Cost effectiveness of pembrolizumab for unresectable metastatic melanoma after progression with ipilimumab in England.

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OBJECTIVES

Pembrolizumab (MK-3475) is a humanised, anti-programmed cell death (PD-1) monoclonal IgG4 antibody. It is involved in the blockade of immune suppression and reactivation of anergic T-cells in cancer patients. It is believed that due to the high specificity and affinity for PD-1, against which it displays pure antagonist properties, pembrolizumab has the potential to improve the effectiveness of treatment for advanced melanoma patients.

The objective of this study was to assess the cost effectiveness of pembrolizumab to treat unresectable or metastatic melanoma in patients progressing after treatment with ipilimumab and a BRAF or MEK inhibitor (if tested positive for the BRAFV600 mutation), in England. The relevant comparator was best supportive care (BSC), including chemotherapies such as dacarbazine.

METHODS

A three state partitioned survival model was developed over a 30 year time horizon (Figure 1). Movement between health states was determined by progression-free survival (PFS) and overall survival (OS) data using interim results from KEYNOTE-002 (KN-002). KN-002 is a Phase II randomised controlled clinical trial comparing pembrolizumab to investigators choice of chemotherapy in patients progressing after treatment with ipilimumab and a BRAF or MEK inhibitor (if tested positive for the BRAFV600 mutation).

Figure 1: Model Diagram

A two part curve fit was applied to the PFS for the pembrolizumab arm: 1. Kaplan–Meier (KM) curves were used until Week 13 at which point all patients should have received their first scan; 2. A Gompertz parametric curve fit after this.

In the case of the chemotherapy arm the PFS curve showed that the number of patients that are progression-free and alive was approximately 0% at the end of the trial so just KM data were used. The OS data in KN002 and the atypical survival profiles for immunotherapies in clinical practice suggested that it was inappropriate to use a standard parametric curve fit based only upon within trial data to extrapolate long term survival. A three part curve was used for the pembrolizumab arm: 1. KM data from the KN-002 trial were used for the duration of available reliable data (one year); 2. A curve which consists of long-term ipilimumab survival data for previously treated patients² for the duration of observed survival (1-10 years); 3. Melanoma survival registry data plus general population mortality data³ (10+ years)

This model assumes that all patients that survive up to one year in the pembrolizumab trial have the same future survival prospects (conditional survival probability) as was seen in the ipilimumab trials until the limit of available data; they also have similar survival to historical advanced melanoma patients who lived to 10 years treated with chemotherapy.

Due to the high level of crossover in the trial (68/179 on the control arm), presentation of an intent-to-treat analysis for overall survival is inappropriate. In accordance with NICE Decision Support Unit guidance, the two-stage method was selected for adjustment in the model base case, as crossover occurred within the trial upon progression (hazard ratio (HR) = 0.63). Two alternative methods were tested: inverse probability of censoring weighting (IPCW) (HR=0.68), although this method is limited due to low sample size and high percentage crossover and rank-preserving structural failure time (RPSFT), which was deemed inappropriate as equal to post- and pre-progression could not be safely assumed.

Health-related quality of life data were collected in the KN-002 trial using the EQ-5D. It was collected at Weeks 0, 3, 6, 12, 24 and 36, and the end of treatment and at a 30-day safety follow-up visit. Quality of life was included in the model based on time to death, as in previous economic evaluations, the phase II and phase III data for BSC were not collected for pembrolizumab second-line NICE submission (TA268). The mean body surface area from the KN-002 trial was used to calculate the required dosing for BSC.

The monthly Index of Medical Specialities (MIMS®) and Drugs and pharmaceutical electronic market information (eMit®) were used to obtain drug costs for the intravenous (IV) chemotherapies which make up best supportive care which are all delivered via IV continuous infusion. A previous analysis has been reported in previous submissions for metastatic melanoma. In the base case pembrolizumab is administered as simple chemotherapy as administration takes less than 30 minutes; this was considered to be most appropriate by clinicians. Administration costs and resource use costs were sourced from National Health Service (NHS) reference costs and from the PSSRU 2014. The cost of terminal care was sourced from Georgiou and Bardes (2014). The results of economic analysis were summarised using a cost-effectiveness acceptability curve (CEAC) (Figure 3a) shows that there is an 87% chance of pembrolizumab being cost effective when compared to BSC at the £50,000 per QALY threshold. When the treatment duration was limited to 24 months, the uncertainty in the probabilistic model results was reduced. With the treatment duration limitation applied to the model the deterministic ICER was £31,764 and the probabilistic mean ICER was £33,841.

RESULTS

The estimated mean overall survival was 3.10 years for pembrolizumab and 1.51 years for BSC. At the end of the 30-year time horizon, 9.9% of patients were projected to be still alive in the pembrolizumab cohort and 0.1% in the BSC cohort. Patients treated with pembrolizumab accrued an expected 2.26 quality-adjusted life years (QALYs) compared to 1.07 among patients in the BSC cohort. The resulting cost per QALY was £42,923, showing pembrolizumab to be a cost-effective option compared to BSC for patients who are considered to be end of life.

Table 2: Utility Values

<table>
<thead>
<tr>
<th>Technologies</th>
<th>Total costs</th>
<th>QALYs</th>
<th>Incremental costs</th>
<th>Incremental QALYs</th>
<th>ICER (Cost/QALY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BSC</td>
<td>£51,959.06</td>
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<td>1.07</td>
<td>0.57</td>
<td>£67,615</td>
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<tr>
<td>Pembrolizumab</td>
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<td>1.07</td>
<td>0.52</td>
<td>£31,764</td>
</tr>
<tr>
<td>Pembrolizumab</td>
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The cost-effectiveness acceptability curve (CEAC) (Figure 3a) shows that there is an 87% chance of pembrolizumab being cost effective when compared to BSC at the £50,000 per QALY threshold. When the treatment duration was limited to 24 months, the uncertainty in the probabilistic model results was reduced. With the treatment duration limitation applied to the model the deterministic ICER was £31,764 and the probabilistic mean ICER was £33,841.

The CEAC when considering this treatment limitation (Figure 4) indicates an 87% chance of pembrolizumab being cost effective at the £50,000 per QALY threshold.

One-way sensitivity analysis showed the input that most affects the ICER is the curve fit parameters assumed for PFS.

CONCLUSION

As an end of life therapy for patients in England with advanced melanoma previously treated with ipilimumab, pembrolizumab is a cost-effective therapeutic option when compared to best supportive care (including conventional chemotherapy).

REFERENCES