.42 QALYs; Canada -1.24 to -0.91 QALYs; Australia -1.34 to -0.98 QALYs. This approach suggests that country-specific prices result in Australia obtaining best value for money and the U.K. likely the worst, taking into account the country-specific opportunity cost of investment in the new technology.

Discussion

We performed a cost-effectiveness analysis of pembrolizumab versus chemotherapy in 2nd line advanced bladder cancer from a global perspective, including 4 countries - U.S., U.K., Canada and Australia. A single treatment with pembrolizumab costs 15-50 times more per cycle compared with chemotherapy. The added cost for pembrolizumab over chemotherapy is lower in the U.K., Australia, and Canada (~$33,000-$36,000) than in the U.S. (~$44,000), resulting in lower ICERs in these

195 countries (~$90,000-$100,000 versus ~$120,000 per QALY gained). Prices vary
196 around the world due to differences in regulations and negotiations with drug
197 companies. U.S. prices are known to be higher than other countries as every FDA
198 approved drug is reimbursed by Medicare without the ability to negotiate[16]. Although
199 the intervention is more expensive in the U.S., due to a higher theoretical WTP
200 threshold it is the only country in which the drug may potentially be considered to be
201 cost-effective.
202 It is important to note that the WTP threshold varies between different countries and
203 is a matter of much debate, as its precise figure is elusive. In the U.S. the WTP
204 threshold is considered to be $50,000-150,000 per QALY[17], although many cancer
205 drugs are in use despite an ICER above this threshold[13]. In the U.K. the WTP
206 threshold is considered to be 20,000-30,000 pounds [25,000-38,000 US $] and 50,000
207 pounds [~65,000 US $] if the drug meets the end-of-life criteria (life-prolonging by
208 more than 3 months in a disease with a prognosis of less than 24 months)[18]. For
209 Canada and Australia there is no explicit WTP threshold for recommendation-making
210 by the pan-Canadian Oncology Drug Review (pCODR)/Canadian Agency in Drug
211 and Technology in Health (CADTH) nor the Australian Pharmaceutical Benefits
212 Advisory Committee (PBAC). We used for this paper a Canadian threshold of 20,000-
213 100,000 CAD [16,000-80,000 US $], as discussed by Laupacis et al[19] and an
214 Australian threshold of 40,000-75,000 AUD [32,000-60,000 US $], as conferred by
215 George et al[20]. The World Health Organization[21] recommends using a WTP threshold
216 of two to three times the gross domestic product per capita per disability-adjusted life-
217 year (DALY) averted. These different thresholds and their impact on the decision
218 whether pembrolizumab is cost-effective are presented in Table 2. In August 2017 the
219 U.K. National Institute for Health and Care Excellence (NICE) announced that

pembrolizumab is not cost-effective for metastatic bladder cancer due to its high cost, despite meeting the end-of-life criteria[22].

Our analysis was limited by data availability and our assumptions. We assumed that survival benefits, utilities, and AE incidence and management were standard between countries. We used American data for mean BSA, which might differ slightly between countries. We did not include taxes on drug costs for any country, as tax rates and criteria are different between countries. We did not account for crossover, and in the trial 12.9% of patients in the chemotherapy arm received subsequent immunotherapy. This may potentially underestimate the survival benefit with pembrolizumab. In the sensitivity analyses we used a range for certain values to account for possible inaccuracies, as described above. Such inaccuracies may include differences between the trial participants and real world patients, as it is likely that in the real world pembrolizumab will be given to frailer patients due to its low toxicity. Also as there are no third line approved therapies, at first radiographic progression many real world patients are likely to continue therapy until the next evaluation to account for the possibility of pseudo-progression. Both differences may cause a lower utility and an increased cost of pembrolizumab, thus increasing the ICER. As vinflunine is not FDA approved and is not regularly used in clinical practice in any of the countries examined we decided not to incorporate it in the analysis. When incorporating vinflunine costs into the model the U.K. ICER changes from $91,995 to $81,850, and is still considered not to be cost-effective. To account for the possibility of no survival benefit with second-line chemotherapy we added a structural sensitivity analysis of pembrolizumab versus placebo (eTable 3 in supplement). The modeling of AEs included only significantly different incidence rates of grade 3 to 4 toxicity between treatments, thus immune-related AEs were not included due to few events. As the

recent FDA approval[3] of 5 checkpoint inhibitors in second-line therapy of advanced bladder cancer changes the standard-of-care, future research would potentially include all second-line treatments with a network meta-analysis. Such an analysis would likely find pembrolizumab to be more cost-effective than the other checkpoint inhibitors, as it is the only one to currently demonstrate a survival benefit. Pembrolizumab has also recently gained approval in cisplatin-ineligible first-line advanced bladder cancer based on the Keynote 052 trial and is examined as monotherapy or in combination with chemotherapy in first-line ongoing trials. As the treatment of bladder cancer continues to rapidly evolve, there is an increasing need for the use of cost-effectiveness analyses to guide coverage decisions by payers and policy makers. This is particularly important in the United States, where drug prices are usually higher.

Conclusion

Costs and WTP thresholds vary between countries. Compared to the other countries examined, U.S. drug prices were found to be highest, leading to the highest ICER. Nevertheless, due to a higher WTP threshold, pembrolizumab may potentially be considered cost-effective in the U.S., but not in the other countries.

263 Tables and Figures

264 **Table 1 - Treatment costs**

Treatment cost ($ per cycle)	**U.S., *n* (range)**	**U.K., n (range)**	**Canada, n (range)**	**Australia, n (range)**
Pembrolizumab	9,691 (7,753-11,629)	6,816 (5,453-8,180)	7,053 (5,643-8,464)	7,563 (6,051-9,076)
Administration - Pembrolizumab	136 (109-163)	317 (254-381)	92 (74-111)	52 (41-62)
Chemotherapy	310 (248-372)	22 (18-26)	46 (37-55)	81 (65-97)
Administration - Chemotherapy	411 (329-493)	323 (258-387)	154 (123-185)	80 (64-96)
Adverse Event cost ($ per event)				
Anemia	1,881 (1,505-2,258)	756 (604-907)	464 (371-557)	781 (625-938)
Neutropenic fever	11,565 (9,252-13,789)	1,632 (1,305-1,958)	4,244 (3,395-5,093)	4,523 (3,622-5,433)

265

266 Values in parentheses are the lower and upper bounds of the range used in sensitivity
267 analyses. All costs are displayed in U.S. dollars, which were converted from local
268 currencies at the exchange rates on September 1, 2017[23].

269

270

271 **Table 2 - Base case results**

Country	Incremental cost	Incremental effectiveness (QALY)	ICER	WTP threshold	Cost-effective?
U.S.	$44,325	0.36	$122,557/QALY	$100,000 - 150,000[17]	Yes
U.K.	$33,271	0.36	$91,995/QALY	$25,000-65,000[18]	No
Canada	$33,869	0.37	$90,099/QALY	$16,000-80,000[19,*]	No
Australia	$36,154	0.36	$99,966/QALY	$32,000-60,000[20,*]	No

272

273 All costs are displayed in U.S. dollars, which were converted from local currencies at
274 the exchange rates on September 1, 2017[23].

275 * For Canada and Australia there is no explicit WTP threshold for recommendation-
276 making.

277 Abbreviations: QALY, quality adjusted life year; ICER, incremental cost-
278 effectiveness ratio; WTP, willingness-to-pay.

279

280 **Figure 1 – Markov model**

281

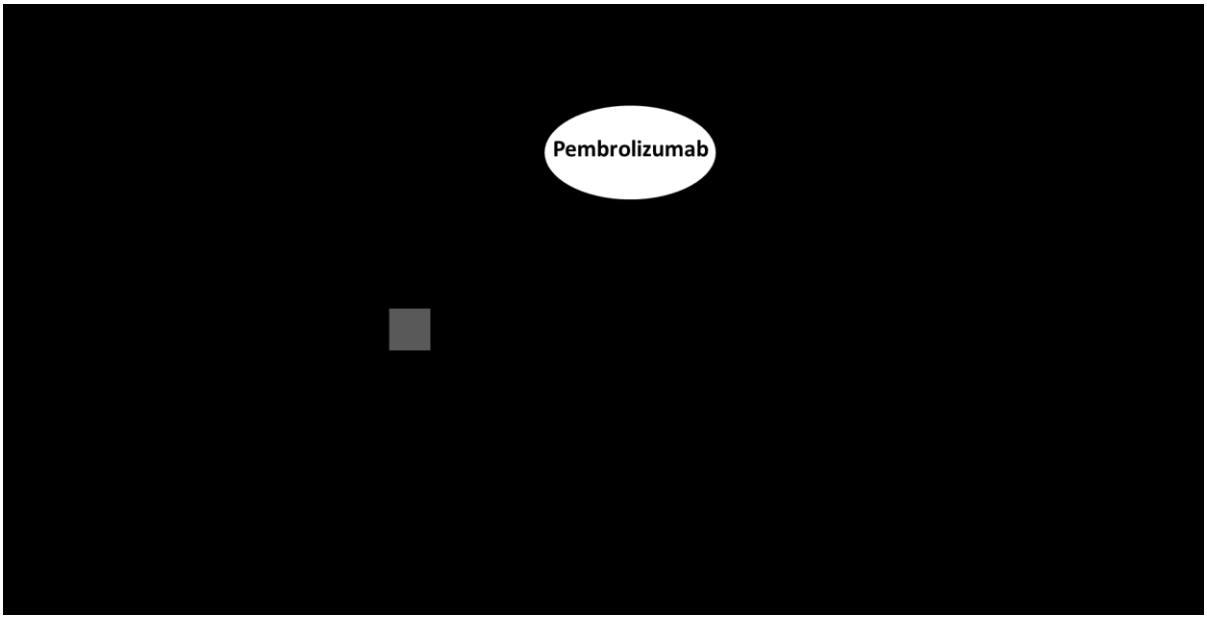
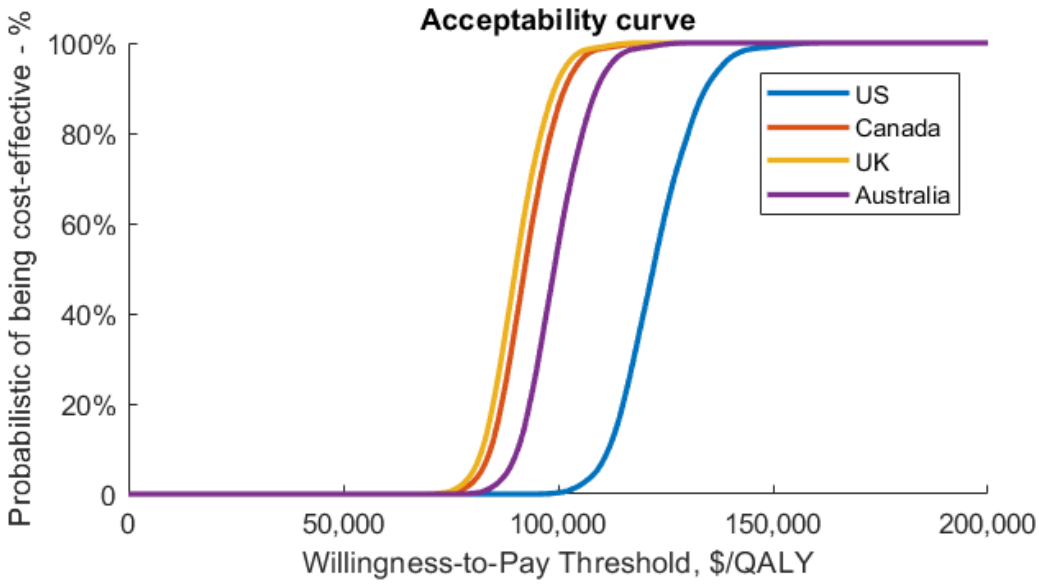


Figure 2 - Cost-effectiveness acceptability curves in U.S. dollars



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Supplemental Material

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eTable 1: Drug costs

Country	Currency	Drug	Drug cost	Administration cost	Premedication cost	Total cost per cycle	Total cost per month
U.S.	USD	Pembro	9,691	136	0	9,827	14,038.5
U.S.	USD	Chemo	310.8	409	2.5	722.3	1,031.8
U.K.	GBP	Pembro	5,260	245.1	0	5,505.1	7,864.4
U.K.	GBP	Chemo	16.8	245.1	4	265.9	379.8
Canada	CAD	Pembro	8,800	115.1	0	8,915.1	12,735.8
Canada	CAD	Chemo	57.1	190.3	1.8	249.2	356
Australia	AUD	Pembro	9,523.8	65	0	9,588.8	13,698.2
Australia	AUD	Chemo	102.5	97.9	3.2	203.6	290.8

eTable 2: Adverse event costs

Country	Currency	Drug	Anemia cost	Incidence	Total Anemia cost	FN* cost	Incidence	Total FN* cost	Total AE cost
U.S.	USD	Pembro	1,881.3	0.8%	15	11,565.6	0.0%	0	15
U.S.	USD	Chemo	1,881.3	7.8%	146.7	11,565.6	7.0%	821.1	967.8
U.K.	GBP	Pembro	583	0.8%	4.6	1,259	0.0%	0	4.6
U.K.	GBP	Chemo	583	7.8%	45.4	1,259	7.0%	88.1	133.5
Canada	CAD	Pembro	579	0.8%	4.6	5,295.7	0.0%	0	4.6
Canada	CAD	Chemo	579	7.8%	45.1	5,295.7	7.0%	370.6	415.7
Australia	AUD	Pembro	984.1	0.8%	7.8	5,701.3	0.0%	0	7.8
Australia	AUD	Chemo	984.1	7.8%	76.7	5,701.3	7.0%	399	475.7

*FN = febrile neutropenia

eTable 3: Structural sensitivity analysis – Pembrolizumab versus Placebo

Country	Incremental cost	Incremental effectiveness (QALY)	ICER	WTP threshold	Cost-effective?
U.S.	$48,137	0.36	$133,083/QALY	$100,000-150,000[16]	Yes
U.K.	$35,026	0.36	$96,834/QALY	$25,000-65,000[17]	No
Canada	$35,222	0.37	$97,377/QALY	$16,000-80,000[18,*]	No
Australia	$37,579	0.36	$103,894/QALY	$32,000-60,000[19,*]	No

All costs are displayed in U.S. dollars, which were converted from local currencies at the exchange rates on September 1, 2017[22].

* For Canada and Australia there is no explicit WTP threshold for recommendation-making.

Costs

We adjusted all cost estimates for each individual country. All costs were sourced between 2013 and 2017 and were converted from local currency to U.S. dollars using the exchange rates on September 1, 2017: one U.S. dollar was equivalent to 0.77 U.K. pounds, 1.25 Australian dollars and 1.24 Canadian dollars[1]. We did not include sales tax.

U.S. Costs

For US prices we used the 2016 average sales price by the Centers for Medicare and Medicaid services plus 4.2% to simulate Medicare reimbursement. Administration costs and adverse event costs were calculated according to the Medicare physician fee schedule for 2016. The costs for grade 3/4 AEs were based on diagnosis related group (DRG) codes. The fees for outpatient physician visits were based on Current Procedure Terminology codes[2,3].

U.K. Costs

To estimate the unit price for generic drugs, we used the U.K. Department of Health Commercial Medicines Unit electronic Medicines Information Tool[4]. To estimate the unit price for patented drugs, we used the U.K. list price as published in the British National Formulary[5]. This represents the national Drug Tariff arising from negotiation on a 5-year cycle as part of the Pharmaceuticals Pricing and Reimbursement Scheme. Costs for chemotherapy administration and outpatient physician visits were taken from the National Health Service (NHS) Reference costs, which are published annually on the basis of average costs returned by individual NHS healthcare providers[6].

Canada Costs

To estimate the unit price of drugs, we used the Ontario Drug Benefit Formulary[7] and Sunnybrook Pharmacy Stores Department (Kelvin Chan, personal communication). The costs of chemotherapy supervision were estimated by duration of nursing and pharmacy time as estimated by Cancer Care Ontario[8] and multiplied by their estimated hourly wage[9]. The outpatient physician visits cost was obtained from the Ontario Schedule of Benefits[10]. In Ontario, Canada, there is a differential pricing structure for clinic visits based on the number of prior visits. In order to make appropriate comparisons between countries and not to adjust the overall design of the model, we estimated the price of a single clinic visit as the mean of the first

five clinic visits. Although any difference in actual prices would likely have only a tiny impact on the model results, these differences would be accounted for in the subsequent sensitivity analyses.

Australia Costs

Drug prices were collected from the 2017 Pharmaceutical Benefits Scheme prices[11]. This is a federally funded pharmaceutical scheme with nationwide coverage. Administration costs and physician visits were based on the 2017 Medicare Benefits Schedule prices for outpatient health services[12]. Blood products were based on the 2017 National Blood Authority Australia prices[13].

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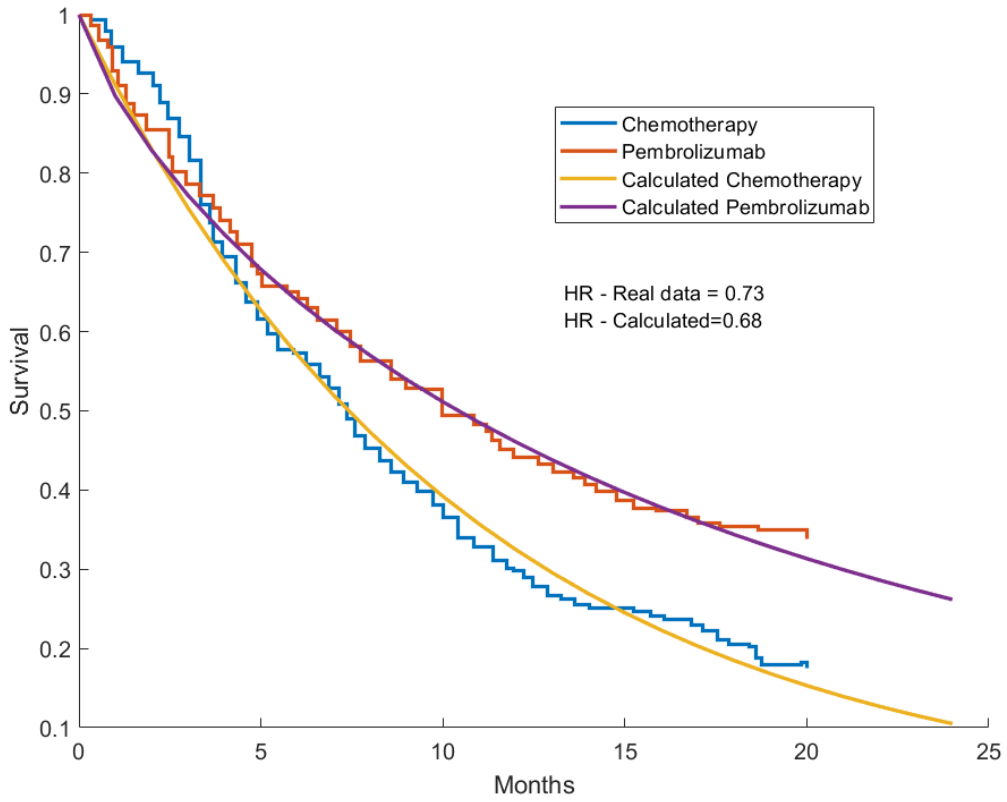
eFigure 1: Overall Survival Curve- Pembrolizumab versus Chemotherapy



eFigure 2: Progression-free Survival Curve- Pembrolizumab versus Chemotherapy