PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Initial Economic Guidance Report

Ipilimumab (Yervoy) for First Line Advanced Melanoma

December 22, 2014

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1 ECONOMIC GUIDANCE IN BRIEF

1.1 Background

The main economic analysis **submitted to pCODR by Bristol-Myers-Squibb** compared ipilimumab to dacarbazine for BRAF V600-negative patients and ipilimumab to vemurafenib for BRAF V600-positive patients for the treatment of previously untreated unresectable or metastatic melanoma. Ipilimumab is administered intravenously; dacarbazine is administered intravenously; vemurafenib is administered orally.

According to the pCODR Clinical Guidance Panel (CGP), this comparison is appropriate and reflects clinical practice. The submitter also provided the results of an economic analysis comparing ipilimumab versus dabrafenib; however, the EGP was unable to provide conclusions on the results of this analysis as the submitter provided limited information regarding this analysis.

Patients considered the following factors important in the review of ipilimumab, which are relevant to the economic analysis: increased response, decreased side effects and increased overall survival. These three factors have been accounted for in an adequate manner in the economic model.

The **Provincial Advisory Group (PAG)** considered that the following factors would be important to consider if implementing a funding recommendation for ipilimumab, and which are relevant to the economic analysis.

Enablers to the implementation of ipilimumab include:

- Treating with ipilimumab first, eliminating the need for dacarbazine, based on feedback from clinicians requesting the use of ipilimumab in the first line.

Barriers to the implementation of ipilimumab include:

- Lack of randomized controlled trial data at the 3 mg/kg dose;
- High cost drug;
- Drug wastage;
- Chair time of up to 3 hours;
- Monitoring of immune-mediated reactions;
- Number of patients requiring re-induction;
- Potential for dose-creep to 10 mg / kg, dependant on the results of an ongoing clinical trial;
- Need to travel to an outpatient chemotherapy centre.

This economic analysis addressed treatment with ipilimumab first, eliminating the need to first use dacarbazine. The high cost of the drug, drug wastage, chair time, monitoring of immune-mediated reactions, and the number of patients requiring re-induction were addressed in the economic evaluation. The potential for dose-creep to 10 mg/kg was not addressed in the economic evaluation; however, a more than three-fold increase in dose would increase the incremental cost of ipilimumab which would increase the ICER. The need to travel to an outpatient chemotherapy centre was not addressed in the economic evaluation as it took a health-care system perspective and not a societal perspective. It should be noted that there is no randomized clinical trial data at the 3 mg/kg dose and

therefore the economic model relies on clinical efficacy data from the 10 mg/kg dose (based on the assumption by the submitter that the two doses are equivalent clinically).

Ipilimumab costs $5,800 per 50 mg vial (unit cost of $116 / mg). At the recommended dose of 3 mg/kg, the cost of ipilimumab is $29,000 per three-week cycle based on an average body surface area of 1.87 m^2. Dacarbazine costs $189.76 per 600 mg vial (unit cost of $0.32 per mg). At the recommended dose of 850 mg per m^2, the cost of dacarbazine is $503 per three-week cycle based on an average body surface area of 1.87 m^2. Vemurafenib costs $47 per 240 mg tablet (unit cost of $0.19 / mg). At the recommended dose of 960 mg daily, the cost of vemurafenib is $7819 per three-week cycle.

1.2 Summary of Results

1.2.1 Ipilimumab vs Dacarbazine for BRAF V600 Mutation-Negative Disease

The EGP's best estimate of the incremental cost-effectiveness ratio (ΔC / ΔE) is between $165,389 and $197,382 per QALY when ipilimumab is compared with dacarbazine. This range of ICERs provided by the EGP reflects a large amount of uncertainty due to the clinical data used to inform the model.

The incremental cost-effectiveness ratio was based on an estimate of the extra cost (ΔC) and the extra clinical effect (ΔE). The EGP's best estimate of:

- the extra cost of ipilimumab is between $108,880 and $110,343. The greatest factors that influence the costs are the drug costs and the time horizon.
- the extra clinical effect of ipilimumab is between 0.525 and 0.667 quality-adjusted life years (ΔE). The greatest factors that influence the effects are the modeling of utilities by progression (and not by survival). The EGP noted that there is a large amount of uncertainty in this extra clinical effect given the lack of evidence at the 3 mg/kg dose in this group of patients.

The EGP based these estimates on the model submitted by Bristol-Myers Squibb and reanalyses conducted by the EGP. The reanalysis conducted by the EGP using the submitted model showed that when:

- the time horizon chosen was set to 20 years, as per feedback from the CGP based on survival of this population, the extra cost of ipilimumab is $110,593 ($\Delta C_1$) and the extra effect is 0.724 (ΔE_1), which increases the estimated incremental cost-effectiveness ratio to $152,690 (from $151,014).
- wastage for both ipilimumab and dacarbazine are included in the economic model, the extra cost of ipilimumab is $111,187 ($\Delta C_2$), which decreases the estimated incremental cost-effectiveness ratio to $150,699 (from $151,014).
- the overall survival parametric function is the best fitting function (log-normal), the extra clinical effect of ipilimumab is 0.684 (ΔE_2), which increases the estimated incremental cost-effectiveness ratio to $163,162 (from $151,014).
- The best case estimate of the above three parameters is $165,389, with an extra cost for ipilimumab of $110,343 (ΔC) and an extra clinical effect of ipilimumab of 0.667 (ΔE).

- overall survival is a naïve comparison with no risk adjustment, the extra clinical effect of ipilimumab is 0.640 (ΔE_3), which increases the estimated incremental cost-effectiveness ratio to $171,586 (from $151,014).
- The best case estimate of the above four parameters (time horizon, wastage, best fitting parametric function for overall survival, and no risk adjustment) is $188,157, with an extra cost for ipilimumab of $108,880 (ΔC) and an extra clinical effect of ipilimumab of 0.579 (ΔE).
- utilities are modeled by progression (and not by survival, as modeling by survival counts the benefits of survival twice), the extra clinical effect of ipilimumab is 0.626 (ΔE_1), which increases the estimated incremental cost-effectiveness ratio to $178,099 (from $151,014).
- The best case estimate of the above five parameters is $207,197, with an extra cost for ipilimumab of $108,880 (ΔC) and an extra clinical effect of ipilimumab of 0.525 (ΔE).
- Treatment duration for dacarbazine is modeled assuming that a patient will be treated until progression and not by the median duration observed in a trial setting, the extra cost of ipilimumab is $107,427 ($\Delta C_3$) and the extra effect is 0.743 (ΔE_4), which decreases the estimated incremental cost-effectiveness ratio to $144,530 (from $151,014).
- The best case estimate of the above six parameters is $197,382, with an extra cost for ipilimumab of $104,586 (ΔC) and an extra clinical effect of ipilimumab of 0.530 (ΔE).

The EGPs estimates differed from the submitted estimates.

According to the economic analysis that was submitted by Bristol-Myers Squibb, when ipilimumab is compared with dacarbazine:

- the extra cost of ipilimumab is $111,419 (ΔC). Costs considered in the analysis included drug costs, follow-up costs, terminal care and adverse events costs.
- the extra clinical effect of ipilimumab is 0.738 quality-adjusted life years (ΔE) and 1.071 life years (ΔE). The clinical effect considered in the analysis was based on overall survival, progression-free survival, adverse events, treatment duration and utilities.

So, the submitter estimated that the incremental cost-effectiveness ratio (ΔC / ΔE) was $151,014 per QALY or $104,058 per life year gained.

1.2.2 Ipilimumab vs Vemurafenib for BRAF V600 Mutation-Positive Disease

The EGP's best estimate of the incremental cost-effectiveness ratio (ΔC / ΔE) is between $9,231 and $216,773 per QALY when ipilimumab is compared with vemurafenib. This range of ICERs provided by the EGP reflects a large amount of uncertainty due to the clinical data used to inform the model.

The incremental cost-effectiveness ratio was based on an estimate of the extra cost (ΔC) and the extra clinical effect (ΔE). The EGP's best estimate of:

- the extra cost of ipilimumab is between -$2,051 and $35,828. The greatest cost drivers include the proportion of patients receiving 2nd line treatment, drug costs, treatment duration and the inclusion of 2nd line therapy.
- the extra clinical effect of ipilimumab is between 0.165 and 0.222 quality-adjusted life years (ΔE). The factors that most impact the clinical effects are the modeling of utilities by progression (and not by survival). The EGP noted that there is a large amount of uncertainty in this extra clinical effect given the lack of evidence at the 3 mg/kg dose in this group of patients.

The EGP based these estimates on the model submitted by Bristol-Myers Squibb and reanalyses conducted by the EGP. The reanalysis conducted by the EGP using the submitted model showed that when:

- the time horizon chosen was set to 20 years, as per feedback from the CGP based on survival of this population, the extra cost of ipilimumab is $2,933 ($\Delta C_1$) and the extra effect is 0.309 (ΔE_1), which decreases the estimated incremental cost-effectiveness ratio to $9,488 (from $10,776).
- the overall survival parametric function is the best fitting function (log-normal), the extra clinical effect of ipilimumab is 0.284 (ΔE_2), which increases the estimated incremental cost-effectiveness ratio to $12,556 (from $10,776).
- overall survival is a naïve comparison with no risk adjustment, the extra clinical effect of ipilimumab is 0.260 (ΔE_3), which decreases the estimated incremental cost-effectiveness ratio to $9,523 (from $10,776).
- The best case estimate of the above three parameters is $9,231, with an extra cost for ipilimumab of $2,051 (ΔC) and an extra clinical effect of ipilimumab of 0.222 (ΔE).
- utilities are modeled by progression (and not by survival, as modeling by survival counts the benefits of survival twice), the extra clinical effect of ipilimumab is 0.212 (ΔE_4), which increases the estimated incremental cost-effectiveness ratio to $16,126 (from $10,776).
- The best case estimate of the above four parameters is $13,440, with an extra cost for ipilimumab of $2,051 (ΔC) and an extra clinical effect of ipilimumab of 0.153 (ΔE).
- second line therapies are included for both ipilimumab and vemurafenib, based on input from the CGP, the extra cost of ipilimumab is $19,182 ($\Delta C_2$), which increases the estimated incremental cost-effectiveness ratio to $61,677 (from $10,776). It should be noted that estimates of effects were not included for second-line therapies.
- the proportion of patients moving on to second-line therapy increases to 90% for ipilimumab -> vemurafenib and 70% for vemurafenib ->ipilimumab, based on input from the CGP, the extra cost of ipilimumab is $37,379 ($\Delta C_3$), which increases the estimated incremental cost-effectiveness ratio to $122,185 (from $10,776). It should be noted that estimates of effects were not included for second-line therapies.
- The best case estimate of the above six parameters is $216,773, with an extra cost for ipilimumab of $33,828 (ΔC) and an extra clinical effect of ipilimumab of 0.165 (ΔE).

The EGPs estimates differed from the submitted estimates.

According to the economic analysis that was submitted by Bristol-Myers Squibb, when ipilimumab is compared with vemurafenib:

- the extra cost of ipilimumab is $3,417 (ΔC). Costs considered in the analysis included drug costs, follow-up costs, terminal care and adverse events costs.
- the extra clinical effect of ipilimumab is 0.317 quality-adjusted life years (ΔE) and 0.477 life years (ΔE). The clinical effect considered in the analysis was based on overall survival, progression-free survival, adverse events, treatment duration and utilities.

So, the Submitter estimated that the incremental cost-effectiveness ratio (ΔC / ΔE) was $10,776 / QALY or $7,158 per life year gained.

1.3 Summary of Economic Guidance Panel Evaluation

If the EGP estimates of ΔC, ΔE and the ICER differ from the submitter's, what are the key reasons?

In the ipilimumab versus dacarbazine model, the main differences came from the modeling of overall survival and utilities. Overall survival was examined with the best fitting curve and with no risk adjustment. Utilities were examined by progression, and not by time-to-death.

In the ipilimumab versus vemurafenib model, the main differences came from the modeling of utilities as well as the inclusion of second-line therapies for both treatments and the proportion of patients moving on to 2nd line treatments. Modeling of utilities were examined by progression, and not by time-to-death as in the main analysis. When utilities are modeled by time-to-death, any gains in survival are accounted for twice in the model: once, in the effects and again through the utilities. The inclusion of 2nd line therapies, despite having no effectiveness data, was examined as PAG has raised sequencing as a potential barrier to implementation and the costs around this were significant.

Were factors that are important to patients adequately addressed in the submitted economic analysis?

Yes. Patients stated that though ipilimumab provided improvement, there were side effects. The economic model incorporated survival improvement, quality of life and adverse events.

Is the design and structure of the submitted economic model adequate for summarizing the evidence and answering the relevant question?

Yes, the design of the economic model was adequate and the model allowed for manipulation of several important parameters. However, in a partitioned survival analysis, it is not possible to explore confidence intervals around the survival estimates. Given that ipilimumab is a type of immunotherapy, it can potentially improve survival in both pre-progression and post-progression states. Therefore, the use of a partition survival analysis may be reasonable.

For key variables in the economic model, what assumptions were made by the Submitter in their analysis that have an important effect on the results?

The source of data for overall survival and progression-free survival for ipilimumab came from a pooled dataset from chemotherapy-naïve patients. Upon examination from the Methods team, this dataset was found to have a high degree of uncertainty and conclusions drawn from it may be unreliable, due to the lack of information regarding the analysis methods used, the different designs of the included studies and the different objectives of the included studies (please see Section 7 of the Clinical Guidance Report for additional details and a critical appraisal of the pooled dataset). The EGP was not able to account for this limitation, as no other dataset is available. The use of these data, in contrast with a naïve comparison from the CA184-204 trial (ipilimumab 10 mg / kg + dacarbazine), had a large impact on the results.

There was no head-to-head trial to inform comparative efficacy across the treatments considered. No indirect comparison was done either. Data to inform dacarbazine and vemurafenib in the economic model (for OS and PFS) were taken from their respective treatment arms in different clinical trials (CA184-204 for dacarbazine and BRIM3 for vemurafenib), and then compared to the pooled dataset for ipilimumab. In order to account for baseline population differences, the submitter adjusted overall survival by baseline mortality risk in the main analysis. Though the rationale behind this adjustment may be justified as population differences may exist between trials, it is difficult to ascertain the necessity of this adjustment. In addition this risk adjustment, if appropriate, would only account for known differences in the population and not differences in trial design and setting. It should be noted that the EGP was not able to account for the lack of comparative efficacy and this represents a significant limitation.

In addition to this, for ipilimumab versus dacarbazine, the largest cost drivers were drug costs, the time horizon (an assumption made by the submitter) and the way utilities were modeled. The EGP was uncertain with the modeling of utilities by time, and examined modeling utilities by disease progression in a modification analysis. Various time horizons were also explored in modifications to the main analysis as the CGP expressed that 35 years is not the most appropriate time horizon for this population.

For ipilimumab versus vemurafenib, the largest cost drivers were the number of patients receiving 2nd line treatment, drug costs, treatment duration (treat to progression versus median duration of clinical trial), and the inclusion of second-line of therapy. These estimates, and any potential limitations, were examined in modifications to the main analysis.

Were the estimates of clinical effect and costs that were used in the submitted economic model similar to the ones that the EGP would have chosen and were they adequate for answering the relevant question?

The majority of the clinical inputs were not adequate. The clinical data for ipilimumab was informed by a pooled dataset, where several limitations were identified with the analysis by the Methods team (please see Section 7 of the accompanying *Ipilimumab in Advanced Melanoma* Clinical Guidance Report). Because of these limitations, there is increased uncertainty in the economic results. As there is no other source of data for ipilimumab 3 mg/kg, it was not possible to explore the uncertainty around these data. Neither the dacarbazine nor vemurafenib clinical inputs were informed by head-to-head trials, nor were they informed by indirect comparisons (through a network meta-analysis). Instead, clinical data were taken from individual treatment arms of separate clinical trials. The cost inputs used in the economic model were adequate.

1.4 Summary of Budget Impact Analysis Assessment

What factors most strongly influence the budget impact analysis estimates?

The largest cost drivers of the budget impact analysis are the number of ipilimumab doses and the cost of ipilimumab. The Provincial Advisory Group has noted that a barrier to the implementation of ipilimumab would be the high cost of treatment.

What are the key limitations in the submitted budget impact analysis?

The main limitations of the budget impact analysis are the assumptions around the number of patients who need to be treated and the uptake of ipilimumab in the first-line setting. As the CGP has noted that there is a need for this drug, the uptake of ipilimumab could be higher which would significantly increase the budget impact.

1.5 Future Research

What are ways in which the submitted economic evaluation could be improved?

The current economic model could be improved with using data inputs with less uncertainty or by conducting methodologically sound indirect comparisons. Further, utilities by progression may account for survival benefit twice—once from actual survival and a second time by utilities being assigned based on survival. Determining utilities by survival may not accurately reflect increases or decreases in a patient's quality of life from treatment.

Is there economic research that could be conducted in the future that would provide valuable information related to ipilimumab for advanced melanoma?

A randomized clinical trial examining ipilimumab 3 mg/kg in the first line setting with standards of care, and that also collects utilities alongside the trial, would provide valuable information and reduce uncertainty in the results of an economic analysis.

2 DETAILED TECHNICAL REPORT

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in Section 1. Pursuant to the *pCODR Disclosure of Information Guidelines*, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations.

3 ABOUT THIS DOCUMENT

This Final Economic Guidance Report was prepared by the pCODR Economic Guidance Panel and supported by the pCODR Melanoma Clinical Guidance Panel and the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding resource implications and the cost-effectiveness of [drug name and indication]. A full assessment of the clinical evidence of [drug name and indication] is beyond the scope of this report and is addressed by the relevant pCODR Clinical Guidance Report. Details of the pCODR review process can be found on the pCODR website (www.pcodr.ca).

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Economic Guidance Report was handled in accordance with the *pCODR Disclosure of Information Guidelines*. There was no non-disclosable information in the Economic Guidance Report provided to pERC for their deliberations.

This Final Economic Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Economic Guidance Report supersedes the Initial Economic Guidance Report. Note that no revisions were made in between posting of the Initial and Final Guidance Reports.

The Economic Guidance Panel is comprised of economists selected from a pool of panel members established by the pCODR Secretariat. The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package and the Economic Guidance Panel Terms of Reference, which are available on the pCODR website (www.pcodr.ca). Final selection of the pool of Economic Guidance Panel members was made by the pERC Chair in consultation with the pCODR Executive Director. The Economic Guidance Panel is editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

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