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## **Cost-Effectiveness of Pembrolizumab in Second-Line Advanced Bladder Cancer**

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1 **Abstract**

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

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

10 **Design, Setting, and Participants:** We developed a Markov model to compare the  
11 costs and effectiveness of pembrolizumab with those of chemotherapy in the second-  
12 line treatment of advanced bladder cancer based on the Keynote 045 study. Drug costs  
13 were acquired for the following countries: U.S., U.K., Canada and Australia. All costs  
14 were converted from local currency to U.S. dollars at the exchange rates in September  
15 2017.

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

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

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

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

32

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

39

40

41

## 42 **Introduction**

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

58

59 The growing cost of cancer care in the era of immunotherapy is of great concern for  
60 public and private payers and for individual patients around the world. This concern  
61 triggered both the American<sup>5</sup> and European<sup>6</sup> oncology societies to develop value  
62 frameworks for cancer drugs. A standard, well validated method to examine a drug's  
63 value is by a cost-effectiveness analysis (CEA), which considers both cost and  
64 efficacy in its specific indication. As drug prices and willingness to pay thresholds  
65 vary around the world<sup>7</sup>, the CEA estimates the value in a specific setting and is not  
66 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

## 71 **Methods**

### 72 Model Structure

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

80

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

86

### 87 Mortality estimates

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

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

97

#### 98 Utility estimates

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

109

#### 110 Cost estimates

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



120

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

133

#### 134 Sensitivity analysis

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

144

145

146 Structural sensitivity analysis

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

150

151 Net Benefit Calculation

152 Net Health Benefit (NHB) expresses the ICER on a single scale in units of QALYs. It  
153 requires pre-specification of a fixed monetary value of a QALY, which can be  
154 considered to be the opportunity cost of losing one QALY from a health system<sup>14,15</sup>.

155 This is equivalent to a back-calculated cost-effectiveness threshold. Using this, we  
156 calculated the country-specific value of pembrolizumab, subject to local pricing, using  
157 the value-metric of incremental NHB per person treated (expressed in QALYs where  
158 higher values represent higher value).

159

160 **Results**

161 Base Case Results

162 Pembrolizumab generated a gain of 0.36 QALYs over chemotherapy for the U.S.,  
163 U.K. and Australia, and 0.37 QALY for Canada (due to different discounting rates).

164 In the U.S., U.K., Canada, and Australia, in comparison with the base case results, the  
165 ICER, meaning the additional cost of pembrolizumab versus chemotherapy was  
166 \$122,557, \$91,995, \$90,099, and \$99,966 per QALY gained, respectively. Table 2  
167 demonstrates these base case results.

168

169 Sensitivity Analyses

170 The results of univariate sensitivity analyses are presented in the tornado diagram (in  
171 supplemental material). The parameters with the greatest influence on the ICER were  
172 those of the overall survival extrapolation. The effects of other parameters were  
173 negligible. The results of the probabilistic sensitivity analyses are shown in the cost-  
174 effectiveness acceptability curves (Fig 2). These curves show the probability that  
175 pembrolizumab is cost-effective across increasing willingness-to-pay (WTP)  
176 thresholds. These results demonstrated 100% probability in all countries analyzed that  
177 pembrolizumab is cost-effective compared to chemotherapy at WTP thresholds of  
178 \$150,000 per QALY.

179

#### 180 Country-Specific Value Estimates

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

187

#### 188 **Discussion**

189 We performed a cost-effectiveness analysis of pembrolizumab versus chemotherapy  
190 in 2<sup>nd</sup> line advanced bladder cancer from a global perspective, including 4 countries -  
191 U.S., U.K., Canada and Australia. A single treatment with pembrolizumab costs 15-  
192 50 times more per cycle compared with chemotherapy. The added cost for  
193 pembrolizumab over chemotherapy is lower in the U.K., Australia, and Canada  
194 (~\$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<sup>16</sup>. 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<sup>17</sup>, although many cancer  
205 drugs are in use despite an ICER above this threshold<sup>13</sup>. 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)<sup>18</sup>. 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<sup>19</sup> and an  
214 Australian threshold of 40,000-75,000 AUD [32,000-60,000 US \$] as conferred by  
215 George et al<sup>20</sup>. The World Health Organization<sup>21</sup> 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

220 pembrolizumab is not cost-effective for metastatic bladder cancer due to its high cost,  
221 despite meeting the end-of-life criteria<sup>22</sup>.

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

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

257

## 258 **Conclusion**

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

263 Tables and Figures264 **Table 1 - Treatment costs**

<b>Treatment cost (\$ per cycle)</b>	<b>U.S., <i>n</i> (range)</b>	<b>U.K., <i>n</i> (range)</b>	<b>Canada, <i>n</i> (range)</b>	<b>Australia, <i>n</i> (range)</b>
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)
<b>Adverse Event cost (\$ per event)</b>				
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<sup>23</sup>.

269

270

271 **Table 2 - Base case results**

Country	Incremental cost	Incremental effectiveness (QALY)	ICER	WTP threshold	Cost-effective ?
<b>U.S.</b>	\$44,325	0.36	\$122,557/QALY	\$100,000 - 150,000 <sup>17</sup>	Yes
<b>U.K.</b>	\$33,271	0.36	\$91,995/QALY	\$25,000-65,000 <sup>18</sup>	No
<b>Canada</b>	\$33,869	0.37	\$90,099/QALY	\$16,000-80,000 <sup>19,*</sup>	No
<b>Australia</b>	\$36,154	0.36	\$99,966/QALY	\$32,000-60,000 <sup>20,*</sup>	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<sup>23</sup>.

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

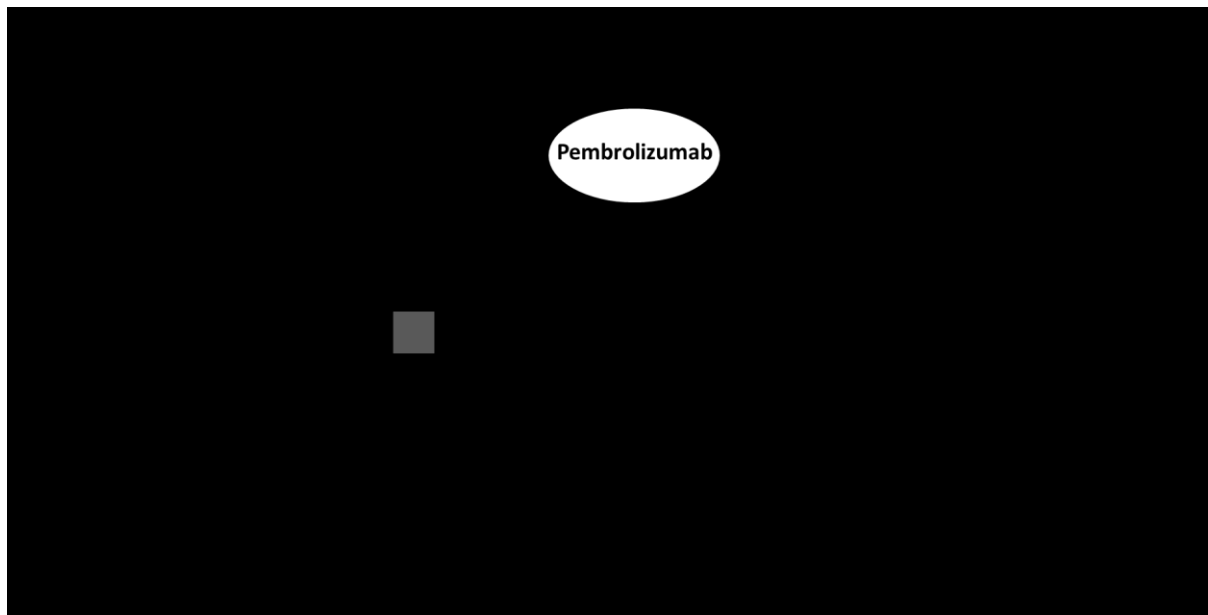
277 Abbreviations: QALY, quality adjusted life year; ICER, incremental cost-  
 278 effectiveness ratio; WTP, willingness-to-pay.

279

280 **Figure 1 – Markov model**

281





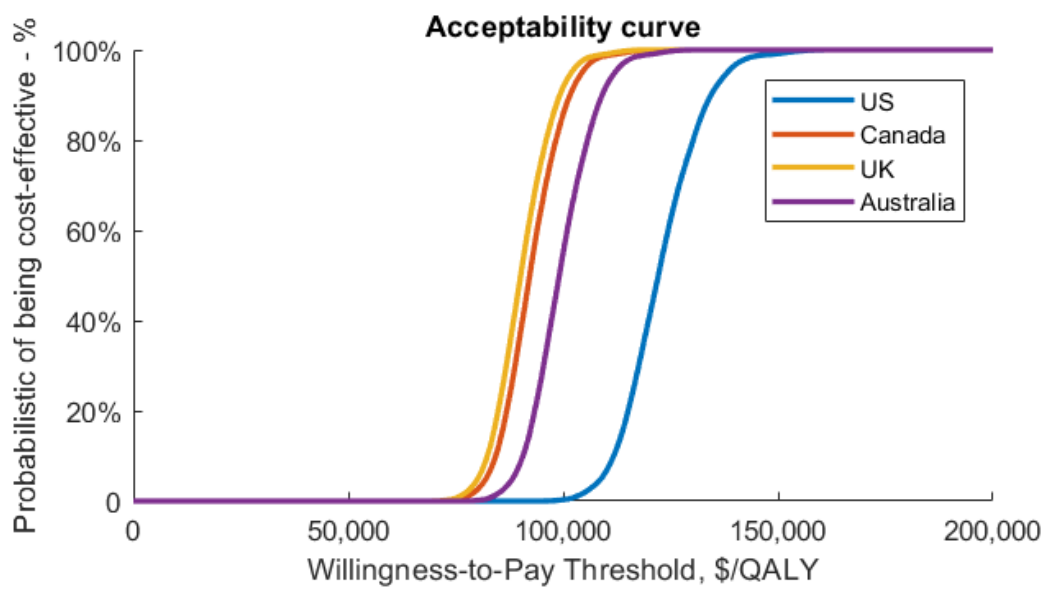
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287 **Figure 2 - Cost-effectiveness acceptability curves in U.S. dollars**

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# Cost-Effectiveness of Pembrolizumab in Advanced Bladder Cancer

## 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 <sup>16</sup>	Yes
U.K.	\$35,026	0.36	\$96,834/QALY	\$25,000-65,000 <sup>17</sup>	No
Canada	\$35,222	0.37	\$97,377/QALY	\$16,000-80,000 <sup>18,*</sup>	No
Australia	\$37,579	0.36	\$103,894/QALY	\$32,000-60,000 <sup>19,*</sup>	No

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

\* 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<sup>1</sup>. 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<sup>2,3</sup>.

### **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<sup>4</sup>. To estimate the unit price for patented drugs, we used the U.K. list price as published in the British National Formulary<sup>5</sup>. 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<sup>6</sup>.

### **Canada Costs**

To estimate the unit price of drugs, we used the Ontario Drug Benefit Formulary<sup>7</sup> 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<sup>8</sup> and multiplied by their estimated hourly wage<sup>9</sup>. The outpatient physician visits cost was obtained from the Ontario Schedule of Benefits<sup>10</sup>. 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<sup>11</sup>. 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<sup>12</sup>. Blood products were based on the 2017 National Blood Authority Australia prices<sup>13</sup>.

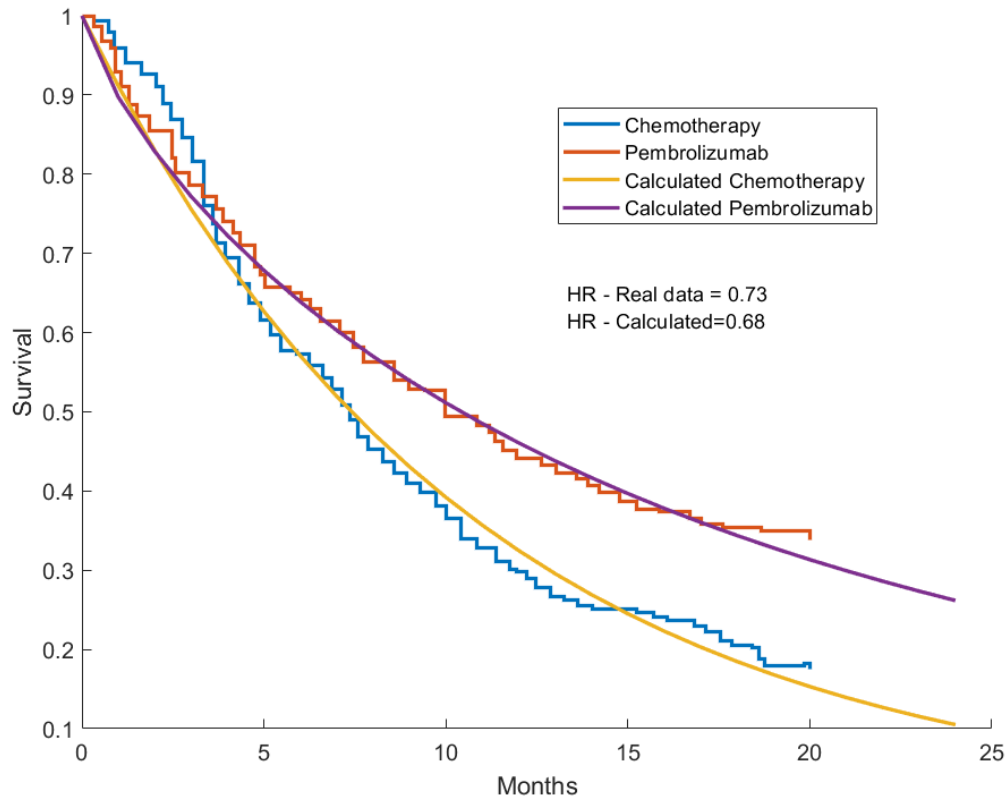
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**eFigure 1: Overall Survival Curve- Pembrolizumab versus Chemotherapy**



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

