VALUE IN HEALTH ▮ (2017) ▮▮▮–▮▮▮

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/jval

Cost-Effectiveness of Pembrolizumab for Advanced Melanoma Treatment in Portugal

Luis Silva Miguel, PhD[1,*], *Francisca Vargas Lopes, PharmD*[2], *Bernardete Pinheiro, MSc*[1], *Jingshu Wang, PhD*[3], *Ruifeng Xu, PhD*[3], *James Pellissier, PhD*[3], *Pedro Almeida Laires, MSc*[2]

[1]*Research Centre on the Portuguese Economy – CISEP, ISEG/Universidade de Lisboa, Lisboa, Portugal;* [2]*MSD, Paço de Arcos, Portugal;* [3]*Merck & Co., Inc., Kenilworth, NJ, USA*

ABSTRACT

Background: The aim of this study was to assess the cost-effectiveness of pembrolizumab in treating patients with ipilimumab-naïve advanced melanoma in Portugal. **Methods:** A cost-effectiveness model was developed to analyze the costs and consequences of treatment with pembrolizumab compared to treatment with ipilimumab in patients with advanced melanoma not previously treated with ipilimumab. The model was parameterized by using data from a head-to-head phase III randomized clinical trial, KEYNOTE-006. Extrapolation of long-term outcomes was based on approaches previously applied, combining ipilimumab data and melanoma patients' registry data. The analysis was conducted from the perspective of the Portuguese National Health Service, and a lifetime horizon (40 years) was used. Portugal-specific disease management costs were estimated by convening a panel of six clinical experts to derive health state resource use and multiplying the results by national unit costs. To test for the robustness of the conclusions, we conducted deterministic and probabilistic sensitivity analyses. **Results:** Pembrolizumab increases life expectancy in 1.57 undiscounted life-years (LYs) and is associated with an increase in costs versus that of ipilimumab. The estimated incremental cost-effectiveness ratio is €47,221 per quality-adjusted life-year (QALY) and €42,956 per LY. Deterministic sensitivity analysis showed that the results were robust to the change of most input values or assumptions and were sensitive to time on treatment scenarios. According to the probabilistic sensitivity analysis performed, pembrolizumab is associated with a cost per QALY gained inferior to €50,000 in 75% of the cases. **Conclusions:** Considering the usually accepted thresholds in oncology, pembrolizumab is a cost-effective alternative for treating patients with advanced melanoma in Portugal.

Keywords: advanced melanoma, cost-effectiveness, ipilimumab, pembrolizumab.

Introduction

Melanoma is a tumor of melanocytes, which are specialized cells present in the epidermis [1], and develops more frequently in the skin. However, it could also develop in other organs and tissues [2]. Although it represents only 4.5% of skin cancers, it is responsible for most of the associated mortality [3].

The five-year survival rate depends on the stage at diagnosis, being >90% when diagnosed in early stages (IA and IB) but only about 40% and 20% when diagnosed in stages IIIC and IV, respectively [4]. The incidence data available suggests that in 2012, about 232,130 new cases were diagnosed globally, with 104,192 cases recorded in Europe [5]. In Portugal, according to the same source, 1011 new cases were estimated. Data from the 2008 National Oncological Registry revealed an incidence of 861 cases (incidence rate of 8.2 per 100,000) and 216 deaths (mortality rate of 2.0 per 100,000). The analysis of the incidence rate by age group showed an increase after 25 years, but especially after age 50 years [6].

In the past, the treatment options available for advanced melanoma were scarce and mainly included standard chemotherapy with dacarbazine, temolozomide, fotemustine, taxanes, and platinum compounds. However, in recent years, the general treatment methods have undergone considerable change, with the introduction of target treatments (BRAF and MEK inhibitors) and immunotherapy (ipilimumab, an anti-cytotoxic T-lymphocyte-associated protein-4] antibody), which proved to be promising alternatives.

Pembrolizumab is a humanized monoclonal antibody directed toward the programmed death-1 (PD-1) receptor. As immunotherapy, it blocks the cellular pathway that prevents the immune system from fighting melanoma cells, consequently enabling the body's immune cells to fight the disease. The efficacy and safety of pembrolizumab in treating advanced melanoma have been demonstrated in several clinical trials, including the KEYNOTE-006 (KN-006) study by Robert et al. [7], in which 834 patients with advanced melanoma (stages III unresectable or IV) were randomized to receive pembrolizumab or ipilimumab. In Europe,

The authors have indicated that they have no conflicts of interest with regard to the content of this article.

* *Address correspondence to:* Luis Silva Miguel, Research Centre on the Portuguese Economy – CISEP -ISEG/ULisboa, Lisboa, Portugal.
E-mail: luis.silvamiguel@medicina.ulisboa.pt.

1098-3015$36.00 – see front matter

http://dx.doi.org/10.1016/j.jval.2017.05.009

pembrolizumab is labeled to treat adult patients with advanced melanoma, in the dosing regimen of 2 mg/kg every 3 weeks [8].

The advent of immunotherapy represents a major advance in the treatment of advanced melanoma. However, it is likely to significantly increase costs and may impact health care budgets. This added cost must be weighed against the potential long-term benefits to make an informed choice of the therapies targeting this disease.

Thus, the objective of this study was to estimate the cost-effectiveness of pembrolizumab versus ipilimumab in patients with advanced melanoma not previously treated with ipilimumab, from the Portuguese National Health Service perspective. Ipilimumab is considered the most adequate comparator for pembrolizumab because it is now established as the standard of care for treating advanced melanoma in Portugal.

Methods

Model Structure

A partitioned state-transition model, developed by Merck & Co., Inc., Kenilworth, NJ [9] and adapted to Portugal, was used to estimate the costs and quality-adjusted life-years (QALYs) associated with the use of pembrolizumab or ipilimumab in patients with advanced melanoma.

The model, programmed in Microsoft Excel (Microsoft Corp., Redmond, WA), allows for the prediction of disease evolution among three mutually exclusive health states: progression-free survival (PFS), post-progression (PP), and death (Fig. 1). As in the KN-006 trial, in our study, all simulated patients began in the PFS state, facing the risk of both progression and death. After progression, patients only face the risk of death, assuming that there is no possibility of moving back to the PFS state. The simulation was carried out in weekly cycles, with half-cycle correction, for a period of 40 years during which all patients were expected to die. The analysis adopted a partitioned-survival model approach, calculating the proportion of patients in each health state at each cycle. As each health state was associated to a specific cost and quality-of-life adjustment weight (or utility), it was possible to calculate the cumulative costs, life-years (LYs), and QALYs over the time horizon.

Model Inputs

Clinical and epidemiologic data

Clinical data were based predominantly on the KN-006 trial [7], a randomized, controlled, open-label, and three-arm pivotal study of two dosing regimens of intravenous pembrolizumab (10 mg/kg every 2 or 3 weeks) versus ipilimumab (3 mg/kg every 3 weeks, with a maximum of four cycles) in ipilimumab-naïve patients with unresectable or metastatic melanoma. Study participants included mainly patients who were in first line treatment (65.8% were treatment-naïve) but also patients in second line (34.2% had received one previous treatment, mainly BRAF or/and MEK inhibitors). Patients who had received previous therapy with cytotoxic T-lymphocyte-associated protein-4, PD-1, or PD-L1 inhibitors were excluded from the KN-006 trial. The primary endpoints were PFS (defined as the time from randomization to documented disease progression according to RECIST V1.1 criteria or death from any cause) and overall survival (OS; defined as the time from randomization to death from any cause). The cohort comprised individuals with a mean age of 61 years, and there were more males (59.6%) than females.

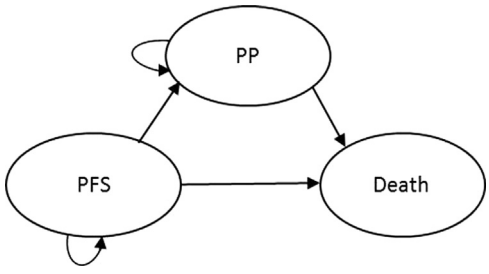

Figure 1 – Model structure. PFS, progression-free survival; PP, post-progression.

Modeled PFS was estimated by using Kaplan-Meier (KM) data until at least 10% of the patients were still at the risk of progression—week 60 for pembrolizumab and 48 for ipilimumab. Then, the best-fit parametric functions were chosen to extrapolate PFS data—Weibull distribution for pembrolizumab and lognormal for ipilimumab. The choice of different parametric functions for each arm was based on the Akaike information criterion and the Bayesian information criterion (Appendix, Table S.1). Once there was no clinical justification for this assumption, the imposition of a common parametric function was tested in the sensitivity analysis.

Modeled OS was also based on KM trial data until 10% of the patients were at risk—week 69 for pembrolizumab and 68 for ipilimumab. After these time points, the expected long-term OS data were elicited from the Schadendorf et al. [10] study and from the American Joint Committee on Cancer (AJCC) registry [11].

Since the study by Schadendorf et al. [10] followed patients treated with ipilimumab, its KM data could be used in the respective arm until 10% of the patients in the pooled study were at risk of death (week 313). In this study, with a follow-up of up to 10 years, it was found that the survival curve reaches a plateau around year 3, creating a long right tail for the OS curve. Given that parametric functions do not capture this effect—which is expected to be common to immunotherapies—and that there are no long-term data for pembrolizumab, the Schadendorf et al. data were also used to project OS with pembrolizumab. Nevertheless, to estimate the survival of pembrolizumab-treated patients, it was necessary to apply an OS hazard ratio (HR) over the hazard of ipilimumab.

As this HR should be derived from a common parametric model [12], we decided to fit a joint model to OS data. Several parametric functions (exponential, Weibull, Gompertz, lognormal, and log-logistic) were fitted to the KN-006 OS data, having decided, according to the Akaike information criterion and the Bayesian information criterion, to select the lognormal curve (see Appendix, Table S.1). The resulting HR, which varies from 0.36 (week 0) to 0.78 (week 70) and 0.85 (week 313), was used between weeks 70 and 313 to calculate the death hazard of pembrolizumab. A constant HR of 0.69, based on the KN-006 trial [7], was tested in the sensitivity analysis. Parameters for PFS and OS were estimated by using survival and flexsurv libraries from software R version 3.2.0 (R Development Core Team, Vienna, Austria).

Following long-term ipilimumab data, the OS was based on the melanoma registry data from the AJCC. Since survival depends on the stage at diagnosis, two published [13] Weibull curves were considered (for patients diagnosed at stages IIIC and IV, respectively), and weighted according to the stage distribution at the baseline in KN-006 (4% for stage IIIC and 96% for stage IV). As the AJCC registry records only melanoma-specific mortality, additional gender- and age-specific all-cause mortality rates for Portugal were applied within this period [14]. The modeling options for survival outcomes are presented in Table 1.

The impact of adverse events (AEs) grades 3 to 5 was also considered. In addition, grades 2 to 5 diarrhea events, and endocrine disorders of any grade were included. The incidence