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

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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 with 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 cost 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 United States (US), United Kingdom (UK), Canada, and Australia. All costs were converted from local currency to US 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 limitations: Pembrolizumab generated a gain of 0.36–0.37 QALYs compared with chemotherapy. Our analysis established the following incremental cost-effectiveness ratios (ICERs) for pembrolizumab versus chemotherapy in second-line advanced bladder cancer treatment: US $122 557/QALY; UK $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 US, 20 000–50 000 pounds for the UK (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 with the other countries examined, US drug prices were found to be the highest, leading to the highest ICER. With standard WTP thresholds, pembrolizumab may be considered cost-effective in the US but not in the other countries examined.
Patient summary: This article assessed the cost-effectiveness of pembrolizumab for the treatment of patients with metastatic bladder cancer who had previously failed one treatment regimen. It would cost $122 557 in the United States, $91 995 in the United Kingdom, $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 United States because of the differences in willingness-to-pay thresholds.

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1. Introduction

Metastatic bladder cancer is a lethal disease, with only 5% of patients surviving 5 yr [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 five checkpoint inhibitors gaining Food and Drug administration (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 (OS) benefit in this indication based on the Keynote 045 study [4]. This pivotal phase III study demonstrated a 2.9-mo improved median OS with pembrolizumab compared to chemotherapy (10.3 vs 7.4 mo, hazard ratio: 0.73). Responding patients on pembrolizumab tended to have longer responses, and the flattening of the survival curve for pembrolizumab hints toward 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 cost-effectiveness analysis (CEA), which considers both cost and efficacy in its specific indication. As drug prices and willingness-to-pay (WTP) thresholds vary around the world [7], CEA estimates the value in a specific setting and is not exchangeable between countries. The objective of this study was to estimate the cost-effectiveness of pembrolizumab for the second-line treatment of advanced bladder cancer from the perspective of payers in multiple countries, specifically the United States (US), United Kingdom (UK), Canada, and Australia.

2. Patients and methods

2.1. 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 mo over a 5-yr 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 transitioned 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).

2.2. 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 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 Supplementary material).

2.3. Utility estimates

To compute the total QALYs in the Markov models, survival time was adjusted by the health-related quality of life. 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. The EORTC QLQ-C30 score was assessed at cycles one to four and then every two cycles for up to 1 yr. 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

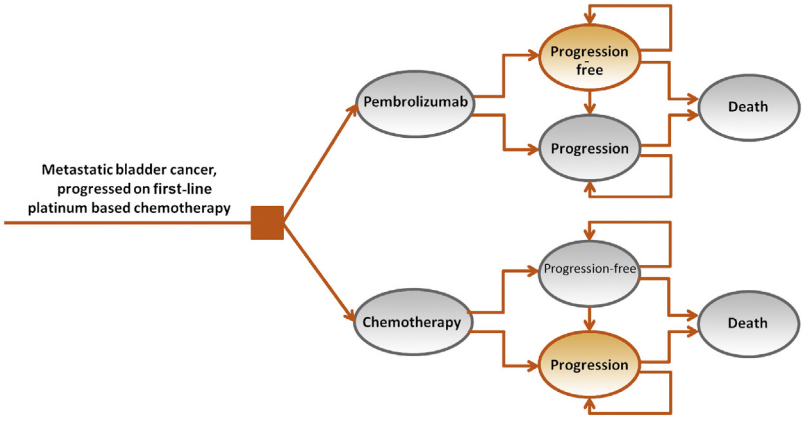

Fig. 1 – Markov model.

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