pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Ipilimumab (Yervoy) for Advanced Melanoma

April 18, 2012

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1 ECONOMIC GUIDANCE IN BRIEF

1.1 Background

The main economic analysis **submitted to pCODR by** Bristol-Myers Squibb is a cost-utility and cost-effectiveness analyses that compared ipilimumab (Yervoy) to [redacted] for previously treated patients with unresectable (stage IIIC) or metastatic (stage IV) melanoma. *(Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by manufacturer that it can be publicly disclosed).* [redacted] is a systemic chemotherapy agent and ipilimumab is a systemic immunotherapy. *(Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by manufacturer that it can be publicly disclosed).* Both are administered intravenously.

According to the pCODR Melanoma Clinical Guidance Panel, dacarbazine is considered the standard of care of patients with advanced melanoma. As such, the Submitter's main analysis used the appropriate comparator. The Submitter modified the main analysis to include routinely used therapies including chemotherapy monotherapy ([redacted]), chemotherapy combination therapy ([redacted]), immunotherapy ([redacted]), plus best supportive care. *(Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by manufacturer that it can be publicly disclosed).*

The following factors were considered by **patient advocacy groups** to be important in the review of ipilimumab and were relevant to the economic analysis: survival, side-effects, quality of life and the ability to continue to work and engage in usual activities. A full summary of patient advocacy group input is provided in the pCODR Clinical Guidance Report. Factors important to patients were addressed in the economic analysis as follows:

- The cost-effectiveness analysis was conducted from a Ministry of Health or government payer perspective, therefore the analysis did not include non-medical direct and indirect costs that are typically faced by the patient but only those costs relevant to the government payer perspective. However, this perspective is appropriate for pCODR because drug funding recommendations must be considered from a health system perspective.

- The analysis took into account overall survival and side effects of treatments.

- The Submitter incorporated quality of life in the submitted model by applying utility scores to measure the model outcomes in quality-adjusted life years (QALYs).

The **Provincial Advisory Group (PAG)** considered that the dosing issues would be the most important factor to consider if implementing a funding recommendation for ipilimumab. PAG also considered that additional costs of monitoring for potential serious side effects

may be important for the overall cost-effectiveness of ipilimumab. A full summary of PAG input is provided in the pCODR Clinical Guidance Report.

- PAG noted that there is a difference in dosage depending on whether ipilimumab is used in the first-line setting (10mg/kg) or the second-line setting (3 mg/kg).(Hodi 2010, Robert 2011). While, treatment outcomes and side effect profiles are unknown for the use of the 10 mg/kg dosage in the second-line setting, PAG noted that dose escalation in the second-line setting may be observed and could lead to additional costs.

- Additional dosing issues included the potential for patients to receive more than four doses of ipilimumab and the possibility of drug wastage.

- The submitter did not make any modifications to their main analysis to address potential changes in dosing, however, re-analyses were conducted by the pCODR Economic Guidance Panel to address these issues.

- The submitted analysis concluded that the medical management issues with respect to patient follow-up and monitoring had little impact on the incremental cost-effectiveness ratio. The submitter did not however make any modifications to the main analysis demonstrating an impact on management of side effects.

At the list price and at a strength of 50 mg per 10 mL, ipilimumab costs $5800.00. At the recommended dose in the second-line setting of 3 mg/kg intravenously every three weeks for four doses, the cost per 28-day course of ipilimumab is $32,480.00. One dose of ipilimumab costs $24,360 and four doses costs $97,400 assuming a body mass of 70 kg and no wastage.

The list price of dacarbazine, one of the standard therapies used to treat advanced melanoma, is $200.20 per 600 mg/mL vial. At the recommended dose of 200 to 250 mg/m^2, administered intravenously on days one to five every 21 to 28 days, and assuming a body mass of 70 kg and a body surface area of 1.7 m^2, the average cost of dacarbazine per day is between $20.26 and $33.76 in a 28-day course. The average cost per 28-day course of dacarbazine is between $567.230 and $945.39.

1.2 Summary of Results

The Economic Guidance Panel's best estimate of the incremental cost-effectiveness ratio (ΔC/ΔE) is approximately $269,299 per QALY when ipilimumab 3 mg/kg is compared with [redacted]. *(Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by manufacturer that it can be publicly disclosed).* **The Economic Guidance Panel based these estimates on the model submitted by Bristol-Myers Squibb and reanalyses conducted by the Panel.**

This incremental cost-effectiveness ratio (ICER) was based on an estimate of the extra cost (ΔC) and the extra clinical effect (ΔE). The Economic Guidance Panel's best estimate of the incremental cost-effectiveness ratio is based on key assumptions for resource use, clinical inputs and utility as submitted in the economic evaluation by BMS. Overall survival

and progression-free survival estimates were informed by the Hodi 2010 trial. Resource use for medical follow-up was estimated using two retrospective database analyses, and Canadian key opinion leader inputs. Costs assigned to resource use were obtained from Ontario costing sources. Utility values were based on a Canadian cross-sectional study eliciting utilities, using the standard gamble technique among 87 general public participants. The Economic Guidance Panel's best estimate assumed the price of ipilimumab as submitted to pCODR.

In addition, the Economic Guidance Panel made two changes to the submitted economic evaluation.

- The submitted analysis assumes [redacted] for comparators. *(Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by manufacturer that it can be publicly disclosed).* The Economic Guidance Panel re-analyses assumed that there would be wastage and concluded that drug wastage will increase the cost-utility ratio by 6.4%. However, the absence of information regarding the stability of opened vials limits information regarding the predicted drug costs.
- In the submitted analysis, survival beyond the trial period (median patient follow-up of approximately 17 to 28 months across treatment arms) is based on extrapolation, however, no data or biomedical theory exists to test whether this assumption is reasonable. As a result, the Economic Guidance Panel conducted re-analyses for both extrapolations methods and the **time horizon**. While, the submitter assumed a [redacted] year time horizon for the main analysis, the Economic Guidance Panel assumed a five year time horizon in their reanalyses. *(The manufacturer, as the primary data owner, did not agree to the disclosure of some economic information, therefore, this information was redacted from guidance reports provided to pERC and has been redacted in this publicly available guidance report. This information will remain redacted until notification by manufacturer that it can be publicly disclosed).* This was based on input and consensus from the pCODR Melanoma Clinical Guidance Panel that five years was a more reasonable time horizon for patients with advanced melanoma. In addition, discounting future survival benefits in a rapidly innovative environment, such as melanoma treatment, contributed to the Economic Guidance Panel reasoning for a 5 year time horizon. The Economic Guidance Panel recognized that this assumption effectively and completely discounts all survival benefits beyond 5 years.

The Economic Guidance Panel's best estimate of the incremental cost-effectiveness ratio is approximately $1,077,198/QALY when ipilimumab 10 mg/kg is compared with [redacted]. *(Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by manufacturer that it can be publicly disclosed).*

- This reanalysis conducted by the Economic Guidance Panel using the submitted model took into account changes to the time horizon and ipilimumab drug wastage, as noted above. In addition, to address PAG input and input from the pCODR Melanoma Clinical Guidance Panel related to potential practice patterns, the use of **ipilimumab at 10 mg/kg** was estimated as compared to the 3mg/kg dosage used in the submitted analysis. Based on the model, the Economic Guidance Panel estimated that the

difference in incremental cost-utility ratio is exactly four-fold when increasing the dose from 3 mg/kg to 10 mg/kg. The Economic Guidance Panel assumed that the resulting cost-utility ratio is a best guess estimate and that the treatment outcomes and side effect profiles associated with the higher dose exactly offset each other. Data evaluating ipilimumab 10 mg/kg in previously treated patients would be required to verify this assumption.

The Economic Guidance Panel did not provide a best estimate if **more than four ipilimumab doses** were received by a patient. However, an increase in the number of ipilimumab doses would likely lead to an increase in drug price and the resulting ICER. In consultation with the pCODR Melanoma Clinical Guidance Panel, the Economic Guidance Panel considered that an assumption of four doses was reasonable but acknowledged that some patients may receive more than four doses, which could result in further costs relative to benefit.

The Economic Guidance Panel estimates are conservative and assume that the costs of **monitoring for potential serious side effects** are reasonable in ipilimumab patients. The pCODR Melanoma Clinical Guidance Panel noted that, initially, resources may need to be directed toward educating oncologists to recognize and treat these side effects at an early stage.

The Economic Guidance Panel best estimates are based on the submitted ipilimumab price. However, additional reanalyses conducted by the Panel noted that a **10% decrease in the ipilimumab price** results in a 12.9% decrease in the cost-utility ratio.

The Economic Guidance Panels estimates differed substantially from the submitted estimates.

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

- The extra cost of ipilimumab ranged from $70,247 to $118,942.
- The extra clinical effect of ipilimumab ranged from 0.676 QALYs to 0.749 QALYs.

(Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by manufacturer that it can be publicly disclosed).

So, the incremental cost required for one QALY ranges from $103,839 to $166,186

The Economic Guidance Panel's estimates ranged from $269,299/QALY to $1,077,198/QALY. The lower estimate differs from the Submitter's only in the consideration of time horizon and drug wastage. The upper end of the range, however, is based on an additional consideration of the 10 mg/kg dose of ipilimumab. Depending on variations in clinical practice with respect to dosage and number of doses, cost-effectiveness estimates may lie somewhere within this range.

1.3 Summary of Economic Guidance Panel Evaluation

If the Economic Guidance Panel estimates of ΔC, ΔE and the ICER differ from the Submitter's, what are the key reasons?

The Economic Guidance Panel estimates differ substantially from those provided by the submitter. Dosage, time horizon, and wastage contributed to these differences. The Economic Guidance Panel estimates do not include a single estimate but rather are provided in a range where the lower estimate is based on 3 mg/kg ipilimumab dosing and the upper range is based on 10 mg/kg ipilimumab dosing. Depending on variations in clinical practice with respect to dosage and number of doses, cost-effectiveness estimates, may lie somewhere within this range. Incorporation of a five year time horizon and assumption of drug wastage is applied to all estimates within the range. The Economic Guidance Panel noted that these estimates are dependent on the ipilimumab price submitted by Bristol-Meyers Squibb Canada. A 10% decrease in the price of ipilimumab will result in a 12.9% decrease in the incremental cost-utility ratio.

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

In part. The primary concern of the patients is survival which was adequately addressed in the model. Unfortunately, there is only a single trial (Hodi 2010) with less than five years of follow-up data. Although the submitters main analysis assumed benefits to [redacted] years, the Economic Guidance Panel reanalyses only supported the magnitude of the benefit provided in the first five years. *(The manufacturer, as the primary data owner, did not agree to the disclosure of some economic information, therefore, this information was redacted from guidance reports provided to pERC and has been redacted in this publicly available guidance report. This information will remain redacted until notification by manufacturer that it can be publicly disclosed).* The patient advocacy groups identified employment and financial issues as a concern that is not addressed in an analysis from the perspective of a government payer. However, this perspective is appropriate for pCODR because drug funding recommendations must be considered from a health system perspective.

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

Yes, the design and structure of the economic model was adequate. The submitted model was used to estimate the impact of dosing, wastage and drug price through the calculation of elasticities which were then applied to the reported analysis.

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?

Many of the key resource, clinical and utility assumptions were considered appropriate by the Economic Guidance Panel. The submitter added to sparse published data with expert opinion, surveys and chart reviews. These appeared to accurately reflect practice patterns and expected utility benefits.

Modelling survival was the key clinical input for the economic evaluation and assumptions around the time horizon have an important effect. Incremental survival benefits accruing ipilimumab were generated from a single phase-III randomized controlled trial in the second-line setting (Hodi 2010). However, no data are available that could be used to infer treatment costs and outcomes beyond the trial horizon and no implications for the ICER may be hypothesized. While, the submitter assumed a [redacted] year time horizon for the main analysis, the Economic Guidance Panel assumed a five year time horizon in their reanalyses. *(The manufacturer, as the primary data owner, did not agree to the disclosure of some economic information, therefore, this information was redacted from guidance reports provided to pERC and has been redacted in this publicly available guidance report. This information will remain redacted until notification by manufacturer that it can be publicly disclosed).* This was based on input and consensus from the pCODR Melanoma Clinical Guidance Panel that five years was a more reasonable time horizon for patients with advanced melanoma. In addition, discounting future survival benefits in a rapidly innovative environment, such as melanoma treatment, contributed to the Economic Guidance Panel reasoning for a five year time horizon. The Economic Guidance Panel estimates of clinical effect effectively and completely discount all survival benefits beyond five years as there is no evidence to support the extrapolations.

Overall survival and progression-free survival for all comparators were assumed to be equivalent to the gp100 plus placebo arm of the main clinical trial evaluating ipilimumab in the second-line setting (Hodi 2010), where ipilimumab was compared with gp100 vaccine. The gp100 vaccine is an experimental therapy not currently used in Canada, however, the effectiveness of [redacted] and all other comparators included in the economic evaluation was assumed to be equivalent to gp100 in this analysis. *(Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by manufacturer that it can be publicly disclosed).* A systematic review and synthesis of available data for overall survival noted that the overall survival observed in the gp100 plus placebo arm of Hodi 2010 was representative of overall survival observed for routinely used melanoma therapies (Kotapati 2011). Further, an algorithm adequately adjusted for all patient characteristics. Given that this algorithm is based on a meta-analysis of all phase-II trials, the assumption is reasonable (Korn 2008).

The economic analysis is confounded by the fact that the analysis considers ipilimumab only in previously treated patients. In the absence of an effective first-line therapy oncologists may switch from first-line to second-line therapy as soon as possible. The most significant assumption not considered in the Submitter's analysis was the potential for variations in dosing that may occur in clinical practice such as dose escalation to the higher ipilimumab drug dose of 10mg/kg in previously treated patients.

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

Other than drug costs that did not account for variations in dosing, all other cost inputs appeared reasonable. Although the treatment of toxicities is expected to be high initially, these costs are expected to rapidly decline with training and clinician experience in managing toxicities.

1.4 Summary of Budget Impact Analysis Assessment

What factors most strongly influence the budget impact analysis estimates?

A budget impact analysis (BIA) was submitted to determine the impact, from the public payers' perspective, of the introduction of ipilimumab over a three-year time horizon. The BIA contains assumptions regarding epidemiology, current treatment patterns, costs, and market assumptions. A clinical expert panel estimated market shares. A combination of literature and primary data collection was used to generate epidemiological and cost inputs. The model results are most sensitive to assumptions regarding the percentage of patients currently receiving first-line treatment, market shares, the source of its market share and drug costs.

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

As in the main analysis, ipilimumab dosing is perhaps the most sensitive input and the lack of analyses considering changes to dosing was the key limitation in the BIA. If estimates of the use of ipilimumab 10 mg/kg were to be incorporated, the BIA would be inflated four-fold. Wastage was recognized by the Economic Guidance Panel as an important consideration [redacted] the submitter's main analysis. *(Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by manufacturer that it can be publicly disclosed).* Increased costs associated with monitoring and management of side effects was recognized as important by the PAG but considered by the Economic Guidance Panel to have a minimal impact over the long-term.

1.5 Future Research

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

Consensus to be reached to establish the dosing and duration. Specifically, the effectiveness and toxicities associated with providing 10 mg/kg as opposed to 3 mg/kg needs to be addressed. A trial has been requested by the FDA comparing ipilimumab 3mg/kg versus ipilimumab 10 mg/kg. Data from this trial would be able to inform an evaluation of the real-world cost-effectiveness of ipilimumab.

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

There are no other economic evaluations of either drug regimen. The submitter conducted valuable research establishing the current standard of care, obtaining utilities and estimation of costs. However, a complete validation of the provided inputs though independent research would be valuable.

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 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 ipilimumab (Yervoy) for advanced melanoma. A full assessment of the clinical evidence of ipilimumab 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*. The manufacturer, as the primary data owner, did not agree to the disclosure of some economic information, therefore, this information was redacted from the Guidance Reports provided to pERC for their deliberations and has been redacted in this publicly available Guidance Report.

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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pan-Canadian Oncology Drug Review Manufacturer Submission: YervoyTM (ipilimumab): 5 mg/mL, 10 mL and 40 mL vials; Company: Bristol-Myers Squibb Canada. Montreal (QC): Bristol-Myers Squibb Canada; 2011 Dec 13.

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