pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pCODR EXPERT REVIEW COMMITTEE (pERC)
FINAL RECOMMENDATION

The pan-Canadian Oncology Drug Review (pCODR) was established by Canada's provincial and territorial Ministries of Health (with the exception of Quebec) to assess cancer drug therapies and make recommendations to guide drug-funding decisions. The pCODR process brings consistency and clarity to the cancer drug assessment process by looking at clinical evidence, cost-effectiveness and patient perspectives.

pERC Final Recommendation
Upon consideration of feedback from eligible stakeholders, pERC members considered that criteria for early conversion of an Initial Recommendation to a Final Recommendation were met and reconsideration by pERC was not required.

Drug: Ipilimumab (Yervoy) **Submitted Funding Request:** For the first-line treatment of adult patients with advanced (unresectable or metastatic) melanoma	
Submitted By: Bristol-Myers Squibb Canada	**Manufactured By:** Bristol-Myers Squibb Canada
NOC Date: September 10, 2014	**Submission Date:** August 15, 2014
Initial Recommendation: December 4, 2014	**Final Recommendation:** December 22, 2014

pERC RECOMMENDATION

The pCODR Expert Review Committee (pERC) recommends funding ipilimumab (Yervoy) for the treatment of adults with advanced (unresectable or metastatic) melanoma, conditional on cost effectiveness being improved to an acceptable level. Funding should be for a dosing schedule of 3mg/kg, every 3 weeks for 4 doses as a first-line therapy for patients with primary cutaneous unresectable stage IIIC or IV melanoma, regardless of BRAF mutation status, who have an ECOG PS ≤1 and are not currently receiving immunosuppressive therapy. If brain metastases are present, patients should be asymptomatic or stable.

The Committee made this recommendation because it was satisfied that, despite limitations in the clinical data, there is an overall clinical benefit of ipilimumab compared with dacarbazine. However, pERC acknowledged that there was considerable uncertainty around the magnitude of the clinical benefit at the 3mg/kg dose compared to 10mg/kg, as there is no direct evidence available which compares the two doses for efficacy and safety. This led to a wide range of incremental cost-effectiveness ratio estimates. Therefore, at the submitted price and the Economic Guidance Panel's best estimates of the incremental cost-effectiveness ratio, ipilimumab could not be considered cost-effective versus relevant comparators.

POTENTIAL NEXT STEPS FOR STAKEHOLDERS

Pricing Arrangements to Improve Cost-Effectiveness
Given that pERC was satisfied, despite uncertainties in the clinical data, that there is a net clinical benefit of ipilimumab in the first line setting, jurisdictions may want to consider pricing arrangements and/or cost structures that would improve the cost-effectiveness of ipilimumab to an acceptable level.

Optimal Sequencing of Ipilimumab and Other Therapies Unknown
pERC concluded that the optimal sequencing of ipilimumab and other treatments now available for the treatment of BRAF positive metastatic melanoma is currently unknown. pERC was therefore unable to make an informed recommendation on sequencing of treatments in the first line setting for this patient population. However, pERC recognized that provinces will need to address this issue upon implementation of ipilimumab funding in the first line setting and noted that collaboration among provinces to develop a common approach would be of value.

Awaiting Evidence to Reduce Uncertainty concerning the Magnitude of Clinical Benefit
pERC noted the considerable uncertainty in the magnitude of clinical benefit of ipilimumab at the 3mg/kg compared to 10mg/kg dose. pERC agreed that study CA184-169, a recently completed randomized controlled trial comparing 3mg/kg vs. 10mg/kg dose of ipilimumab in previously untreated patients, will provide data to address this uncertainty.

Optimal Strategy for Re-induction
pERC noted that evidence was not available to support the optimal strategy for re-induction of patients with ipilimumab at the time of disease progression. pERC however noted that there may be uncommon instances where re-induction is considered to be beneficial when other strategies (e.g. clinical trials) are not available or appropriate for patients. pERC therefore agreed that a process, based on provincial guidelines, to allow for the review and approval of individual cases by oncologists with expertise in melanoma, should be made available to assess those uncommon instances.

Access to Expertise in Managing Side Effects
pERC noted that some of the potential immune-related side effects of ipilimumab are dangerous and require the expertise of oncologists experienced in dealing with these side effects. Therefore pERC strongly supports that administration of ipilimumab be restricted to treatment centers that have the professional expertise to monitor and manage these potential side effects.

SUMMARY OF pERC DELIBERATIONS

pERC noted that unresectable stage III or stage IV melanoma carries a poor prognosis with a median survival of only approximately 6 months with only 25% of patients with the late stage disease surviving to one year. The most commonly used first line therapy in untreated patients with metastatic melanoma who do not harbour a BRAF mutation is dacarbazine (DTIC).Patients that have the BRAF V600 mutation may be treated with a BRAF or MEK inhibitor. pERC noted that dacarbazine has not shown an advantage in survival or quality of life in randomized trials. Patients responding to BRAF or MEK inhibitors generally experience a short duration of response often followed by rapid progression of disease. Median duration of response with BRAF targeting agents is less than 7 months. Given the available treatment options, pERC agreed that there is a need for more effective and tolerable treatment options in the first line setting for this patient population.

pERC's Deliberative Framework for drug funding recommendations focuses on four main criteria:	
CLINICAL BENEFIT	PATIENT-BASED VALUES
ECONOMIC EVALUATION	ADOPTION FEASIBILITY

pERC discussed the evidence presented on the efficacy of ipilimumab, in the first line setting, and concluded that there is a net clinical benefit associated with the dose of 3mg/kg every 3 weeks for 4 doses. pERC considered several factors in formulating this conclusion. The submitter's funding request and the national and international regulatory approval for ipilimumab in the first line setting are at the 3mg/kg dose. pERC agreed that there was a statistically and clinically significant benefit in survival in the study comparing 10mg/kg ipilimumab-DTIC to DTIC-placebo in favour of the ipilimumab treatment arm. This survival advantage was maintained over the course of the follow-up period. This potentially long term survival advantage was demonstrated in approximately 20% of patients who required no further systemic treatment, a benefit which pERC considered to be a very clinically meaningful outcome. Given that prospective randomized controlled trials evaluating the 3mg/kg dose in the first line setting are not currently available, pERC considered evidence from a pooled analysis and two retrospective observational studies evaluating the activity of ipilimumab in the first line setting. While acknowledging the limitations of the data, the Committee noted that the 1 and 2 year survival rates provided through these multiple data sets were similar to those seen in the second line setting, where efficacy of the 3mg/kg dose has previously been demonstrated. pERC agreed with the Clinical Guidance Panel regarding the consistency of data that suggested the benefit of the lower dose is likely to be similar to the 10mg dose, with the caveat that the exact magnitude of benefit with the 3mg/kg dose is unknown. Although efficacy is expected to be similar, pERC noted higher rates of grade 3/4 immune-related adverse events with the 10mg/kg dose that with the 3mg/kg dose. Additionally, pERC considered that it is likely not biologically plausible for an immunotherapy to be less effective in the first line compared to second line setting. An ongoing study is comparing 10mg/kg versus 3mg/kg and is expected to report its results in 2016. While pERC anticipates that this study may reduce the uncertainty in the estimates of effectiveness for ipilimumab 3 mg/kg, it did not consider it appropriate to withhold recommending ipilimumab in the first line setting from patients until the result of this study is presented, as the Committee was satisfied with the evidence suggesting activity of the lower dose in the first line setting. pERC noted that patients with brain metastasis were excluded from the 10mg study and the pooled analysis, while they were included in the two retrospective observational studies. pERC, therefore, agreed that it would be reasonable to use ipilimumab in first line patients with brain metastases if those metastases are asymptomatic or stable as the intent of treatment is targeting the peripheral disease and not the brain metastases.
pERC also discussed the available first line treatment options for patients and noted that DTIC has not been shown to have a demonstrated survival or quality of life advantage in randomized trials. In light of the presented evidence and apparent need for alternative treatment options, pERC agreed that ipilimumab, at 3mg/kg, provides a net clinical benefit in the first line setting. pERC also noted that ipilimumab should be used as a monotherapy, as there is no evidence that its use in combination with DTIC provides additional efficacy. pERC also agreed that ipilimumab maintenance treatment should not be administered as there is no evidence to support any added efficacy from maintenance therapy.

pERC noted that quality of life reporting was limited. pERC noted that quality of life is an important outcome and that trial investigators and manufacturers, should collect good data in clinical trials on this important outcome for patients.

pERC discussed the toxicity profile of ipilimumab and noted a continuing concern for immune-related adverse events. While the Committee agreed that there is now better knowledge and experience in managing these potentially serious or life threatening adverse events, pERC agreed that patients should continue to be referred to specialized cancer treatment centers with experience in managing immune-related adverse events. pERC also agreed that the toxicity profile of ipilimumab is not expected to be worse than was observed in the second line setting, where it was studied at the 3mg/kg dose.

pERC reviewed patient advocacy group input that indicated patients value effective treatment options with reduced toxicity, improved quality of life, and improved survival. Given this input, pERC considered that ipilimumab in the first line setting aligns with patient values as it provides a treatment alternative to DTIC, a treatment with limited efficacy.

pERC discussed the cost-effectiveness of ipilimumab at 3 mg/kg in previously untreated patients and concluded that ipilimumab is not cost-effective when compared to DTIC and unknown in relation to vemurafenib. pERC accepted the Economic Guidance Panel's (EGP) estimates and noted several limitations in the submitted analysis. pERC noted uncertainty in the clinical data inputs used to provide cost effectiveness estimates as the comparison between ipilimumab vs. DTIC and ipilimumab vs. vemurafenib were based upon a naive (side by side) comparison of a pooled analysis and two separate arms from different trials. pERC agreed that there was uncertainty in these clinical inputs which introduced a large amount of uncertainty in the cost-effectiveness estimates provided by the EGP. pERC also considered that the price of ipilimumab would need to be reduced substantially in order for it to be considered cost-effective relative to DTIC. In addition, pERC noted some assumptions in the submitted model had a substantial impact on the cost-effectiveness estimates. First, pERC agreed that the utilities used for ipilimumab in the model were overestimated in comparison to DTIC. Secondly, in the comparison to vemurafenib, the inclusion of second line patients and the proportion of them receiving second line treatment had a large impact on the incremental cost-effectiveness ratio (ICER). Overall, pERC accepted the EGP's re-analysis estimates and concluded that ipilimumab is not cost effective relative to DTIC.

pERC considered the feasibility of implementing a funding recommendation for ipilimumab. pERC considered that the optimal sequencing of agents in this setting is currently unknown. However, pERC recognized that provinces may need to address this issue upon implementation of funding and noted that the development and implementation of an evidence-informed provincial guideline would help to guide consistency in drug funding. pERC also noted the Provincial Advisory Group's (PAG) concern on the optimal dose of ipilimumab; however, pERC was confident in concluding the lower dose of ipilimumab (3mg/kg) is active and likely provides net clinical benefit in the first line setting. pERC, however, agreed that results from the on-going study assessing the optimal dose of ipilimumab in the first line setting will help to better inform the magnitude of benefit. pERC discussed that drug wastage is an important concern for PAG and noted that it was incorporated into the economic analysis and seen to have a minimal impact on the ICER in relation to other parameters. pERC also discussed the high cost of ipilimumab and noted that the cost of ipilimumab would need to be reduced substantially as it has a substantial impact on the cost-effectiveness estimates. While noting that the number of patients with metastatic melanoma is relatively small, pERC agreed that this may increase if patients become eligible in the first-line setting. pERC noted that the budget impact analysis is sensitive to the number of patients eligible for ipilimumab in the first- line setting and agreed that jurisdictions will need to consider this during implementation. pERC also noted that the introduction of ipilimumab in the first line setting will impact the number of patients eligible to receive ipilimumab in the second-line as there is no evidence to suggest any benefit from continuation onto second line ipilimumab after progression with first line use. pERC, however, agreed that re-induction of patients with ipilimumab after disease progression is a clinically reasonable option in some instances but should be informed by provincial guidelines and a process to allow for review/approval of individual cases by oncologists with expertise in melanoma.

EVIDENCE IN BRIEF

pERC deliberated upon:

- a pCODR systematic review
- other literature in the Clinical Guidance Report providing clinical context
- an evaluation of the manufacturer's economic model and budget impact analysis
- guidance from pCODR clinical and economic review panels
- input from one patient advocacy groups (Melanoma Network of Canada)
- input from pCODR's Provincial Advisory Group.

Feedback on the pERC Initial Recommendation was also provided by:

- input from pCODR's Provincial Advisory Group.
- one patient advocacy group (Melanoma Network of Canada)
- the Submitter (Bristol Myers Squibb Canada)

The pERC initial recommendation was to fund ipilimumab (Yervoy) for the treatment of adults with advanced (unresectable or metastatic) melanoma, conditional on cost effectiveness being improved to an acceptable level. Feedback on the pERC Initial Recommendation indicated that the manufacturer, patient advocacy group and pCODR's Provincial Advisory Group agreed with the initial recommendation. The pERC Chair and pERC members reviewed the feedback and it was determined that the pERC Initial Recommendation was eligible for early conversion to a pERC Final Recommendation without reconsideration by pERC because there was unanimous consensus from stakeholders on the recommended clinical population outlined in the pERC Initial Recommendation.

OVERALL CLINICAL BENEFIT

pCODR review scope

The pCODR review evaluated the use of ipilimumab, either alone or in combination, on patient outcomes, compared to commonly used therapies, placebo, or best supportive care in the treatment of patients with unresectable melanoma (stage III or stage IV) who had no previous systemic therapy.

Studies included

The pCODR systematic review included the CA184-024 study (Robert et al 2011); a randomized, double-blind trial that compared the use of ipilimumab (10 mg/kg) plus dacarbazine (DTIC, 850 mg/m^2) versus DTIC (850 mg/m^2) plus placebo in patients with previously untreated unresectable stage III or stage IV melanoma.

Patient populations: ECOG 0-1

The baseline characteristics of patients in study CA184-024 were balanced between the treatment arms. The mean age of patients was 57.5 vs. 56.4 years in the ipilimumab-DTIC vs. DTIC-placebo group, respectively. Approximately 71% and 29% of patients in each arm had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, respectively. Patients with CNS metastases, ocular or mucosal melanoma, patients on chronic steroids or immune suppressive agents or with a history or autoimmune disease were excluded from the trial.

Key efficacy results: Potential long term survival advantage in patients

The key efficacy outcome deliberated upon by pERC was overall survival, which was the primary outcome for the CA184-024 study. The study demonstrated a statistically and clinically significant benefit in median overall survival (11.2 vs. 9.1 months, respectively; hazard ratio (HR) 0.72, 95% CI 0.59 to 0.87) and progression-free survival (median 2.76 vs. 2.6 months, respectively; HR 0.76 95% CI0.63 – 0.93, p=0.006) in favour of ipilimumab-DTIC. pERC considered the survival advantage observed in approximately 20% of patients beyond the three year mark, as was evident in the tail of the Kaplan-Meier survival curve, to be a clinically meaningful patient outcome.

As the trial did not differentiate patients based upon BRAF mutation status, pERC agreed that ipilimumab should be made available to both BRAF mutation negative and positive patients. pERC was, however, unable to speak to the optimal sequencing of therapies for patients with a BRAF mutation in this setting

and noted that jurisdictions will need to consider this during implementation. Although pERC noted that patients with brain metastasis were excluded from the study, the Committee agreed that it would be reasonable to use ipilimumab in first line patients with brain metastases who are asymptomatic or stable

Ipilimumab Dose: Likely similar efficacy of 3mg/kg and 10mg/kg dose

Given that prospective, randomized controlled trials evaluating the 3mg/kg dose in the first line setting are not currently available, pERC considered evidence from a pooled analysis and two retrospective observational studies suggesting activity of ipilimumab at the 3mg/kg dose in the first line setting. While there were differences in baseline patient characteristics between the three studies, pERC noted that the survival curves provided through these multiple data sets were similar to those seen in the second line setting trial, where the efficacy of the 3mg/kg dose has previously been demonstrated (pERC Final Recommendation for Ipilimumab for Advanced Melanoma 2012, Hodi 2010). pERC discussed this consistency of results in multiple lines of therapy and agreed with the CGP that the 3mg/kg dose is expected to be similar in efficacy to the 10mg/kg dose. pERC also noted the present lack of a tolerable and effective first line treatment options that provide durable responses for patients and concluded that there was sufficient patient need for the committee to recommend ipilimumab move to the first line setting. pERC noted that patients with brain metastases were included in the two retrospective observational studies (9/120 (7.5%) in the CA184-338 study and 28/90 (31.1%) in the CA184-332 study). While acknowledging the limitations in this evidence in drawing any conclusions, pERC agreed that it would be reasonable to use ipilimumab in first line patients with brain metastases who are asymptomatic or stable. As patients with disease of ocular and mucosal primary origin were excluded from the study, pERC is unable to comment on the efficacy of ipilimumab in these patient populations.

pERC discussed the challenges of assessing the magnitude of clinical benefit of the 3mg/kg dose in comparison to ipilimumab 10 mg/kg, to vemurafenib, or even to dacarbazine in the absence of comparative data and noted that the availability of the retrospective observational and pooled analysis of RCT's helped inform pERC's deliberations. pERC, however, noted that study CA184-169, assessing the optimal dose of ipilimumab, is expected to report results in 2016, and will reduce the uncertainty in the estimates of effectiveness for ipilimumab 3 mg/kg compared to 10 mg/kg. While acknowledging the uncertainty in the magnitude of the benefit, overall, pERC was confident that there is a net clinical benefit associated with ipilimumab at the 3mg/kg dose. pERC acknowledged that, if the final results of this study suggest superior efficacy of the 10mg/kg dose, a re-submission including a new economic evaluation would be required.

Quality of life: Minimal reporting

pERC reviewed the health-related quality of life (HRQOL) data provided for ipilimumab from the CA184-024 (Robert et al.) study and noted that results were only reported in abstract form. Patients in both groups reported a decline in the average Global Health Status (GHS) score from baseline (ipilimumab-dacarbazine, -6.5; dacarbazine-placebo, -10.0), indicating worsening health status; however, no p-value or 95% CI was reported for this comparison. pERC noted that quality of life is important to patients and while the trial investigators and manufacturers collected this data, the limited reporting on the quality of life results, the methods used to collect the data, and the lack of validated minimal clinically important differences made it difficult to interpret the results.

Safety: Most immune-related adverse events now better understood and reversible

pERC noted that immune-related adverse events occurred in a higher proportion of patients treated with ipilimumab-DTIC than in those treated with DTIC-placebo, 77.7% versus 38.2%, respectively. The most common adverse events were dermatologic disorders, diarrhea, and elevated ALT/AST. The study by Robert et al. also had a higher rate of withdrawal due to adverse events in the ipilimumab + DTIC vs. DTIC-placebo arm (38.5 vs. 8%, respectively), most of which were due to immune-related adverse events. While the committee agreed that well defined algorithms have now been developed to manage these potentially serious adverse events, pERC agreed that patients should continue to be referred to specialized cancer treatment centers with experience in managing immune related adverse events. The adverse events that are not amenable to rapid reversal are the endocrine side effects, which generally require several weeks to months to reverse; about 46% of patients receiving ipilimumab-DTIC will require long-term steroid replacement. pERC also noted that grade 3 or higher adverse events occurred with a higher proportion in the ipilimumab-DTIC vs. DTIC+ placebo arm, 56.3% vs. 27.5%, respectively.

While immune-related adverse events were the most common adverse events in both the 10mg/kg study and the data set for the 3mg/kg dose, pERC noted that grade 3/4 immune-related AE's were higher in the 10mg/kg study.

Need: Active treatments with durable response

It is estimated that 6,500 Canadians will be diagnosed with melanoma in 2014, and approximately 1,050 patients will die of melanoma in 2014. Unresectable stage III or stage IV melanoma carries a poor prognosis with a median survival of approximately 6 months with only about 25% of patients with late stage disease surviving to one year.

Recently, new therapies have improved the prognosis and a small proportion experience long term survival. Vemurafenib has become the first-line treatment of advanced unresectable melanoma in patients harbouring the V600 BRAF mutation. This mutation occurs in approximately 50% of all melanoma tumours. Dabrafenib is a similar targeted oral BRAF inhibitor which has a slightly different toxicity profile and which is similarly efficacious in the therapy of patients with BRAF mutant metastatic melanoma. Treatment resistance to a BRAF inhibitor is, however, almost always inevitable with a median duration of response to a BRAF inhibitor of less than 7 months. While BRAF inhibitors have become available for patients harbouring mutations, DTIC remains as the mainstay of treatment in the first line setting for patients without the BRAF mutation. pERC, however, noted that DTIC has limited benefit and there is no evidence that chemotherapy offers an increased quality of life or overall survival benefit. Overall, pERC considered that there is a need for new and effective therapies for patients with unresectable stage III or stage IV metastatic melanoma which provides durable improvements in survival and quality of life.

PATIENT-BASED VALUES

Values of patients with metastatic melanoma: Quality of life and effective treatment option

Patient advocacy group input indicated that there are limited therapies available for patients with advanced melanoma and new effective therapies which extend life expectancy are very important. Patients indicated that while treatment options for some melanoma patients are improving, they still remain limited, and for some types of melanoma, are almost non-existent. DTIC is understood to cause tumour regression infrequently and patients do not generally have confidence in its effectiveness. Patients also report experiencing detrimental impacts on their quality of life due to current therapies as they often have very severe and lasting side effects including liver failure, nausea, debilitating depression, headaches, loss of memory, diarrhea, hair loss, fatigue, confusion, rigors and other flu like symptoms.

pERC noted that ipilimumab demonstrated improvements in overall and progression-free survival, with potential long term survival benefit in approximately 20% of patients. pERC agreed this aligned with the patient value of having access to effective treatments with a durable survival advantage. pERC noted that quality of life was a patient-expressed value and that the pCODR Melanoma Clinical Guidance Panel considered that quality of life data from the CA184-024 study had several limitations. Therefore, the impact of ipilimumab on quality of life could not be fully assessed. pERC noted that quality of life is an important outcome and that trial investigators and manufacturers, should collect good quality data in clinical trials which is important to patients.

Patient values on treatment: manageable side effects and improved response

Most patients reported being treated with DTIC or interferon with 26% of respondents indicating that they had some regression or stabilization of disease for less than 3 months. However, none of the respondents indicated a durable response beyond 6 months with these treatments. Patients indicate that access to first line ipilimumab would be beneficial as response rates for current therapies remain limited while the majority of patients reporting experience with ipilimumab reported durable response for over 2 years.

pERC considered input from patients that indicated they are willing to accept side effects and the serious side effects associated with ipilimumab can generally be effectively managed. According to patients, short term side effects are the most widely acceptable while lasting side effects that affect quality of life are sometimes unacceptable. While ipilimumab has been known to cause significant immune related adverse side effects, pERC agreed that it aligned with this patient value. Physicians have now become more familiar with the drug and in most cases are able to effectively manage these side effects. Nonetheless, pERC re-iterated its position that patients should be referred to specialized cancer

treatment centers with the medical expertise and experience in managing immune related adverse events. Patients noted that they would be willing to take all the necessary steps to manage side-effects given that other current therapies often have similar severe and lasting side effects.

ECONOMIC EVALUATION

Economic model submitted: cost-effectiveness and cost-utility analysis

The pCODR Economic Guidance Panel assessed cost-effectiveness and cost-utility analyses comparing 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.

Basis of the economic model: clinical and economic inputs

Costs considered in the analysis included drug costs, follow-up costs, terminal care and adverse events costs.

The key clinical outcomes considered in the analysis were overall survival, progression-free survival, adverse events, treatment duration and utilities. pERC noted that the source of data for overall survival and progression-free survival for ipilimumab came from a pooled dataset of chemotherapy-naïve patients, which was considered to have a high degree of uncertainty. pERC also noted that the data for the DTIC and vemurafenib arm came from two separate trials. Given the potential differences that may exist between populations in the different trials, pERC noted that the there was considerable uncertainty in the estimates of clinical effect used in the submitted and the EGP's re-analysis estimates.

Drug costs: High cost of drug, wastage

Ipilimumab costs $5,800 and $23,200.00per 50 mg and 200mg vial, respectively (unit cost of $116 / mg). At the recommended dose of 3 mg/kg every 3 weeks for 4 doses, the cost of ipilimumab is $1,160.00 per day and $32, 480.00 per 28 day cycle. pERC noted that ipilimumab is administered based on body weight (Kg). In instances where vial sharing is not feasible, such as in small treatment centers, there is a likelihood of wastage of any excess drug. The EGP's re-analysis included drug wastage into the evaluation and noted that, relative to factors such as the drug cost, wastage did not have a big impact on the ICER.

Dacarbazine costs $189.76 per 600 mg vial (unit cost of $0.32 per mg). At the recommended dose of 850 mg per m^2IV days 1-5 every 21-28 days and using a body surface area (BSA) of 1.7 m^2, the cost of dacarbazine is $20.26 – $33.76 per day and $567.23 – 945.39 per 28 day cycle. Vemurafenib costs $46.54 per 240 mg tablet (unit cost of $0.19 / mg). At the recommended dose of 960 mg daily, the cost of vemurafenib is $372.34 per day and $10,425.41 per 28 day cycle.

Cost-effectiveness estimates: Uncertainty in clinical inputs, drug cost

pERC discussed the Economic Guidance Panel's best estimate of the incremental cost-effectiveness ratio in untreated patients which was between$165,389 and $197,382 per QALY for the comparison to DTIC and between $9,231 and $216,773 per QALY for the comparison to vemurafenib. pERC accepted the EGP's reanalyses and concluded that ipilimumab is not cost-effective in comparison to DTIC and unknown in comparison to vemurafenib. pERC discussed the uncertainty with the clinical evidence used to model overall survival and progression free survival, derived from a naïve comparison made from a pooled analysis and two arms from different clinical trials. Although adjustments were made to balance baseline differences in mortality, pERC agreed with the EGP and concluded that there is no knowledge of what potential differences there may have been among the three studies, normally accounted for through randomization, which could have impacted the results. pERC also noted that the EGP was not able to explore the uncertainty in the clinical inputs as an alternative data source was not available. Given the underlying limitations with the clinical inputs, pERC noted that a large amount of uncertainty is present in the cost-effectiveness estimates provided by the EGP.

pERC noted that the cost of ipilimumab is high and has a large impact on the cost-effectiveness estimates. In considering this, pERC agreed that the price of ipilimumab would need to be reduced substantially in order for it to be considered cost-effective.

pERC noted that the time horizon was shortened in the EGP's reanalysis from 35 to 20 years, based on clinical input from the CGP. While this shortening did not have a substantial impact on the cost effectiveness estimates, pERC agreed with the CGP that the real time horizon is between 10-20 years. pERC noted a better understanding on the long term effects of immunotherapies has accrued in the

interval since its previous review of ipilimumab in the second-line setting and considered it reasonable to use a time horizon between 10 and 20 years in the current analysis. The submitted model, however, did not allow the EGP to explore a time horizon in that range as it had set intervals in 10 year increments.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: sequencing, budget impact

pERC considered the feasibility of implementing a funding recommendation for ipilimumab. pERC noted PAG's concern about the optimal dose of ipilimumab. Given the presented evidence for the 10mg/kg dose, the consistency of outcome data across multiple sources supporting the activity of ipilimumab in the first line setting and the Clinical Guidance Panel's conclusion that the 3mg/kg dose is at least as effective as the 10mg dose, pERC was confident in recommending the 3mg/kg dose in the first line setting. pERC, however, agreed that results from the CA184-169 study, assessing the optimal dose of ipilimumab in the first line setting, will definitively address the comparative efficacy. pERC considered that the optimal sequencing of agents in this setting is currently unknown. pERC, however, recognized that provinces may need to address this issue upon implementation of funding and noted that the development and implementation of an evidence-based guideline would be of value to guide consistency in drug funding.

pERC acknowledged that drug wastage is an important concern for PAG and noted that it was addressed in the EGP's re-analysis. While acknowledging the EGP's conclusion that wastage had minimal impact on the cost-effectiveness estimates, pERC noted that this was relative to factors such as the high cost of ipilimumab. Additionally, pERC noted that the cost of ipilimumab would need to be reduced substantially as it had the greatest impact on the cost-effectiveness estimates.

pERC noted that while the number of patients with metastatic melanoma is relatively small, the number of patients eligible for ipilimumab is likely to increase when the treatment becomes available in the first line setting. Given that the submitted budget impact analysis was sensitive to the number of patients eligible for ipilimumab in the first line setting, pERC agreed that jurisdictions will need to carefully consider the potential impact this may have on their budget. pERC noted PAG's concern for dose creep with the use of the 10mg/kg dose in first-line setting. Until evidence is available to demonstrate superior efficacy of the 10mg/kg dose over the 3mg/kg, pERC agreed that there is no compelling reason to switch to the higher dose if a patient does not respond favorably to the lower dose.

pERC noted input from PAG on the higher percentage of patients receiving re-induction in real world experience. While no evidence was provided supporting the optimal strategy for the re-induction of patients, pERC agreed that a process, based on provincial guidelines, to allow for the review and approval of individual cases by oncologists with expertise in melanoma, should be made available.

DRUG AND CONDITION INFORMATION

Drug Information	• monoclonal antibody that blocks cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) • 5mg/mL (50mg/10mL and 200mg/40mL) reviewed by pCODR • Dosed at3 mg/kg administered intravenously over a 90-minute period every 3 weeks for a total of four doses
Cancer Treated	• Advanced or metastatic melanoma, with no previous immunotherapy
Burden of Illness	• In 2014, 6500 new cases of primary melanoma were diagnosed in Canada and approximately 1100 individuals will die each year • Incidence is relatively small compared to other cancers, but has been steadily increasing and prognosis remains poor for patients with advanced disease • Affects a younger population and causes a disproportionate number of years of life lost
Current Standard Treatment	• BRAF and MEK inhibitors for patients with BRAF mutation positive disease • Dacarbazine for patients with BRAF mutation negative disease • Temozolomide
Limitations of Current Therapy	• Limited evidence that chemotherapy offers any benefit in either improving quality of life or extending overall survival. Side effects of therapies not always tolerated • Treatment resistance to a BRAF inhibitor is common and the duration of response to a BRAF inhibitor is short

ABOUT THIS RECOMMENDATION

The pCODR Expert Review Committee (pERC)

Recommendations are made by the pCODR Expert Review Committee following the pERC Deliberative Framework. pERC members and their roles are as follows:

Dr. Anthony Fields, Oncologist (Chair)
Dr. Maureen Trudeau, Oncologist (Vice-Chair)
Dr. Scott Berry, Oncologist
Bryson Brown, Patient Member
Dr. Matthew Cheung, Oncologist
Mario de Lemos, Pharmacist
Dr. Sunil Desai, Oncologist
Mike Doyle, Economist
Dr. Bill Evans, Oncologist
Dr. Allan Grill, Family Physician
Dr. Paul Hoskins, Oncologist
Danica Wasney, Pharmacist
Carole McMahon, Patient Member Alternate
Jo Nanson, Patient Member
Dr. Tallal Younis, Oncologist

All members participated in deliberations and voting on the initial recommendation except:

- Carole McMahon who did not vote due to her role as a patient member alternate

Because the pERC Initial Recommendation met the criteria for early conversion to a pERC Final Recommendation, reconsideration by pERC was not required and deliberations and voting on the pERC Final Recommendation did not occur.

Avoidance of conflicts of interest

All members of the pCODR Expert Review Committee must comply with the *pCODR Conflict of Interest Guidelines*; individual conflict of interest statements for each member are posted on the pCODR website and pERC members have an obligation to disclose conflicts on an ongoing basis. For the review of ipilimumab (Yervoy) for first line advanced melanoma, through their declarations, six members had a real, potential or perceived conflict and based on application of the *pCODR Conflict of Interest Guidelines*, none of these members were excluded from voting.

Information sources used

The pCODR Expert Review Committee is provided with a *pCODR Clinical Guidance Report* and a *pCODR Economic Guidance Report*, which include a summary of patient advocacy group and Provincial Advisory Group input, as well as original patient advocacy group input submissions to inform their deliberations. pCODR guidance reports are developed following the pCODR review process and are posted on the pCODR website. Please refer to the pCODR guidance reports for more detail on their content.

Consulting publicly disclosed information

pCODR considers it essential that pERC recommendations be based on information that may be publicly disclosed. All information provided to the pCODR Expert Review Committee for its deliberations was handled in accordance with the *pCODR Disclosure of Information Guidelines*. There was no non-disclosable information in this recommendation document.

Use of this recommendation

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