A Cost-Effectiveness Analysis of Nivolumab Compared with Ipilimumab for the Treatment of BRAF Wild-Type Advanced Melanoma in Australia

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Abstract

Purpose: The aim of this study was to evaluate the cost-effectiveness of nivolumab versus ipilimumab for the treatment of previously untreated patients with BRAF-advanced melanoma (BRAF-AM) from an Australian health system perspective. Methods: A state-transition Markov model was constructed to simulate the progression of Australian patients with BRAF-AM. The model had a 10-year time horizon with outcomes discounted at 5% annually. For the nivolumab group, risks of progression and death were based on those observed in the nivolumab arm of a phase III trial (nivolumab vs. dacarbazine). Progression-free survival and overall survival were extrapolated using parametric survival modeling with a log-logistic distribution. In the absence of head-to-head evidence, overall survival and progression-free survival for ipilimumab were estimated on the basis of an indirect comparison using published data. Costs of managing AM were estimated from a survey of Australian clinicians. The cost of ipilimumab in Australia. The cost of nivolumab was based on expected reimbursement prices in Australia. Quality-of-life data were obtained within the trial using the EuroQol five-dimensional questionnaire. Results: Compared with ipilimumab, nivolumab therapy over 10 years was estimated to yield 1.58 life-years and 1.30 quality-adjusted life-years per person, at a (discounted) net cost of US $39,039 per person. The incremental cost-effectiveness ratios for nivolumab compared with ipilimumab were US $25,101 per year of life saved and $30,475 per quality-adjusted life-year saved. Conclusions: Nivolumab is a cost-effective means of preventing downstream mortality and morbidity in patients with AM compared with ipilimumab in the Australian setting. Keywords: cost-effectiveness analysis, immunotherapy, melanoma, oncology.

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Background

Melanoma accounts for approximately 2% of new cancer cases worldwide [1], and some estimates suggest that the global incidence is doubling every 10 to 20 years [2]. Relative to the population, the burden of melanoma in Australasia is one of the highest in the world, with a mean age-standardized rate that is double to triple that of other developed countries [3,4]. Until recently, patients diagnosed at later stages of the disease had poor survival prognoses, with median survival ranging from 8 to 10 months, and only 5% to 10% survived to 5 years [5].

Because immune-based therapies have the ability to harness the body’s immune system to reverse cancer-related immune suppression and T-cell deactivation [6], these offer promise for the prevention and treatment of melanoma. Despite this, early treatments acting on the immune system were not able to demonstrate marked prolongation of patient survival in metastatic melanoma [7]. In 2011, a new monoclonal antibody, ipilimumab, was approved by the Food and Drug Administration [8]. Ipilimumab, which exerts its effects by inhibiting Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and thereby abrogating T-cell deactivation, has offered significant improvement in clinical outcomes, with as many as 20% of patients surviving beyond 3 years [9]. It is now recommended by the National Comprehensive Cancer Network for the treatment of stage IV BRAF-negative melanoma [10].

Following on from the success of ipilimumab, several new monoclonal antibodies directed against the programmed death-1 protein have been undergoing clinical trials for the treatment of advanced melanoma (AM) [11,12]. One recent international phase III trial (trial CA209066) of 418 adults (>18 years) with BRAF-negative stage III and IV melanoma showed a reduced risk of death in those given the monoclonal antibody nivolumab compared with those given dacarbazine (hazard ratio [HR] = 0.42; 95% confidence interval [CI] 0.25–0.73) [13]. At 1 year, overall survival (OS) was 72.9% (95% CI 65.5–78.9) in the nivolumab group compared with those given dacarbazine. Following on from these results, patients diagnosed at later stages of the disease had improved outcomes, with median survival ranging from 12 to 18 months, and only 5% to 10% survived to 5 years [14].

Results: Compared with ipilimumab, nivolumab therapy over 10 years was estimated to yield 1.58 life-years and 1.30 quality-adjusted life-years per person, at a (discounted) net cost of US $39,039 per person. The incremental cost-effectiveness ratios for nivolumab compared with ipilimumab were US $25,101 per year of life saved and $30,475 per quality-adjusted life-year saved. Conclusions: Nivolumab is a cost-effective means of preventing downstream mortality and morbidity in patients with AM compared with ipilimumab in the Australian setting. Keywords: cost-effectiveness analysis, immunotherapy, melanoma, oncology.

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compared with 42.1% (95% CI 33.0–50.9) in the dacarbazine group and median progression-free survival (PFS) was 5.1 months (95% CI 3.5–10.8) compared with 2.2 months (95% CI 2.1–2.4). There were also fewer serious adverse events identified in the nivolumab group when compared with those taking chemotherapy. In 2015, the European Medicines Agency approved nivolumab for the treatment of patients with AM.

To date, the cost-effectiveness of nivolumab when compared with existing treatments for AM is unknown. In this study, we evaluated the cost-effectiveness of first-line therapy nivolumab versus ipilimumab for patients with BRAF-negative unresectable and/or metastatic melanoma (AM), from the perspective of the Australian public health care system.

Methods

Model Overview

A state-transition Markov model was constructed to simulate the progress of BRAF-negative Australian patients with AM (Fig. 1). The economic evaluation was undertaken from the perspective of the Australian health care system, so no other societal costs, such as lost productivity, patient time costs, or transport costs, were considered. The cost-effectiveness of nivolumab versus ipilimumab was expressed as incremental cost-effectiveness ratios (ICER) in terms of dollar per year of life saved and dollar per quality-adjusted life-year (QALY) gained.

In the base-case analysis, a 10-year time horizon was selected to capture the long-term survival achieved with immunotherapy agents [9]. The cycle length was chosen to align with the assessments of treatment response according to RECIST 1.1 criteria [14] in trial CA209066 (week 9, then every 6 weeks for 12 months, then every 12 weeks thereafter).

Model Structure

The model comprised three health states (Fig. 2). The cohort size was arbitrarily set at 1000.

Probabilities

For the nivolumab group, the risks of underlying progression and death were based on those observed in the nivolumab arm of trial CA209066 (nivolumab vs. dacarbazine) [13]. Because the trial follow-up period ended at 16 months, events occurring beyond this time period were extrapolated using parametric modeling with a log-logistic distribution. Because an initial sharp decline followed by a plateau in OS is a well-known characteristic of long-term survivors receiving cancer immunotherapy [15], the log-logistic distribution was found to best approximate the changing slope of the hazard (Appendix 1).

For the ipilimumab group, transition probabilities were derived from applying HRs to the equivalent transition probabilities in the nivolumab group. In the absence of head-to-head evidence, the HRs were extracted from an indirect comparison analysis of nivolumab versus ipilimumab using data from trial CA209066 and trial MDX010-020 (ipilimumab vs. gp100) [16] (Table 1). Although MDX010-020 was a study of ipilimumab in the second-line setting, efficacy data from this study were used as a surrogate for ipilimumab 3 mg/kg in the first-line metastatic melanoma setting because this was the only randomized controlled study with available results that examined the comparative effectiveness of
ipilimumab at the Australian Therapeutic Goods Administration’s approved dose of 3 mg/kg. Because both dacarbazine and gp100 have been shown to be largely ineffective treatments [17], they were considered comparable in our analyses.

To further assess the validity of the extrapolated HRs, we undertook a naive comparison with published survival data. Our extrapolated survival rate of patients receiving ipilimumab at 3 years was 15.1%. This compares with pooled clinical trial data showing that approximately 21% (95% CI 17%–24%) of the patients receiving ipilimumab (3 mg/kg) survive to 3 years [9]. Although our estimation was slightly below the lower confidence bounds for this study, the pooled analysis contains data from multiple studies with heterogeneous patient populations. Given the lengthy time period of this study, many patients may have also received other treatments subsequent to ipilimumab. It also demonstrates that our estimates of efficacy for both treatment arms were likely to be conservative.

**Utility Estimates**

Utility values for stable and progressive disease health states were obtained from individual patient data collected in trial CA209066 data using the three-level EuroQol five-dimensional questionnaire with reference to Australian-specific weights [13,18,19]. Overall utilities for each health state would already include decrements related to toxicities, so toxicity-related disutilities were not included in the model.

**Costs**

All costs are reported in year 2015 values and have been converted from Australian dollars to US dollars on the basis of the exchange rate on June 19, 2015 (A $1 = US $0.78). Drug costs for ipilimumab were taken from the Pharmaceutical Benefits Scheme (PBS) of Australia [20]. Drug costs for nivolumab were
based on the proposed reimbursement price under the PBS per course of treatment. Both ipilimumab and nivolumab are administered at 3 mg/kg per infusion. Subjects were assumed to weigh 80.14 kg in the base case, which was the mean body weight of Australian patients given ipilimumab in trial MDX010-020 [16]. Drug administration costs were based on the Medicare Benefits Schedule (item 14245) [21], and the cost of each intravenous administration was assumed to be $76.40.

Disease management costs were derived from a 2012 survey of eight clinicians treating patients with AM used for the Australian reimbursement submission of ipilimumab. Resource use in each health state was then assigned a cost value on the basis of published data to determine the overall ongoing routine cost of treating a patient with AM in each health state. All patients, regardless of treatment, were assumed to incur the same health resource utilization. In 2012, monthly costs for the preprogression and postprogression living health states were $2473 and $3004, respectively (see Appendix 2 for itemized costs). Item costs were updated where relevant, and the total updated costs for the preprogression and postprogression health states were increased to $2637 and $3240, respectively. These equated to annual costs of $31,644 and $38,880, respectively. Chronic disease management costs were reduced in the base case by 75% after the first 5 years because patients with AM who have survived more than 5 years are likely to be classified as “disease-free” with significantly reduced ongoing health care resource use [22].

Toxicity costs were applied as a one-off to every subject upon progression. Average costs of treatment-related adverse effects for each group were estimated by multiplying unit costs (Table 2) by the frequency of the adverse effects observed in study MDX010-20 (for ipilimumab) [16] and study CA209066 (for nivolumab) [13]. Adverse effects were stratified by severity: grades 1 to 2 versus grades 3 to 5. The unit costs of treatment-related adverse events were based on a survey of clinicians reporting health care utilization associated with each event [23], and costs for each item from the Medicare Benefits Scheme [21], the PBS [20], and National Hospital Cost Data Collection [24]. The Medicare Benefits Scheme and PBS item costs were current, whereas hospital costs were based on the 2008-2009 National Hospital Cost Data Collection (round 13), this being the most recent period for which data were available for both private and public hospitals. Costs were updated to 2016 values using the Australian Institute for Health and Welfare Health Price Index (Appendix 3) [25]. Because Australian patients can have a mix of public and private health insurance, the model assumed that 75% of the patients were treated in the public hospital system and 25% in the private hospital system.

### Table 2 – Toxicity rates and unit costs.

<table>
<thead>
<tr>
<th>Grade 1/2 events</th>
<th>Events rates (%)</th>
<th>Unit cost ($) *</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ipilimumab (^\dagger)</td>
<td>Nivolumab (^\ddagger)</td>
</tr>
<tr>
<td>Anemia</td>
<td>0.0</td>
<td>8.20</td>
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<tr>
<td>Colitis</td>
<td>2.3</td>
<td>0.5</td>
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<tr>
<td>Diarrhea</td>
<td>22.1</td>
<td>22.9</td>
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<tr>
<td>Erythema</td>
<td>5.3</td>
<td>10.2</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Hepatic failure</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Hypophysitis</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Hypopituitarism</td>
<td>0.8</td>
<td>1.5</td>
</tr>
<tr>
<td>Nausea</td>
<td>22.9</td>
<td>23.30</td>
</tr>
<tr>
<td>Pruritus</td>
<td>23.7</td>
<td>20.8</td>
</tr>
<tr>
<td>Rash</td>
<td>17.6</td>
<td>20.8</td>
</tr>
<tr>
<td>Rash erythematous</td>
<td>0.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Rash pruritic</td>
<td>3.1</td>
<td>0.0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>12.2</td>
<td>10.70</td>
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<table>
<thead>
<tr>
<th>Grade 3-5 events</th>
<th>Events rates (%)</th>
<th>Unit cost</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ipilimumab</td>
<td>Nivolumab</td>
</tr>
<tr>
<td>Anemia</td>
<td>0.0</td>
<td>1.00</td>
</tr>
<tr>
<td>Colitis</td>
<td>5.3</td>
<td>0.5</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4.6</td>
<td>1.9</td>
</tr>
<tr>
<td>Erythema</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>0.8</td>
<td>0.0</td>
</tr>
<tr>
<td>Hepatic failure</td>
<td>0.8</td>
<td>0.0</td>
</tr>
<tr>
<td>Hypophysitis</td>
<td>1.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Hypopituitarism</td>
<td>1.5</td>
<td>0.0</td>
</tr>
<tr>
<td>Nausea</td>
<td>0.0</td>
<td>0.00</td>
</tr>
<tr>
<td>Pruritus</td>
<td>0.0</td>
<td>0.5</td>
</tr>
<tr>
<td>Rash</td>
<td>0.0</td>
<td>0.5</td>
</tr>
<tr>
<td>Rash erythematous</td>
<td>0.8</td>
<td>0.0</td>
</tr>
<tr>
<td>Rash pruritic</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0.0</td>
<td>0.50</td>
</tr>
</tbody>
</table>

\* Components of the unit costs are reported in Appendix 3.
\dagger Ipilimumab’s adverse events rates are based on Clinical Study Report for Trial MDX010-020.
\ddagger Nivolumab’s adverse event rates are based on the Clinical Study Report for Trial CA209066.
No other acute (one-off) costs were assumed in the base case of the model because additional costs were likely to have been partly included in the estimation of chronic disease management costs, especially for progressive disease.

The mean duration of treatment assumed for patients receiving nivolumab was 14.2 doses, which was based on the mean number of doses in trial CA209066 [13]. The mean duration of treatment assumed for patients receiving ipilimumab was 3.4 doses with an 8.8% reinduction rate, as reported in trial MDX010-020 [16]. Annual discount rates of 5% were applied to future costs and outcomes [26].

Sensitivity Analyses

A series of one-way sensitivity analyses were performed to assess the impact of uncertainty surrounding key input parameters in the modeled economic evaluation (Table 1). A probabilistic sensitivity analysis was undertaken assigning probability distributions to key model parameters and undertaking Monte-Carlo simulation [27] with 10,000 iterations.

Microsoft Excel (Microsoft Corporation, Redmond, WA) and @Risk version 7 (Palisade Corporation, New York, NY) were used to create and implement the model. Stata version 13 (College Station, TX) was used to extrapolate the transition probabilities on the basis of individual patient data. TreeAge Pro 2011 (TreeAge software Inc, Williamstown, MA) was used to create the flow diagram.

Results

In the base-case analysis, over 10 years, the average patient with AM receiving nivolumab was predicted to live an average of 3.1 years and 2.5 QALYs at a (discounted) net cost of $178,612 per person. The average patient receiving ipilimumab was predicted to live an average of 1.5 years and 1.2 QALYs at a (discounted) net cost of $138,987 per person. These equated to ICERS of $25,101 per year of life saved and $30,475 per QALY saved.

Sensitivity Analyses

The results of one-way sensitivity analyses showed that the model was sensitive to shortening the time horizon, increasing annual background costs, and decreasing utility values (Fig. 3). Monte-Carlo simulation showed that nivolumab was cost-effective in 59% of 10,000 iterations at a willingness-to-pay threshold of US $35,000 (equivalent to A $45,000 [28]) per QALY gained (Fig. 4). The 5th and 95th percentiles for ICERs were ~$74,490 and $176,650 per QALY gained, respectively.

Discussion

This study examined the cost-effectiveness of nivolumab treatment for patients with AM using a Markov model. We estimated that for patients with BRAF-negative AM at initiation of therapy, the ICER of nivolumab therapy versus ipilimumab was $30,475 per QALY gained. A willingness-to-pay threshold of $35,000 per year of life saved and QALY has been shown to correspond to a probability of being cost-effective in Australia, as recommended by the PBS [29], but end-of-life cancer treatments may have higher willingness-to-pay thresholds [30,31]. Therefore, this ICER is likely to be considered cost-effective in the Australian context.

In our probabilistic sensitivity analysis, nivolumab was found to be cost-effective in 59% of the simulations at a willingness-to-pay threshold of US $35,000, suggesting a high amount of uncertainty. In our one-way sensitivity analysis, shortening the time horizon from 10 to 5 years increased the ICER from $30,475 to $42,664 per QALY gained. This is likely to be related to differences in survival and PFS between nivolumab and ipilimumab becoming more pronounced after 2 to 3 years, reflecting the durable effects of immunotherapy treatment. Similarly, because a substantial proportion of patients receiving nivolumab are expected to survive longer than 5 years, the cost of ongoing disease-related management was also an influential factor in the model. Furthermore, decreasing utility values by 20% resulted in large increases in the cost per QALY ($30,475–$53,330). This is likely to be related to the greater number of people receiving nivolumab who are surviving with nonprogressive disease, which has been associated with improvements in quality of life in other studies [32,33]. Although the utilities reported in this study are higher than those seen in other studies of advanced cancer [34], they are similar to studies of patients with AM [33,35]. Furthermore, Australian members of the general public have assigned higher mean utility scores for partial response and stable disease states in AM when compared with members of the UK general public, suggesting that there may be regional differences [35]. Recent evaluations of therapies in AM have found that although newer treatments have a greater incremental cost when compared with traditional chemotherapies, they confer a substantial benefit in survival [36,37]. Pembrolizumab, a programmed
death-1 inhibitor, was given accelerated approval by the Food and Drug Administration in 2014 for patients with AM who failed on ipilimumab and a BRAF inhibitor, if a BRAF mutation was present [38]. The cost of pembrolizumab in the United States has been set at $12,500 per patient per month, or $150,000 per year [39], and is yet to be finalized in Australia. Given the high burden of melanoma, the Australian public may place a higher value on effective treatments for AM. However, the increasing cost of oncology treatments puts a burden on health budgets because drugs associated with cancer treatment have been estimated to cost approximately $40 billion per year worldwide [40]. Accordingly, the economic evaluation of new treatments is becoming increasingly important.

Because trial CA209066 did not include patients with BRAF-mutated melanoma [13], we did not include this subpopulation in our cost-effectiveness analysis. Results of a Phase III trial of combined nivolumab and ipilimumab in all patients with AM, regardless of BRAF status have recently become available. Because BRAF mutations are carried by nearly half of the patients with melanomas, it is important to evaluate the relative efficacy and cost-effectiveness of nivolumab in this patient group.

This evaluation was undertaken using patient-level data from the primary trial by an academic research team who had full control over the design and conduct of the evaluation. However, there are several limitations to our study that should be noted. Efficacy data from trial CA209066 were used to estimate the risk of progression and death [13]. This trial was stopped after 16 months because of the early demonstration of superior efficacy, and therefore the long-term hazard of death and progression was based on extrapolation, which may have affected the validity of the model. However, we explored various methods to extrapolate long-term findings and the log-logistic distribution most closely approximated the long-term survival of patients receiving immunotherapy on the basis of face validity and goodness-of-fit statistics. Annemans and Asukai [41] have recommended the use of novel methods, including partitioned survival analyses, in treatments with a durable benefit. Nonetheless, we found that the log-logistic distribution approximated real-world data accurately without introducing the potential bias that has been shown to be associated with these methods [42,43]. In the absence of head-to-head data, we used an indirect comparison of nivolumab with ipilimumab. Trial MDX010-20 was undertaken in the second-line setting. Because it was the only suitable study using the correct dose of ipilimumab (3 mg/kg), we used this as a surrogate for the first-line setting. To validate the use of MDX010-020, an indirect comparison was conducted with trial CA184-024 (ipilimumab 10 mg/kg + dacarbazine vs. dacarbazine alone) [44]. No significant difference in the incremental efficacy of ipilimumab was found between first-line and second-line settings. Furthermore, the assumption of proportional hazards may not be upheld. Although these factors may have introduced uncertainty into the model, our extrapolated survival rate of patients receiving ipilimumab at 3 years was similar to published findings. Since this evaluation was undertaken, the results of two new clinical trials have been published [45,46]. As yet, neither of these studies has mature OS data, so an estimation of the OS benefit for these trials would still be required. Furthermore, our estimated HR (based on our indirect comparison) of 0.66 for PFS is within the 99.5% confidence bounds of the HR reported in the recent Checkmate 067 study (HR = 0.57; 99.5% CI 0.43–0.76) when nivolumab and ipilimumab monotherapy are compared. The lack of available evidence regarding the relative efficacy of nivolumab and ipilimumab added uncertainty to our model. Although we explored uncertainty through one-way and probabilistic sensitivity analyses, we did not examine the HRs of OS and PFS as correlated parameters (e.g., as the HR of PFS approaches unity, so does the HR of OS). This may have resulted in an underestimation of the uncertainty associated with our model. Last, ongoing disease-related management costs were based on a survey conducted in a previous study of patients with AM receiving ipilimumab. Although costs were updated to 2015 values, they may not have been reflective of current practice and require further validation.

**Conclusions**

To our knowledge, this is the first study to investigate the cost-effectiveness of nivolumab therapy for the treatment of AM using a Markov model. The results demonstrate that nivolumab is a cost-effective means of preventing downstream mortality and morbidity in AM compared with ipilimumab in the Australian setting. Because there was a high degree of uncertainty in our findings, future head-to-head clinical trials will provide valuable insight into the optimal treatment of AM.

**Supplemental Material**

Supplemental material accompanying this article can be found in the online version as a hyperlink at http://dx.doi.org/10.1016/j.jval.2016.05.013 or, if a hard copy of article, at www.valueinhealthjournal.com/issues (select volume, issue, and article).

**REFERENCES**