pCODR EXPERT REVIEW COMMITTEE (pERC)
INITIAL 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.

Providing Feedback on this Initial Recommendation
Taking into consideration feedback from eligible stakeholders, the pERC will make a Final Recommendation. Feedback must be provided in accordance with *pCODR Procedures*, which are available on the pCODR website. The Final Recommendation will be posted on the pCODR website once available, and will supersede this Initial Recommendation.

Drug:
Pembrolizumab (Keytruda)

Submitted Funding Request:

For the treatment of patients with unresectable or metastatic melanoma

Submitted By:
Merck Canada Inc.

Manufactured By:
Merck Canada Inc.

NOC Date:
May 19, 2015

Submission Date:
April 16, 2015

Initial Recommendation Issued:
October 29, 2015

pERC RECOMMENDATION

The pCODR Expert Review Committee (pERC) recommends funding pembrolizumab (Keytruda) conditional on the cost-effectiveness being improved to an acceptable level. Funding should be in patients with unresectable or metastatic melanoma (stage III or IV) who are naive to ipilimumab treatment and in patients who have failed ipilimumab and, if BRAF mutation positive, a BRAF inhibitor. Treatment should be in patients with an ECOG performance status of 0-1, who have stable brain metastases (if present), using the 2mg/kg dose every three weeks for 24 months or until disease progression, whichever occurs first.

The committee made this recommendation because it was satisfied there is a net clinical benefit with pembrolizumab in patients with unresectable or metastatic melanoma (stage III or IV) who are naive to ipilimumab treatment based on a clinically meaningful improvement in 1 year OS and PFS. pERC further considered pembrolizumab to have an acceptable toxicity profile and a smaller decline in quality of life compared to ipilimumab. Pembrolizumab aligns with patient values. The committee also concluded that there is a net clinical benefit with pembrolizumab in patients with unresectable or metastatic melanoma who have previously been treated with ipilimumab (and a BRAF inhibitor in BRAF mutant patients) but acknowledged that there was considerable uncertainty around the magnitude of the clinical benefit. This conclusion was based on a clinically meaningful improvement in PFS, acceptable toxicity profile and a smaller decline in quality of life for pembrolizumab compared to chemotherapy. Pembrolizumab also aligned with patient values.

The Committee concluded that that pembrolizumab could not be considered cost-effective, in either patient population.

POTENTIAL NEXT STEPS FOR STAKEHOLDERS

Pricing Arrangements to Improve Cost-Effectiveness
Given that pERC was satisfied, that there is a net clinical benefit of pembrolizumab in patients who are ipilimumab naive or in patients who have previously been treated with ipilimumab (and a BRAF inhibitor for BRAF mutant patients), jurisdictions may want to consider pricing arrangements and/or cost structures that would improve the cost-effectiveness of pembrolizumab to an acceptable level.

Transition of Vial Size to 100mg Increases Potential for Wastage
pERC noted the expected transition of the 50mg vial to a larger 100mg vial in the near future and the potential for greater wastage with the larger vial size. pERC noted the EGP estimates included this potential wastage and demonstrated that it had a substantial impact on the cost-effectiveness estimates. pERC therefore agreed that jurisdictions will need to consider mechanisms to minimize wastage upon implementation of a funding recommendation; these may include advocating for maintenance of the availability of the 50mg vial).

Wastage and Budget Impact Likely Impact Adoption Feasibility
pERC also noted that the duration of treatment with pembrolizumab continues until disease progression, unacceptable toxicity or a maximum of 2 years, whichever comes first. In considering the high cost of pembrolizumab, the potential for drug wastage with the larger vial size and the unknown but potentially long duration of treatment, pERC concluded that a substantial reduction in drug price would be required to improve cost-effectiveness and affordability.

Evidence Generation to Understand Optimal Duration of Therapy
pERC noted that pembrolizumab is approved at a dose of 2mg/kg every three weeks until disease progression or for a maximum of 24 months, whichever comes first. pERC acknowledged that there is currently no evidence to identify an optimal duration of treatment with pembrolizumab and agreed that it is important to prospectively collect such data.

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

Optimal Strategy for Re-induction Unknown
pERC noted that evidence was not available to indicate an optimal strategy for re-induction of patients with pembrolizumab 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.

Time Limited Need for Pembrolizumab
At the time of implementing a funding recommendation for pembrolizumab, jurisdictions may consider addressing the short-term,

	time-limited need for pembrolizumab monotherapy for patients who are currently receiving ipilimumab in the first line setting. pERC noted that this time-limited access would mainly be for patients who are not tolerating ipilimumab well and who would otherwise meet the eligibility criteria for pembrolizumab. However, pERC acknowledged that the decision to switch to pembrolizumab or to have a patient complete first line treatment with ipilimumab should be made by the patient and their treating oncologist.

SUMMARY OF pERC DELIBERATIONS

pERC noted that unresectable stage III or stage IV melanoma carries a poor prognosis with a median survival of approximately 6 months and only 25% of patients with late stage disease surviving to one year. Ipilimumab is a commonly used first and second line therapy in patients with metastatic melanoma. While a proportion of patients (approximately 20%) have prolonged response to ipilimumab, the majority of patients experience disease progression. Adverse events with ipilimumab are also significant and potentially life threatening. Patients whose disease harbours a BRAF mutation have the option of treatment with BRAF or MEK inhibitors. Generally patients receiving these targeted therapies experience a short duration of response often followed by rapid progression of disease with the median duration of response being less than 7 months. Treatment options are limited for patients who have progressed on ipilimumab and a BRAF inhibitor and generally include dacarbazine or best supportive care (BSC). pERC noted that dacarbazine has not shown an advantage in survival or quality of life in randomized trials. pERC agreed that there is a need for more effective and tolerable treatment options in patients who are naive to ipilimumab treatment and in patients who have previously been treated with ipilimumab and, in those with a BRAF mutation, a BRAF inhibitor.

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 pembrolizumab, and concluded that there is a net clinical benefit with pembrolizumab for patients who are naive to treatment with ipilimumab and in patients who have previously been treated with ipilimumab and, in those with a BRAF mutation, a BRAF inhibitor. In patients who are naive to treatment with ipilimumab, pERC based its conclusions on the results of KEYNOTE-006, a 3-armed trial which compared pembrolizumab (2 dosing schedules) to ipilimumab in patients who were naïve to ipilimumab treatment. The KEYNOTE-006 trial demonstrated statistically significant and clinically meaningful improvements in 1 year overall survival (OS) and progression free survival (PFS). Quality of life (QoL) declined from baseline in both pembrolizumab arms but did not reach the minimally important difference (MID). A statistically significant and minimally important decline was however measured for the ipilimumab arm when compared to baseline and compared to both pembrolizumab arms.

pERC based its conclusion on net clinical benefit in patients previously treated with ipilimumab and, in those with a BRAF mutation, a BRAF inhibitor, on the results of KEYNOTE-002, a 3-armed trial, which compared pembrolizumab (2 regimens) to chemotherapy. pERC noted statistically significant and clinically meaningful improvements in 6 and 9 month PFS and objective response rate (ORR) in these patients. The committee expressed uncertainty concerning the magnitude of clinical benefit in this patient population as the median PFS was similar between all three arms. OS results were immature at both pre-planned interim analyses presented but the high rate of cross over from the chemotherapy arm to the pembrolizumab arms (48%) may have impacted the OS results. Upon further discussion, pERC noted the separation of the PFS curves beyond the median estimates and questioned the strength of the association between median PFS and magnitude of OS benefit in this, a scenario, where rapid progression is seen in over half of patients regardless of the treatment arm, but followed by a possible and uncertain long duration of response in the active treatment arm. pERC acknowledged that greater emphasis should likely be placed on the long tail of the survival curves and hazard ratios (HR) as an indication for long-term clinical benefit. Throughout pERC's deliberations a variety of opinions were expressed on the evidence supporting net clinical benefit for pembrolizumab in the ipilimumab and BRAF treated setting, where some members did not think the data were mature to allow determination of net clinical benefit. pERC further considered the concordance of results between the KEYNOTE-002 and KEYNOTE-006 studies and the achievement of benefit in a patient population that has already progressed on prior immunotherapy and most members agreed that the strength of the evidence supported the view that pembrolizumab demonstrates activity and clinical benefit in this pre-treated patient population. The committee also agreed that patients in both settings should be treated with the 2mg/kg dose every 3 weeks. This was in alignment with the approved Health Canada dose.

pERC discussed the toxicity profile of pembrolizumab in both patient populations and agreed that the toxicity associated with pembrolizumab was manageable compared to ipilimumab and compared to chemotherapy. The lower incidence of immune-related adverse events, such as colitis and hypophysitis, AE's that are potentially life threatening and difficult to manage in ipilimumab treatment, was noted to be a clinically meaningful advantage.

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 pembrolizumab, in both treatment settings, aligned with patient values.

pERC discussed the cost-effectiveness of pembrolizumab at 2 mg/kg every 3 weeks and concluded that pembrolizumab is not cost-effective when compared to ipilimumab, in patients naïve to ipilimumab treatment and when compared to dacarbazine and BSC, in patients previously treated with ipilimumab and, if BRAF mutation positive, a BRAF inhibitor. pERC accepted the Economic Guidance Panel's (EGP) re-analysis estimates and noted several limitations in the submitted analysis. The biggest impact on the cost-effectiveness estimates was due to differences in the long term extrapolation of the OS data. pERC discussed the short duration of follow up available for both studies and the submitter's assumption that pembrolizumab treatment conferred lasting benefit in a proportion of patients, similar to benefit observed with previous immunotherapies. pERC agreed that there is currently no evidence to support such an assumption concerning the magnitude and duration of long term benefit and accepted the EGP's reanalysis that used alternative data sources to extrapolate long term data. In addition, pERC also noted that assumptions around the time horizon, utility estimates, potential wastage with the introduction of a 100mg vial and potential price reduction of ipilimumab impacted the cost-effectiveness estimates significantly. pERC also considered that pembrolizumab has a high cost and would need a substantial price reduction in order for it to be considered cost-effective. Overall, pERC accepted the EGP's re-analysis estimates and concluded that pembrolizumab is not cost effective relative to ipilimumab, dacarbazine and BSC.

pERC considered the feasibility of implementing a funding recommendation for pembrolizumab. pERC considered that the optimal sequencing of agents in this setting is currently unknown. pERC also noted the absence of evidence on the comparative efficacy and safety of pembrolizumab and nivolumab. 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 noted that the transition from a 50mg to a 100mg vial size will be an important concern for drug wastage. The inclusion of wastage in the economic analysis was seen to have a substantial impact on the ICER in comparison with other parameters. Input from the pCODR Provincial Advisory group (PAG) noted that vial sharing is likely possible in larger treatment centers but likely not possible in smaller centers. pERC noted that the budget impact analysis is sensitive to pembrolizumab's market share, treatment duration, patient weight and number of cases of advanced melanoma and agreed that jurisdictions will need to consider these factors during implementation. While pERC acknowledged that the number of eligible patients in both settings is small, the introduction of pembrolizumab as an additional treatment option is likely to have a significant impact on the budget. pERC noted that there is currently no evidence to suggest any benefit from re-induction with pembrolizumab after disease progression. pERC, however, agreed that re-induction is a clinically reasonable option in some instances which 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 three patient advocacy groups [Canadian Skin Patient Alliance (CSPA), Melanoma Network of Canada (MNC) and Save Your Skin Foundation (SYSF)] and input from pCODR's Provincial Advisory Group.

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of the review is to evaluate the safety and efficacy of pembrolizumab compared with

- ipilimumab as a first-line therapy on patient outcomes in treatment of patients with unresectable or metastatic melanoma (stage III or IV).
- standard of care or best supportive care in the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab therapy and, if BRAF mutation positive, a BRAF inhibitor.

Studies included

The pCODR systematic review included two fully published randomized controlled trials: KEYNOTE-006 006 which randomized patients to pembrolizumab (10 mg/kg every 2 weeks, n=279), pembrolizumab (10 mg/kg every 3 weeks, n=277) and ipilimumab (3 mg/kg every 3 weeks for 4 cycles, n=278). KEYNOTE-002 which randomized patients to pembrolizumab (2 mg/kg IV once every 3 weeks, n=178), pembrolizumab (10 mg/kg IV once every 3 weeks, n=179) or investigators' choice chemotherapy (n=171). pERC discussed the various dosing schedules used in the two trials and agreed that use in the clinical setting should follow the 2mg/kg every 3 weeks schedule. This was in alignment with the approved Health Canada dose.

The pCODR review also provided contextual information through a critical appraisal of a manufacturer provided network meta-analysis (NMA) to estimate the treatment effects of pembrolizumab relative to competing interventions for the treatment of advanced-stage melanoma in patients naïve to treatment with ipilimumab. pERC discussed the limitations identified in this analysis and agreed that some implausible assumptions needed to be made to accept the results of the NMA (eg. equal efficacy between ipilimumab and dacarbazine in one scenario). pERC therefore agreed with the Clinical Guidance Panel and concluded that there was uncertainty in drawing conclusions based on the results of the NMA.

Patient populations: patients naïve to ipilimumab or treated with ipilimumab and, if BRAF mutation positive, a BRAF inhibitor

Baseline characteristics were well balanced between the three treatment arms in both studies. In KEYNOTE-006 the median age of patients was 62 years and 60% were men. The trial only included patients with an ECOG PS of 0 (68-70%) or 1 (30-32%). Patients also had previous BRAF or MEK inhibitor (18%, 16% and 20%) or chemotherapy (13%, 15% and 10%) in the 2-week regimen, 3-week regimen and ipilimumab arms, respectively. Patients were treated with pembrolizumab until disease progression or for a maximum of 24 months or, unacceptable toxicity, investigator decision to discontinue or withdrawal of patient consent.

In KEYNOTE-002 the median age was 61.5 years (range 18 to 89 years) and 61% of patients were male. The majority of patients had an ECOG PS of 0 or 1 (55% and 45%, respectively). All patients had previously been treated with ipilimumab and 26%, 41% and 32% had received 1, 2 or ≥3 previous lines of therapy, respectively. Previous BRAF/MEK inhibitors were also received by all patients with a BRAF mutation. Patients were treated with pembrolizumab until disease progression, unacceptable toxicity, physician decision to discontinue, withdrawal of patient consent or other reasons. Of the 179 patients allocated to the chemotherapy group, 86 (48%) crossed over to pembrolizumab treatment upon disease progression, with 46 randomly assigned to receive 2 mg/kg and 40 to receive 10 mg/kg. pERC noted the high proportion of patients crossing over and agreed that this likely impacted the OS results.

Key efficacy results: Significant improvement in PFS in both studies

The key efficacy outcome deliberated on by pERC were progression free survival and overall survival, the co-primary outcomes for both studies.

Based on a statistically significant and clinically meaningful improvement in 1 year OS and PFS (KEYNOTE-006), pERC concluded that there was a net clinical benefit in patients naive to ipilimumab treatment. One year OS were 74.1% vs. 68.4% vs. 58.2% respectively in the 2-week regimen, 3-week regimen and ipilimumab arms (HR 0.63 95% CI 0.47 – 0.83, p<0.0005 for 2-week regimen and HR 0.69 95% CI 0.52-0.90, p=0.0036 for 3-week regimen when compared to ipilimumab). Median OS was not reached for all arms at the second interim analysis. Median PFS was 5.5 vs. 4.1 months vs. 2.8 months respectively in the 2-week regimen, 3-week regimen and ipilimumab arms (HR 0.58 95% CI 0.46-0.72, p<0.001 for 2-week regimen and HR 0.58 95% CI 0.47-0.72, p<0.001 for 3-week regimen when compared to the ipilimumab arm). The 6-month PFS was 47.3%, 46.4% and 26.5% for the 2-week regimen, 3-week regimen and ipilimumab arms, respectively. Results were also consistent across subgroups for both PFS and OS.

In the ipilimumab treated patients, pERC noted that statistically significant improvements in progression-free survival (PFS) was observed in favour of the pembrolizumab arms at 6 (34%, 38% and 16%) and 9 months (24%, 29% and 8%) in the 2mg, 10mg and chemotherapy arms, respectively. Median PFS was however similar among the three arms, (2.9, 2.9 and 2.7 months for the 2mg, 10 mg pembrolizumab and chemotherapy arms, respectively). pERC emphasized that the effect of pembrolizumab is demonstrated in the shape of the survival curves and HR's which show a persistent separation following rapid progression seen in over half of patients regardless of the treatment arm. Longer term survival data would be required to determine the magnitude of this benefit; however, the proportion of patients in the PFS state at 6 (34%, 38% and 16%) and 9 (24%, 29% and 8%) months demonstrate benefit in the pembrolizumab arms. While OS data was not available as yet, pERC considered that the high rate of crossover (48%) from the chemotherapy arm to the pembrolizumab arms may have impact on the eventual OS results. Overall response rate (ORR) was 21%, 25% and 4% in patients receiving the 2mg, 10mg and chemotherapy, respectively.

Quality of life: Less decline in QoL with pembrolizumab

Quality of life was measured in both studies using EORTC QLQ-30 scale at week 12. QoL decreased in all three arms for both studies, although less of a decline was measured in the pembrolizumab arms compared to the ipilimumab arm for both studies (KEYNOTE-006: -2.3 vs. -2.6 vs. -9.9, respectively in the 2-week regimen, 3-week regimen and ipilimumab arms; KEYNOTE-002: -2.6 vs. -2.55 vs. -9.13, respectively in the 2mg, 10mg and chemotherapy arms). A statistically significant and minimally important decline was however measured for the ipilimumab arm compared to baseline and both pembrolizumab arms. pERC noted that only 458 (54.9%) patients among 834 randomized patients in KEYNOTE-006 participated in the quality of life assessment at both baseline and week 12.

Safety: Not insignificant but manageable toxicity

pERC discussed the safety profile of pembrolizumab in both settings and agreed that the toxicity associated with pembrolizumab was manageable compared to either ipilimumab or chemotherapy. In KEYNOTE-006, rates of grade 3-5 adverse events were similar between the three arms (37.8% vs. 33.2% vs. 36% respectively, in the 2-week regimen, 3-week regimen and ipilimumab arms). Among grade 3-5 AEs attributed to a study drug by investigators, 13.3%, 10.1%, and 19.9% occurred in patients in the three arms, respectively). More patients in the ipilimumab arm experienced withdrawals due to adverse effects than in either pembrolizumab arm (7.2% vs. 10.5% vs. 14.5%, respectively in the 2-week, 3-week and ipilimumab arms). Median time to onset of a grade 3-5 AE was also prolonged in the pembrolizumab arms (59 vs. 64 vs 39.5 days, respectively in the 2-week regimen, 3-week regimen and ipilimumab arms). Grade 3-5 immune related AE's were low in both pembrolizumab arms. The most frequent presumed immune or autoimmune side effects in the pembrolizumab arms were hypothyroidism (10.1%, 8.7% and 2%) and hyperthyroidism (6.5%, 3.2% and 2.3%). Rates of grade 3-5 colitis (1.8%, 2.5% and 7%) and hypophysitis (0.4%, 0.4% and 1.6%) were higher in the ipilimumab arm than the 2-week regimen or 3-week regimen. In KEYNOTE-002, rates of treatment related grade 3-4 adverse events were similar between the pembrolizumab arms and higher in the chemotherapy arm (11% vs. 14% vs. 26% respectively, in the 2mg, 10mg and chemotherapy arms). The rate of all cause grade 3-5 AE's, although not disclosed by the submitter, were similar between arms but numerically higher (by approximately 20% per arm) as compared to treatment related grade 3-4 AE's. There were no 'treatment-related' deaths. Immune-mediated grade 4 or 5 adverse events were not reported. Withdrawals due to grade 3-5 AE's occurred in 9%, 14% and 8% of patients in the three arms respectively. Overall pERC agreed that the toxicity

associated with pembrolizumab was manageable compared to either ipilimumab or chemotherapy. The low incidence of immune related adverse events such as colitis and hypophysitis, AE's that are potentially life threatening and difficult to manage with ipilimumab treatment, was noted to be a clinically meaningful improvement.

Burden and Need: manageable toxicity profile

It is estimated that 6,500 Canadians will be diagnosed with melanoma in 2014, and approximately 1,100 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 and only about 25% of patients with late stage disease surviving to one year.

Vemurafenib and Dabrafenib are BRAF inhibitors that target the V600 mutation and are approved for use in the first line setting. While improvements in RR, PFS, and OS have been demonstrated with BRAF inhibitors, resistance to these targeted therapies ultimately develop and patients experience rapid and often unrelenting disease progression. The immune checkpoint inhibitor, ipilimumab, has shown improved outcomes independent of BRAF status in metastatic melanoma. While median OS with ipilimumab is modest, a proportion of patients treated with ipilimumab (approximately 20%) will experience prolonged disease control lasting many years. As only a minority of patients respond to ipilimumab used in the first or second line setting, treatment options for ipilimumab refractory patients are very limited and patients typically have short survival. Adverse events with ipilimumab are also significant and potentially life threatening, with approximately 15% of patients experiencing grade 3 or 4 immune mediated side effects that require management and monitoring, including risks for severe and fatal events (in particular, colitis).

pERC noted that there is currently no effective standard treatment for metastatic melanoma in patients previously treated with ipilimumab and that there is a need for such therapies. It was discussed that commonly used systemic therapies include dacarbazine, temozolomide and interleukin-2 but there is limited evidence that these treatments improve overall survival. pERC also noted that patients with metastatic melanoma are often younger than those affected by other types of cancer and while this cancer may affect a small patient population, incidence is increasing and it cannot be considered a rare disease. Overall, pERC considered that there is a need for new and effective therapies for patients with unresectable stage III or stage IV metastatic melanoma that provide durable improvements in patient survival and quality of life.

PATIENT-BASED VALUES

Values of patients with metastatic melanoma: QoL, improved survival and manageable toxicity

Patient advocacy group input indicated that there are limited therapies available for patients with advanced melanoma and new effective therapies which extend life expectancy, have reduced toxicity profile and provide improvements in quality of life are very important. Patients indicated that current therapies for advanced melanoma are limited and have significant side-effects that have a negative impact on the quality of life for both the patient and the caregiver. Patients commonly experience pain, scarring, fatigue, disrupted sleep and fear, depression and anxiety as a result of their disease. As related to current treatments, patients experience a myriad of symptoms attributed to treatments including fatigue, insomnia, irritability, flu-like symptoms (chills, sweats, diarrhea, vomiting), headaches and weight loss. In some patients, significant and devastating side effects result in patients deciding not to use the available treatments.

pERC noted that pembrolizumab demonstrated improvements in progression-free survival and in 1 year OS in ipilimumab naïve patients, and was associated with a manageable toxicity profile, including minimal immune related side effects. pERC agreed this aligned with the patient value of having access to effective treatments with a durable survival advantage and manageable toxicity profile. pERC noted that QoL was a patient-expressed value and while it declined in all arms of both studies, the decline was less in patients treated with pembrolizumab and did not reach a clinically meaningful threshold.

Patient values on treatment: less decline in QoL, manageable toxicity profile

Patients indicated an expectation to live longer, with fewer side effects and have a good quality of life or potential lasting response with pembrolizumab. The majority of patients who had experience with

pembrolizumab indicated the drug was well tolerated with few side effects. These side-effects include skin rash, fatigue, weakness, diarrhea, colitis, headaches, while a small proportion reported having no side effects. Overall, side-effects with pembrolizumab were reported to be manageable, and treatment improved their quality of life, with patients indicating that the side effects associated with pembrolizumab were worth the benefits of the treatment. pERC noted that input from patients aligned with the results of both studies included in the pCODR systematic review.

ECONOMIC EVALUATION

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

The pCODR Economic Guidance Panel assessed cost-effectiveness and cost-utility analyses comparing pembrolizumab to ipilimumab in patients with unresectable or metastatic melanoma who are naive to ipilimumab treatment and pembrolizumab to dacarbazine or BSC in patients with unresectable or metastatic melanoma who were previously treated with ipilimumab.

Basis of the economic model: long term extrapolation of OS based on previous ipilimumab data

Costs included were cost of treatment, adverse events management costs, disease management costs and terminal care costs.

Key clinical effects considered in the analysis included PFS, OS and utilities. pERC noted that the estimates for OS were based on extrapolation using data from previous ipilimumab studies and registry data. pERC considered the appropriateness of this data source and noted that there is uncertainty in the assumptions that a proportion of patients will experience a sustained benefit , as was observed with ipilimumab. pERC therefore accepted the EGP's use of alternative data sources to model long term survival and explore the uncertainty in the data that currently has a short follow up period.

Drug costs: High cost of drug, wastage

Pembrolizumab costs $2200.00 per 50mg vial; at the recommended dose of 2mg/kg once every 21 days, the average cost per day in a 28-day course of pembrolizumab is $293.33 and the average cost per 28-day course is $8,213.34. Based on information from the submitter, the vial size of pembrolizumab will transition to a 100mg liquid vial in the near future. The sensitivity analysis conducted by the submitter and the EGP to incorporate the introduction of the 100mg vial is based on the assumption that a 100mg vial costs $4400.00 per vial. pERC noted that wastage had a substantial impact on the cost-effectiveness estimates in the ipilimumab naïve population and agreed that the transition of the vial size to the larger 100mg vial and the associated wastage will need to be considered by jurisdictions upon implementation. pERC also discussed that the submitted analysis and EGP's re-analysis estimates reflect an incremental cost-effectiveness ratio of one high cost drug compared to another high cost treatment, and may artificially give the impression of a reasonable incremental cost difference.

Ipilimumab costs $5,800 and $23,200.00 per 50 mg and 200mg vial, respectively. At the recommended dose of 3 mg/kg every 3 weeks for a 28 day cycle, the cost of ipilimumab is $1160.00 per day and $32,480.00 per 28 day cycle. Ipilimumab is administered for a maximum of 4 cycles.

Dacarbazine costs $200.20 per 600 mg per vial. At the recommended dose of 200–250 mg/m^2 IV days 1-5 every 21-28 days, the cost of dacarbazine is $20.26 – $33.76 per day and $567.230 – $945.39 per 28 day cycle.

Cost-effectiveness estimates: extrapolation of long term data

pERC discussed the Economic Guidance Panel's best estimate of the incremental cost-effectiveness ratio in patients naïve to ipilimumab treatment and patients previously treated with ipilimumab and a BRAF inhibitor. In both settings, pERC accepted the EGP's reanalysis estimates and concluded that pembrolizumab is not cost effective. The main factor influencing the estimates for cost-effectiveness was the long term extrapolation of the OS data. pERC discussed the short duration of follow up available for both studies and the submitter's assumption of lasting benefit with pembrolizumab in a proportion of patients, similar to benefit observed with previous immunotherapies. In the absence of longer term data, pERC was unable to accept this assumption of prolonged benefit and agreed with the EGP's use of

alternative data sources to extrapolate survival in both settings. This adjustment had a substantial impact on the ICER.

In addition, pERC also noted re-analysis altering assumptions around the time horizon, the use of utility estimates standardized to Canadian patients, potential wastage with the introduction of a 100mg vial and potential price reduction of ipilimumab all impacted the cost-effectiveness estimates. Overall, the range of estimates provided by the EGP were wide, particularly in the ipilimumab and BRAF inhibitor treated setting and pERC was unable to determine a reasonable estimate. pERC also supported the EGP's caution in providing a re-analysis estimate for the comparison to BRAF inhibitors in the ipilimumab naïve setting, as there was considerable uncertainty in the results of the submitted network meta-analysis. Considering the uncertainty in the long term benefit of pembrolizumab coupled with the high cost and long duration of treatment (a maximum of 2 years), pERC agreed that a substantial price reduction would be needed for pembrolizumab to be considered cost-effective. Overall, pERC accepted the EGP's re-analysis estimates and concluded that, at the submitted price, pembrolizumab is not cost effective relative to ipilimumab, dacarbazine and BSC.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: Treatment duration, vial size change, sequencing of available therapies

pERC considered the feasibility of implementing a funding recommendation for pembrolizumab. pERC noted PAG's concern about the long duration of therapy with pembrolizumab as compared to other immunotherapies with shorter treatment cycles. pERC noted that the mechanism of action of immunotherapies suggest it is reasonable to investigate whether a shorter treatment exposure period can provide optimal response to patients while minimizing exposure to potential side effects. pERC acknowledged that there is currently no evidence to suggest an optimal duration of treatment with pembrolizumab but agreed that it is important for jurisdictions to prospectively collect this data to manage the budget impact of a funding recommendation. 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 a funding recommendation and noted that the development and implementation of an evidence-informed provincial guideline would help to ensure consistency in drug funding. pERC acknowledged that drug wastage is an important concern for PAG, particularly with the transition of the 50mg vial into a 100mg vial, and noted that this concern was addressed in the EGP's re-analysis. pERC noted the EGP's conclusion that wastage had substantial impact on the ICER particularly in the ipilimumab naïve setting and agreed that jurisdictions will need to consider mechanisms to minimize wastage upon implementation of a funding recommendation. Overall, due the high cost of pembrolizumab, the potential for drug wastage with the larger vial size and the unknown but potentially long duration of treatment, pERC concluded that a substantial reduction in drug price would be required to improve cost-effectiveness to an acceptable level. pERC noted that the submitted budget impact analysis was sensitive to the number of patients eligible for pembrolizumab, treatment duration, patient weight and agreed that jurisdictions will need to consider this during implementation.

Finally, pERC noted the absence of evidence supporting the optimal strategy for the re-induction of patients with pembrolizumab and 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	• Immunomodulatory agent • 50mg vial submitted for review • Recommended dose of 2mg/kg every 3 weeks
Cancer Treated	• Unresectable stage III or stage IV Metastatic Melanoma
Burden of Illness	• 6,500 Canadians diagnosed and ~1100 died of melanoma in 2014, • Unresectable stage III or stage IV melanoma carries a poor prognosis. Median survival of approx. 6 months with about 25% of patients surviving to one year.
Current Standard Treatment	• Ipilimumab • Vemurafenib • Dabrafenib • Trametinib • Dacarbazine • Best supportive care (BSC)
Limitations of Current Therapy	• Limited efficacy with ipilimumab, sustained response in ~20% of patients • Immune related toxicity with ipilimumab • Rapid progression following BRAF inhibitors • Toxicity and limited efficacy of dacarbazine

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. Kelvin Chan, Oncologist
Dr. Matthew Cheung, Oncologist
Dr. Craig Earle, Oncologist
Dr. Allan Grill, Family Physician
Dr. Paul Hoskins, Oncologist
Don Husereau, Health Economist
Dr. Anil Abraham Joy, Oncologist
Karen MacCurdy-Thompson, Pharmacist
Carole McMahon, Patient Member Alternate
Dr. Catherine Moltzan, Oncologist
Jo Nanson, Patient Member
Danica Wasney, Pharmacist

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

- Jo Nanson, who was the designated non-voting patient member alternate for this meeting
- Don Husereau who was excluded from voting due to a conflict of interest
- Dr. Anil Abraham Joy, who was in an observing (non-voting) capacity for orientation to pERC

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 pembrolizumab (Keytruda) for metastatic melanoma through their declarations, seven members had a real, potential or perceived conflict and based on application of the *pCODR Conflict of Interest Guidelines*, one of these members was 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*.

Use of this recommendation

This recommendation from the pCODR Expert Review Committee (pERC) is not intended as a substitute for professional advice, but rather to help Canadian health systems leaders and policymakers make well-informed decisions and improve the quality of health care services. While patients and others may use this Recommendation, it is for informational and educational purposes only, and should not be used as a substitute for the application of clinical judgment respecting the care of a particular patient, for professional judgment in any decision-making process, or for professional medical advice.

Disclaimer

pCODR does not assume any legal liability or responsibility for the accuracy, completeness or usefulness of any information, drugs, therapies, treatments, products, processes, or services disclosed. The information is provided "as is" and you are urged to verify it for yourself and consult with medical experts before you rely on it. You shall not hold pCODR responsible for how you use any information provided in this report. This document is composed of interpretation, analysis, and opinion on the basis of information provided by pharmaceutical manufacturers, tumour groups, and other sources. pCODR is not responsible for the use of such interpretation, analysis, and opinion. Pursuant to the foundational documents of pCODR, any findings provided by pCODR are not binding on any organizations, including funding bodies. pCODR hereby disclaims any and all liability for the use of any reports generated by pCODR (for greater certainty, "use" includes but is not limited to a decision by a funding body or other organization to follow or ignore any interpretation, analysis, or opinion provided in a pCODR document).