PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Pembrolizumab (Keytruda) for Metastatic Melanoma

November 16, 2015

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1 GUIDANCE IN BRIEF

1.1 Background

The purpose of this review is to evaluate the safety and efficacy of pembrolizumab:

- compared to ipilimumab as a first-line therapy on patient outcomes in treatment of patients with unresectable or metastatic melanoma (stage III or IV).
- compared to 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.

The review for pembrolizumab was first initiated assessing pembrolizumab in patients with disease progression following ipilimumab therapy. Based upon a request from the pCODR Provincial Advisory Group (PAG) expressing a need for pembrolizumab in the first line setting, an assessment was made for the expansion of the review scope to include the first line indication. This assessment resulted in the scope of the review being expanded to include the first line population.

Pembrolizumab inhibits the PD-1 pathway in antigen presenting or tumor cells which reactivates tumour-specific cytotoxic T lymphocytes and its antitumor immunity. The Health Canada recommended dose of pembrolizumab is 2 mg/kg administered intravenously over 30 minutes every 3 weeks, taken until disease progression or unacceptable toxicity.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

1.2.1 A) Previously untreated with ipilimumab

One randomized controlled trial (RCT), KEYNOTE-006 randomised 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).

Baseline characteristics were well balanced between the three treatment arms. The median age of patients was 62 years and 60% were men. The majority of patients included in the study had an ECOG PS 0 (68-70%) while the remainder had an ECOG PS of 1 (30-32%). The trial only included patients with a PS of 0-1. 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 for 24 months or until disease progression, unacceptable toxicity, investigator decision to discontinue or withdrawal of patient consent.

Efficacy

KEYNOTE-006 demonstrated a statistically significant improvement in overall survival (OS) rates and progression-free survival (PFS), the co-primary endpoints of the study, both in favour of the pembrolizumab arms.

The 1-year OS rate was 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). At the time of the second interim analysis, median OS was not reached in any

treatment arm. Median PFS were 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 rate was 47.3%, 46.4% and 26.5% for the 2-week regimen, 3-week regimen and ipilimumab arms, respectively. Subgroup analysis favoured the pembrolizumab arms for most pre-specified subgroups in PFS and OS. The overall response rate (ORR) was 33.7%, 32.9% and 11.9% in patients taking pembrolizumab 2 weeks regimen, 3-week regimen and ipilimumab arms, respectively.

Quality of life was measured using the EORTC QLQ-30 scale at week 12. Only 458 (54.9%) patients among 834 randomized patients participated in the quality of life assessment at both baseline and week 12. Results showed that QoL decreased in all three arms, although less of a decline was measured in the pembrolizumab arms compared to the ipilimumab arm (–2.3 vs. -2.6 vs. -9.9, respectively in the 2-week regimen, 3-week regimen and ipilimumab arms). A melanoma specific QoL module is still being developed[47]. However, the minimum clinically important differences (MCIDs) for EORTC QLQ-C30 have been established in other types of cancer[48]. A mean difference of 5 to 10 in global health score was considered as small change.

Harms

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 AE 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 that in either pembrolizumab arms (7.2% vs. 10.5% vs. 14.5%, respectively in the 2-week regimen, 3-week regimen 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 arms. The most frequent presumed immune or autoimmune side effects on pembrolizumab q2 week and q3 week were: hypothyroidism (10.1% and 8.7%), hyperthyroidism (6.5% and 3.2%). Rates of grade 3-5 colitis (1.8%, 2.5% and 7%) and hypophysitis (0.4%, 0.4% and 1.6%) were low in the 2-week regimen, 3-week regimen and ipilimumab arms, respectively.

1.2.1 B) Patients previously treated with ipilimumab, and if BRAF mutation positive, a BRAF inhibitor

One randomized controlled trial, KEYNOTE-002, randomized patients to 2 mg/kg IV pembrolizumab once every 3 weeks (n=178), 10 mg/kg IV pembrolizumab once every 3 weeks (n=179) or investigators' choice chemotherapy (n=171).

Baseline characteristics were well balanced between treatment arms. 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. BRAF mutation was found in 23% of all patients with 25% of all patients having previously been treated with a BRAF or MEK inhibitor. Of the 179 patients allocated to the chemotherapy group, 86 (48%) crossed over to pembrolizumab treatment after confirmed disease progression on chemotherapy, with 46 randomly assigned to receive 2 mg/kg and 40 to receive 10 mg/kg. Patients were treated with pembrolizumab until disease progression, unacceptable toxicity, physician decision to discontinue, withdrawal of patient consent or other reasons.

Efficacy

KEYNOTE-002 demonstrated a statistically significant improvement in progression-free survival (PFS) rates at 6 and 9 months in favour of the pembrolizumab arms, the co-primary endpoints of the study. At 6 months PFS rates were 34%, 38% and 16% and at 9 months 24%, 29% and 8% in the 2 mg, 10 mg and chemotherapy arms, respectively. The hazard ratio for death or disease progression (95% CI) was 0.57 (0.45-0.73, p<0.0001) for 2 mg/kg pembrolizumab and 0.50 (0.39-0.64, p<0.0001) for 10 mg/kg pembrolizumab compared with chemotherapy group. Median PFS was however similar among the three arms. Data on OS, a co-primary endpoint, was not analysed as the pre-specified number of deaths had not been reached at the interim analysis. Final overall survival will be assessed after 370 deaths. The differences between pembrolizumab arms and chemotherapy in OS will likely to be underestimated due to the high crossover rate (48%) from chemotherapy to pembrolizumab after disease progression. Overall response rate (ORR) was 21%, 25% and 4% in patients receiving the 2mg, 10mg and chemotherapy, respectively.

Quality of life was measured using the EORTC QLQ-30 scale at week 12. Results showed that QoL decreased in all three arms. This decline was less in the pembrolizumab arms compared to the ipilimumab arm (–2.6 vs. -2.55 vs. -9.13, respectively in the 2mg, 10mg and chemotherapy arms). A melanoma specific QoL module is still being developed[47]. However, the minimum clinically important differences (MCIDs) for EORTC QLQ-C30 have been established in other types of cancer[48]. A mean difference of 5 to 10 in global health score was considered as small change.

Harms

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, while similar between arms, were numerically higher for all three arms (by approximately 20% per arm) as compared to treatment related grade 3-4 AE's. There were no 'treatment-related' deaths.[45] Withdrawals due to grade 3-5 AE's occurred in 9%, 14% and 8% of patients in the three arms respectively. Most common grade 3-4 treatment-related adverse events on pembrolizumab 2mg/kg were fatigue, edema, and myalgia (1% each); and hypopituitarism, colitis, diarrhea, low appetite, hyponatremia, pneumonitis (1% each) for pembrolizumab 10mg/kg. Treatment discontinuation due to treatment-related adverse events occurred in (3%, 7%, and 6% of patients in the 2mg, 10mg and chemotherapy arms, respectively). There were no treatment related deaths.

1.2.2 Additional Evidence

pCODR received input on pembrolizumab for both ipilimumab naïve and ipilimumab refractory patients from 3 patient advocacy groups, [Canadian Skin Patient Alliance (CSPA), Melanoma Network of Canada (MNC) and Save Your Skin Foundation (SYSF)]. Provincial Advisory group input was obtained from eight of the nine provinces participating in pCODR.

- In addition, one supplemental question was identified during development of the review protocol as relevant to the pCODR review of Pembrolizumab and is discussed as supporting information: Critical appraisal of a manufacturer provided a 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.

1.2.3 Interpretation and Guidance

Burden of Illness and Need

Although the number of patients developing melanoma is small compared to breast cancer or lung cancer, melanoma remains the number one cause of cancer death in women age 25 to 35, and causes a disproportionate number of years of life lost. Unresectable stage III or stage IV melanoma carries a poor prognosis. Single agent BRAF and MEK inhibitors have resulted in improved outcomes as compared to standard chemotherapy, however resistance to these agents typically develops within 6 to 8 months. The immune checkpoint inhibitor Ipilimumab results in improvements in the prognosis of metastatic melanoma, but only a minority of patients respond and survival is poor in non-responders; overall only a small proportion will experience long term survival. Most patients with metastatic melanoma succumb to the disease, therefore more effective treatments are needed.

Effectiveness

For patients that were ipilimumab naive, based on the results of the KEYNOTE-006 study, statistically significant improvements in six months PFS rates, one-year estimates of OS and response rates were observed all favoring the 2 and 3 week pembrolizumab regimens over ipilimumab. PFS and OS results for patients on the 2 week regimen arm were also consistent in the subgroup of patients that were previously treated with a BRAF or MEK inhibitor. Quality of life questionnaire (EORTC QLQ-C30) also favored pembrolizumab treated patients over ipilimumab. In patients that were ipilimumab refractory, based on the interim results of the KEYNOTE-002 study, statistically significant improvements in 6 and 9 months PFS, overall response rate and quality of life was demonstrated in favour of both pembrolizumab arms vs chemotherapy.

Safety

Serious and life threatening auto-immune side effects are a major concern with immune check-point inhibitors. Side effect profile shows that pembrolizumab is well tolerated with a relatively low rate of serious immune related side effects which can be managed with well-defined management algorithms. The rate of grade 3-5 side effects was lower on pembrolizumab than ipilimumab for both ipilimumab naïve and ipilimumab treated patients. Hypophysitis and colitis are of major clinical concern and rates were lower on pembrolizumab than ipilimumab. This is of major importance to patients and clinicians.

1.3 Conclusions

The Clinical Guidance Panel concluded that there is an overall net clinical benefit to pembrolizumab in both ipilimumab naïve and ipilimumab refractory unresectable stage III-IV melanoma. This conclusion is based on one well-conducted randomized controlled trial demonstrated a clear statistically significant benefit in 1 year overall survival rate, progression free survival, and response rate in favour of pembrolizumab vs ipilimumab in ipilimumab naïve patients and one randomized phase II trial showed statistically significant benefit in 6 and 9 month PFS rates and RR in favor of pembrolizumab vs investigator choice of chemotherapy in ipilimumab refractory patients. The magnitude of benefit in both ipilimumab naïve and refractory patients in terms of RR, PFS, and OS are clinically meaningful and reflect major improvements in disease management.

The Clinical Guidance Panel also considered that from a clinical perspective:

- Serious and life threatening auto-immune side effects are a major concern with immune check-point inhibitors. The rate of grade 3-5 side effects was lower on pembrolizumab than ipilimumab. Hypophysitis and colitis are of major clinical concern and rates were lower on pembrolizumab than ipilimumab.
- In general the side effect profile shows that pembrolizumab is well tolerated with a relatively low rate of serious immune related side effects which can be managed with well-defined management algorithms. This is of major importance to patients and clinicians.
- Network meta-analysis NMA is a tool used to make indirect comparisons (cross trial comparisons). The quality of evidence comparing pembrolizumab to BRAF inhibitors in the submitted NMA is low, as a result the submitted NMA should not be used to assess the relative efficacy or cost-effectiveness between pembrolizumab and MEK/BRAF inhibitors.
- The CGP is unaware of any evidence to guide optimal sequencing of immune checkpoint drugs (CTLA-4 and PD1 inhibitors) and BRAF/MEK inhibitors. BRAF mutated patients will receive available BRAF/MEK drugs at some point during their therapy, either before or after immune checkpoint inhibitors, thus BRAF/MEK drugs were excluded as a comparator in economic modeling.
- The CGP is unaware of any data that would allow reliable comparison of the clinical impact of pembrolizumab vs nivolumab.
- The optimal duration of pembrolizumab is unknown. In the current studies pembrolizumab was continued until disease progression, unacceptable toxicity, patient/physician decision, or in KEYNOTE-006 until 24 months of therapy. The efficacy of shorter durations of therapy is currently unknown, and will hopefully be addressed in future clinical trials.
- The Health Canada approved dose of pembrolizumab is 2mg/kg every 3 weeks which CGP also endorses. Of note, the discussion section of the KEYNOTE-006 publication states that multiple trials have shown a lack of a dose-response relationship with pembrolizumab.
- In melanoma, there is insufficient evidence to recommend the measurement of PD-L1 to guide the use of pembrolizumab. In addition, there is lack of consistency in the assays and cut-offs used to assess PD- L1.

2 CLINICAL GUIDANCE

This Clinical Guidance Report was prepared to assist the pCODR Expert Review Committee (pERC) in making recommendations to guide funding decisions made by the provincial and territorial Ministries of Health and provincial cancer agencies regarding pembrolizumab for metastatic melanoma. The Clinical Guidance Report is one source of information that is considered in the *pERC Deliberative Framework*. The *pERC Deliberative Framework* is available on the pCODR website, www.cadth.ca/pcodr.

This Clinical Guidance is based on: a systematic review of the literature regarding pembrolizumab conducted by the Melanoma Clinical Guidance Panel (CGP) and the pCODR Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group; and supplemental issues relevant to the implementation of a funding decision.

The systematic review and supplemental issues are fully reported in Sections 6 and 7. Background Clinical Information provided by the CGP, a summary of submitted Patient Advocacy Group Input on pembrolizumab and a summary of submitted Provincial Advisory Group Input on pembrolizumab are provided in Sections 3, 4 and 5 respectively.

2.1 Context for the Clinical Guidance

2.1.1 Introduction

Malignant melanoma is one of the most aggressive forms of skin cancer. Surgery is the cornerstone treatment at early stages of disease. However, treating unresectable or metastatic melanoma remains a challenge as the response rate to systemic therapy is low. The treatments available for unresectable or metastatic melanoma in Canada vary from province to province. Generally, treatment options include immunotherapy (ipilimumab), chemotherapy, interferon-alpha or IL-2 or target therapy (BRAF inhibitors or MEK inhibitors). Response with immunotherapy is limited to 15-20% of patients and associated with significant and potentially life threatening immune related side effects in approximately 15% of patients, requiring management and monitoring, including risks for severe and fatal events (ie colitis). In BRAF mutant patients, resistance to targeted therapies (BRAF/MEK inhibitors) ultimately develops and patients experience rapid and often unrelenting disease progression. Treatment options are also limited for patients who show progression after immunotherapy and/or target therapy.

Pembrolizumab has a Health Canada indication for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab therapy and, if BRAF V600 mutation positive a BRAF or MEK inhibitor as per proposed indication. The recommended dose of pembrolizumab is 2 mg/kg administered intravenously over 30 minutes every 3 weeks. The product monograph recommended patients take pembrolizumab until disease progression or unacceptable toxicity.

Pembrolizumab inhibits the PD-1 pathway in antigen presenting or tumor cells which reactivates tumour-specific cytotoxic T lymphocytes and its antitumor immunity.

2.1.2 Objectives and Scope of pCODR Review

The objectives of this review were:

1. To evaluate the effect of pembrolizumab alone as first-line therapy on patient outcomes compared to ipilimumab in treatment of patients with unresectable or metastatic melanoma (stage III or IV).

2. To evaluate pembrolizumab alone on patient outcomes compared to standard care or best supportive care in treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab therapy and, if BRAF mutation positive, a BRAF or MEK inhibitor.

The review for pembrolizumab was initiated as a second line review only, assessing pembrolizumab alone on patient outcomes compared to standard care or best supportive care in treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab therapy. In accordance with the pCODR Procedures, the pCODR Provincial Advisory Group (PAG) requested additional information on pembrolizumab (Keytruda) which extend beyond the submitted scope of the review. The request by PAG expressed a need for pembrolizumab in ipilimumab naïve patients. Revision of review scope may be considered by pCODR in very limited instances, based on jurisdictional input, feasibility to conduct the revised review and clinical importance. All three criteria for scope modification were met in this case and the scope of the review was expanded to include patient naïve to ipilimumab treatment.

See section 6.2.1 for details on the review protocol.

2.1.3 Highlights of Evidence in the Systematic Review

This section describes highlights of evidence in the systematic review. Refer to section 2.2 for the clinical interpretation of this evidence and section 6 for more details of the systematic review.

2.1.3A Previously untreated with Ipilimumab

The pCODR systematic review included one randomized controlled trial, KEYNOTE-006, a three armed study which compared pembrolizumab 10 mg/kg every 2 weeks and pembrolizumab 10 mg/kg every 3 weeks to ipilimumab. The trial enrolled patients who were 18 years of age or older with histologically confirmed, unresectable stage III or IV melanoma who had received no more than one previous systemic therapy for advanced disease. Patients might or might not have been treated with BRAF inhibitor or MEK inhibitor. Eligible patients were randomized in 1:1:1 ratio to the three treatment arms. Table 6.2 in Section 6.3.2.1 summarizes the trial characteristics of KEYNOTE-006.

Patients were treated with pembrolizumab for 24 months or until disease progression, unacceptable toxicity, investigator decision to discontinue or withdrawal of patient consent. Patients who completed 2 years of treatment were monitored for an additional 24 months and could be eligible for re-induction, upon disease progression, with pembrolizumab to a maximum of 12 months. There was no information available on whether any patients received pembrolizumab as an induction treatment after 2 years of treatment followed by progression. Ipilimumab was taken for 4 cycles (3mg/kg every 3 weeks for 4 cycles) or until disease progression, the onset of unacceptable toxicity, an investigator's decision to discontinue or withdrawal of patient consent.

Baseline characteristics were well balanced between the treatment arms. KEYNOTE-006 randomized 834 patients. The median age of patients was 62 years. Male patients contributed to 60% of the population. Over 80% of patient had been classified as positive for PD-1 expression. BRAF mutation was found in 36% of the patients and 18% of patients had been treatment with BRAF or MEK inhibitors.

The study had PFS and OS as co-primary endpoints. Both pembrolizumab arms showed significant benefit compared to ipilimumab in terms of overall survival and progression-free survival. Similar effect was observed in various subgroups. Table 6.2 summarizes relevant outcomes of KEYNOTE-006.

Quality of life was assessed by the European Organization for Research and Treatment of Cancer QLQ-C30 (EORTC QLQ-30) at week 12. Only 458 (54.9%) patients among 834 randomized patients participated in the quality of life assessment at both baseline and week 12. Results showed that QoL decreased in all three arms, although less of a decline was measured in the pembrolizumab arms compared to the ipilimumab arm (Table 2.1).

Fewer patients from pembrolizumab arms had to withdraw due to adverse effect [20/278 (7.2%) in Q2W arm, 29/277 (10.5%) in Q3W arm] compared with ipilimumab [37/256 (14.5%)]. Statistics comparing pembrolizumab and ipilimumab in withdrawal due to adverse effect was not provided. Both pembrolizumab regimens provided significant benefit in terms of the hazard ratio for experiencing at least one grade 3-5 adverse event compared with ipilimumab [Q2W HR: 0.59 (0.43, 0.80), p<0.001; Q3W HR: 0.52 (0.38, 0.72), p<0.001]. Percentage of patients experienced at least one drug related adverse effect was similar between treatment arms (76.0% in Q2W, 72.9% in Q3W, 73.0% in ipilimumab).

Most common treatment related adverse events of any grade on pembrolizumab were fatigue, diarrhea, rash and pruritus. Less than 1 % of patients experienced these adverse effects at grade 3 or 4 severity except for diarrhea (2.5% and 1.1%). For ipilimumab most common adverse events were pruritus, diarrhea, fatigue and rash. Less than 1 % of patients experienced these adverse effects at grade 3 to 5 severity except for diarrhea (3.1%) and fatigue (1.2%).

Table 2.1 Summary of key outcomes in KEYNOTE-006

	Pembrolizumab every 2 weeks	Pembrolizumab every 3 weeks	Ipilimumab
1-year overall survival (n/N)	207/279 (74.1%)	189/277 (68.4%)	162/278 (58.2%)
Hazard ratio (95%CI) for death comparing pembrolizumab and ipilimumab	0.63 (0.47, 0.83) p<0.0005	0.69 (0.52, 0.9) p=0.0036	---
6-month progression free survival (n/N)	132/279 (47.3%)	129/277 (46.4%)	74/278 (26.5%)
Hazard ratio for disease progression comparing pembrolizumab and ipilimumab	0.58 (0.46, 0.72) p<0.001	0.58 (0.47, 0.72) p<0.001	---
Quality of life (EORTC QLQ-C30, least square mean of overall score change from baseline (95% CI)	-2.3 (-5.21, 0.62)	-2.6 (-5.44, 0.23)	-9.9 (-13.01, -6.72)
Difference of least square mean score between pembrolizumab and ipilimumab	7.6 (3.40, 11.75) p=0.0004	7.3 (3.15, 11.38) p=0.0006	---
Overall response rate (n/N)	94/279 (33.7%)	91/277 (32.9%)	33/278 (11.9%)
Estimated percentage difference in overall response rate between pembrolizumab and ipilimumab	16.1% (7.8, 24.5) p<0.001	17.2% (9.5-25.6) p<0.001	---

The Methods team noted that KEYNOTE-006 has not yet been completed. The assessment of bias was based on the protocol and data from the two interim analyses.

Details regarding randomization and allocation concealment were described in the protocol of KEYNOTE-006. The steps taken to ensure the integrity of randomization and allocation concealment were adequate to minimize the risk of selection bias. KEYNOTE-006 was an open label trial therefore assessment of detection bias was not applicable. The risk of performance bias was also low because steps were taken to ensure the blinding of the independent radiologic reviewers. In addition, risk of attrition bias and reporting bias were also low because efficacy outcomes were analyzed according to intention to treat (ITT) principle and data of all relevant outcomes were submitted to the methods team. Overall, KEYNOTE-006 has low risk of bias.

2.1.3B Patients previously treated with ipilimumab and, if BRAF mutation positive, a BRAF or MEK inhibitor

The pCODR systematic review also included one randomized controlled trial in the second-line review. KEYNOTE-002 enrolled patients with advanced melanoma who have disease progression within 24 weeks of receiving ≥ 2 ipilimumab doses and, if BRAF mutation positive, a BRAF or MEK inhibitor. Eligible patients were randomized to 2 mg/kg IV pembrolizumab once every 3 weeks, 10 mg/kg IV pembrolizumab once every 3 weeks or investigators' choice chemotherapy. Patients and clinicians were blinded to the dosage of pembrolizumab but not blinded to the allocation of pembrolizumab or chemotherapy. The independent review panel was blinded to the allocation of treatment and the dosage of treatment. The 2 mg/kg pembrolizumab dose is the only recommended dose currently approved by Health Canada. Table 6.3 in Section 6.3.2.1 summarizes the trial characteristics of KEYNOTE-002.

KEYNOTE-002 randomized 540 patients. The overall median age was 61.5 years (range 18 to 89 years). Male patients contributed to 61% of the population. ECOG performance status was similar between treatment arms (ECOG PS 0 and 1 in55% and 45%, respectively). BRAF mutation was found in 23% of all patients and 25% of all patients had previously been treated with a BRAF or MEK inhibitor. There was no significant difference in the percentages of patient having BRAF mutation between treatment arms.

KEYNOTE-002 has not yet been completed. The primary outcomes were overall survival and progression free survival (PFS). Overall survival was not analyzed at the interim analysis. The final overall survival analysis was planned after 370 deaths. The estimate for overall survival, if unadjusted, would likely to be underestimated due to the high crossover rate from chemotherapy to pembrolizumab after disease progression. As for August 25th of 2015, the pre-specified number of deaths had not been reached yet. Both pembrolizumab arms showed significant benefit compared to chemotherapy in terms of PFS rates at 6 and 9 months. Median PFS was not different between the three arms (2.9, 2.9 and 2.7 months for the 2mg, 10 mg pembrolizumab and chemotherapy arms, respectively). Table 2.2 summarizes the relevant outcomes of KEYNOTE-002.

Quality of life was assessed by the European Organization for Research and Treatment of Cancer QLQ-C30 (EORTC QLQ-30) at week 12. A negative change in score from baseline would indicate a decrease in the quality of life. In summary, the decrease in quality of life during treatment was significantly less in pembrolizumab arms compared with chemotherapy arms.

There was no difference in withdrawal due to grade 3-5 adverse event between the pembrolizumab arms and chemotherapy arm. Odds ratio (95% CI) when compared with chemotherapy was 1.20 (0.56, 2.58) in 2 mg/kg arm and 1.97 (0.97, 4.00) in 10 mg/kg arm. The number of patients experienced at least one adverse effect was 122/178 (68.5 %) in 2

mg/kg arm, 133/179 (74.3%) in 10 mg/kg arm and 138/171 (80.7%) in chemotherapy arm. The most common adverse effects were fatigue, pruritus, nausea and decreased appetite.

Table 2.2 Summary of key outcomes in KEYNOTE-002

	Pembrolizumab 2 mg/kg	Pembrolizumab 10 mg/kg	Chemotherapy
6-month progression free proportion	34%	38%	16%
9-month progression free proportion	24%	29%	8%
Hazard ratio (95% CI) of death or disease progression comparing pembrolizumab and chemotherapy	0.57 (0.45, 0.73) p<0.0001	0.50 (0.39, 0.64) p<0.0001	---
Quality of life (EORTC QLQ-C30, least square mean of overall score change from baseline (95% CI)	-2.6 (-6.15, 0.96)	-2.55 (-5.99, 0.89)	-9.13 (-12.86, -5.39)
Difference of LS mean score between pembrolizumab and chemotherapy	6.53 (1.53, 11.53) p=0.011	6.57 (1.65, 11.50) p=0.009	---
Overall response rate (n/N)	38/180 (21%)	46/181 (25%)	8/179 (4%)
Difference in overall response between pembrolizumab and chemotherapy (95% CI)	13% (7%, 21%) p<0.0001	18% (11%, 27%) p<0.0001	---

AsKEYNOTE-002 has not yet been completed, the assessment of bias was based on the protocol and data from the interim analysis.

Details regarding randomization and allocation concealment were described in the protocol of KEYNOTE-002. The steps taken to ensure the integrity of randomization and allocation concealment were adequate to minimize the risk of selection bias. The risk of performance bias was also low because steps were taken to ensure the blinding of the independent radiologic reviewers. In addition, risk of attrition bias and reporting bias were also low because efficacy outcomes were analyzed according to ITT principle and data of all relevant outcomes were submitted to the methods team. Overall, the Methods team judged that KEYNOTE-002 has low risk of bias.

2.1.4 Comparison with Other Literature

The pCODR Clinical Guidance Panel and the pCODR Methods Team did not identify other relevant literature providing supporting information for this review.

2.1.5 Summary of Supplemental Questions

Critical appraisal of a manufacturer provided a 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.

Considering that direct comparative data for pembrolizumab vs. ipilimumab (KEYNOTE-006) and pembrolizumab vs. chemotherapy (KEYNOTE-002) are available, the only relevant comparison in this NMA that might have contributed to the pCODR review was that between pembrolizumab and the BRAF inhibitors. After evaluating the evidence presented in this NMA, the methods team concluded that the evidence, which was considered to of low quality, did not provide any addition information that might impact the results of the current review.

Details of the critical appraisal of the NMA are presented in Section 7

2.1.6 Other Considerations

See Section 4 and Section 5 for a complete summary of patient advocacy group input and Provincial Advisory Group (PAG) Input, respectively.

Patient Advocacy Group Input

From a patient perspective, there are both mental and physical impact for patients with metastatic melanoma. Respondents commonly experience pain, scarring, fatigue, disrupted sleep and fear, depression and anxiety. Patient Advocacy Groups 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. Respondents believe that this new therapy will give them hope. With pembrolizumab, there is the expectation that they may live longer, with few side effects and have a good quality of life or potential lasting response. The majority of respondents who have experienced with pembrolizumab indicated the drug was well tolerated with few side effects. These side-effects include skin rash, fatigue, weakness, diarrhea, colitis, headaches. A small number of respondents indicated having experienced no side effects with the treatment. All respondents stated that side-effects to treatment were manageable, and that pembrolizumab improved their quality of life. Respondents also reported tumour shrinkage and for some full disappearance of growth. Respondents also reported liking the dosing profile for pembrolizumab and feel that it is more palatable than other treatments. They expect that the 21-day dosing period will provide some stability in their lives, knowing that they will feel lousy for 21 days and then feel normal afterwards; and the treatment time is also easier to handle – three hours in the clinic versus four-five hours for other treatments.

PAG Input

Input was obtained from eight of the nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation of pembrolizumab for metastatic melanoma. Due to the scope expansion, PAG was provided the opportunity to revise input accordingly.

Clinical factors:

- Therapeutic gap for patients who are ipilimumab refractory and/or resistant to treatment with BRAF inhibitors +/- MEK inhibitors
- Treatment algorithm and/or sequencing with recently available drugs
- Long-term safety and efficacy compared to other treatments available

Economic factors:

- Drug wastage
- Cost-effectiveness compared to other treatments available

2.2 Interpretation and Guidance

Burden of Illness and Need for Improved Therapies

It is estimated that 6,500 Canadians will be diagnosed with melanoma in 2014, and approximately 1050 patients will die of melanoma in 2014. The majority of patients will present with early stage disease and be cured by surgery but those who present with advanced disease or who subsequently relapse, the prognosis remains poor. Although the number of patients developing melanoma is small compared to breast cancer or lung cancer, melanoma remains the number one cause of cancer death in women age 25 to 35, and causes a disproportionate number of years of life lost. Unresectable stage III or stage IV melanoma carries a poor prognosis, and up until very recently the median survival was 6.2 months and only 25.5% of patients survived to one year. There is no evidence that standard cytotoxic chemotherapy improves overall survival or quality of life in metastatic melanoma and objective response rate is low, in the 7-10% range. Single agent BRAF and single agent MEK inhibitors have resulted in improved outcomes as compared to standard chemotherapy for the 40-50% of patients with BRAF mutations, however resistance to these agents typically develops within 6 to 8 months. Immune checkpoint inhibitor Ipilimumab (cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) results in improvements in the prognosis of metastatic melanoma, but only a minority of patients respond and survival is poor in non-responders; overall only a small proportion will experience long term survival. Most patients with metastatic melanoma succumb to the disease, more effective treatments are needed.

Effectiveness

Pembrolizumab in ipilimumab naïve patients

KEYNOTE-006 was an open-label, randomized, phase 3 trial of first and second line therapy in ECOG 0/1 unresectable stage III or IV melanoma who were ipilimumab naive. The trial included 834 patients of which 65% were receiving their first line of systemic therapy. Patients were randomized 1:1:1 to pembrolizumab 10mg/kg every 2 weeks or every y 3 week schedule, or to ipilimumab 3mg/kg every 3weeks for 4 cycles (Ipilimumab). Median age was 62, and 80.5% were classified as PD-L1 positive (at least 1% of tumor cells with membranous staining.) Approximately 36% of patients were BRAF mutation positive and 18% had prior treatment with BRAF/MEK inhibitors, and 9% of patients had brain metastasis. Results were analyzed on an ITT basis and independent radiologic reviewers were blinded to treatment group.

The efficacy of the two pembrolizumab regimens appeared the same, which the authors note is in keeping with prior studies which have demonstrated a lack of a dose-response relationship with this drug. (Of note, this study used 10mg/kg and the dose approved by Health Canada is 2mg/kg q 3 weeks.) Six months PFS (47.3% vs 46.4% vs 26.5%), one-year estimates of OS (74.1% vs 68.4% vs 58.2%), and RR (33.7%, 32.9%, and 11.9%) all favored pembrolizumab every 2 weeks and every 3 weeks respectively over ipilimumab. 6 months PFS HR were 0.58 $p<0.001$ for both every 2 and every 3 week pembrolizumab vs ipilimumab. HR for death for pembrolizumab every 2 weeks vs ipilimumab was 0.63 $p<0.0005$. HR for death for pembrolizumab every 3 weeks vs ipilimumab was 0.69 $p=0.0036$.
For patients receiving pembrolizumab every 2 weeks as compared to ipilimumab, improvements were seen for both PFS and OS in the first and second line setting. In the first line setting PFS HR 0.55 (0.42-0.72) and OS HR 0.58 (0.41-0.84). In the second line setting PFS HR 0.63 (0.44-0.90) and OS HR 0.62 (0.40-0.98). For pembrolizumab every 3 week vs ipilimumab similar improved HRs were also seen for PFS and OS in the first line setting, and a strong trend towards improvement in the second line setting.

Safety from KEYNOTE-006

For Pembrolizumab every 2 weeks, every 3 weeks and ipilimumab grade 3 to 5 adverse events attributed by investigators to study drug were 13.3%, 10.1%, and 19.9% and the rates of permanent discontinuation of drug due to treatment related adverse advent were 4.0%, 6.9% and 9.4%. One death was attributed to ipilimumab (diarrhea related metabolic abnormalities leading to cardiac arrest in a patient with type 2 diabetes). Most common treatment related adverse events of any grade on pembrolizumab every 2 week and every 3 week were: fatigue (20.9% and 19.1%), diarrhea (16.9% and 14.4%), rash (14.7% and 13.4%), pruritus (14.4% and 14.1%) with grade 3 or 4 events occurring in <1% of patients except diarrhea (2.5% and 1.1%). For ipilimumab most common adverse events were: pruritus (25.4%), diarrhea (22.7%), fatigue (15.2%), rash (14.5%) which were grade 3 to 5 in <1% of patients except diarrhea (3.1%) and fatigue (1.2%).

The most frequent presumed immune or autoimmune side effects of any grade on pembrolizumab every 2 week and every 3 week were: hypothyroidism (10.1% and 8.7%), hyperthyroidism (6.5% and 3.2%). Grade 3 to 4 events reported in >1% of pembrolizumab patients were colitis (1.4% and 2.5%), hepatitis (1.1% and 1.8%). The ipilimumab group had an 8.2% rate of colitis and grade 3 to 4 events in >1% of patients: colitis (7%), hypophysitis (1.6%). In addition, quality of life questionnaire (EORTC QLQ-C30) favored pembrolizumab treated patients over ipilimumab.

Patients previously treated with ipilimumab and, if BRAF mutation positive, a BRAF or MEK inhibitor

KEYNOTE-002 was a randomized phase 2 trial that randomized (1:1:1) to two doses of every 3 weekly pembrolizumab 2mg/kg (the Health Canada recommended and approved dose), or 10mg/kg vs investigator choice of chemotherapy in ipilimumab refractory patients (and received prior BRAF/MEK inhibitor if BRAF mutated (25% of patients)). Patients and investigators were blinded to dose of pembrolizumab but not to pembrolizumab vs chemotherapy allocation. The independent review panel was blinded to therapy received. Patients were ECOG 0 or 1 and median age was 61.5 years. The trial is ongoing and interim analysis has reported on PFS. The final analysis will have OS as the primary endpoint. Interim analysis showed improvements in 6months PFS, 9 months PFS, RR and QLQ for pembrolizumab vs chemotherapy. For pembrolizumab 2mg/kg, 10mg/kg and chemotherapy the 6months PFS were (34%, 38% and 16%) and 9months PFS were (24%, 29%, and 8%), RR (21%, 25%, and 4%), all-cause grade 3-5 adverse events were numerically higher in all three arms as compared to treatment related grade 3—4 AE's (by about 20%). Grade 3-4 treatment-related adverse events occurred in 11%, 14%, and 26% of patients in the 2mg, 10mg and chemotherapy arms, respectively. The HR of death or disease progression of pembrolizumab 2mg/kg vs chemo was 0.57 $p<0.0001$ and for pembrolizumab 10mg/kg vs chemo was HR 0.5 $p<0.001$. Most common grade 3-4 treatment-related adverse events on pembrolizumab 2mg/kg were fatigue, edema, and myalgia (1% each). For pembrolizumab 10mg/kg they were hypopituitarism, colitis, diarrhea, low appetite, hyponatremia, pneumonitis (1% each). Treatment discontinuation due to treatment-related adverse events occurred in (3%, 7%, and 6% of patients). There were no reported immune-mediated grade 4 or 5 adverse events. There were no treatment related deaths.

2.3 Conclusions

The Clinical Guidance Panel concluded that there is an overall net clinical benefit to pembrolizumab in both ipilimumab naïve and ipilimumab refractory unresectable stage III-IV melanoma. This conclusion is based on one well-conducted randomized controlled trial demonstrated a clear statistically significant benefit in 1 year overall survival rate, progression free survival, and response rate in favour of pembrolizumab vs ipilimumab in ipilimumab naïve patients and one randomized phase II trial showed statistically significant benefit in 6 and 9 month PFS rates and RR in favor of pembrolizumab vs investigator choice of chemotherapy in ipilimumab refractory patients. The magnitude of benefit in both ipilimumab naïve and refractory patients in terms of RR, PFS, and OS are clinically meaningful and reflect major improvements in disease management.

The Clinical Guidance Panel also considered that from a clinical perspective:

- Serious and life threatening auto-immune side effects are a major concern with immune check-point inhibitors. The rate of grade 3-5 side effects was lower on pembrolizumab than ipilimumab. Hypophysitis and colitis are of major clinical concern and rates were lower on pembrolizumab than ipilimumab.
- In general the side effect profile shows that pembrolizumab is well tolerated with a relatively low rate of serious immune related side effects which can be managed with well-defined management algorithms. This is of major importance to patients and clinicians.
- Network meta-analysis NMA is a tool used to make indirect comparisons (cross trial comparisons). The quality of evidence comparing pembrolizumab to BRAF inhibitors in the submitted NMA is low, as a result the submitted NMA should not be used to assess the relative efficacy or cost-effectiveness between pembrolizumab and MEK/BRAF inhibitors.
- The CGP is unaware of any evidence to guide optimal sequencing of immune checkpoint drugs (CTLA-4 and PD1 inhibitors) and BRAF/MEK inhibitors. BRAF mutated patients will receive available BRAF/MEK drugs at some point during their therapy, either before or after immune checkpoint inhibitors, thus BRAF/MEK drugs were excluded as a comparator in economic modeling.
- The CGP is unaware of any data that would allow reliable comparison of the clinical impact of pembrolizumab vs nivolumab.
- The optimal duration of pembrolizumab is unknown. In the current studies pembrolizumab was continued until disease progression, unacceptable toxicity, patient/physician decision, or in KEYNOTE-006 until 24 months of therapy. The efficacy of shorter durations of therapy is currently unknown, and will hopefully be addressed in future clinical trials.
- The Health Canada approved dose of pembrolizumab is 2mg/kg every 3 weeks which CGP also endorses. Of note, the discussion section of the KEYNOTE-006 publication states that multiple trials have shown a lack of a dose-response relationship with pembrolizumab.
- In melanoma, there is insufficient evidence to recommend the measurement of PD-L1 to guide the use of pembrolizumab. In addition, there is lack of consistency in the assays and cut-offs used to assess PD- L1.

3 BACKGROUND CLINICAL INFORMATION

This section was prepared by the pCODR Melanoma Clinical Guidance Panel. It is not based on a systematic review of the relevant literature.

3.1 Description of the Condition

Melanoma is a malignancy of melanocytes which are distributed throughout the body. Although primary melanoma can occur in a variety of sites, skin is the most common, comprising 95% of cases. In Canada 6500 new cases of primary melanoma were diagnosed in 2014 and approximately 1100 individuals will die from melanoma each year.[1] The incidence of melanoma has been steadily increasing over the past 60 years. Currently the lifetime probability of developing melanoma for women is 1 in 85 and for men is 1 in 67.[2]
Staging of melanoma is based on the current American Joint Committee on Cancer (AJCC) 7th edition classification.[3] The tumour characteristics principally involve the Breslow height, presence or absence of ulceration, and mitotic rate. The detection of microscopic and macroscopic lymph node involvement, lactate dehydrogenase (LDH) and sites of metastatic disease are also incorporated in the staging classification. All of these prognostic factors have important impact upon patient outcomes and also serve to guide management decisions.

3.2 Accepted Clinical Practice

In early stage melanoma, cures are commonly achieved with surgery alone. The primary site is excised with appropriate surgical margins. Depending upon the T stage and location of the primary, a sentinel node biopsy (SNB) may be performed to assess regional nodal status. If the sentinel node contains metastatic disease, then a completion lymph node dissection of the regional basin is often performed. This additional procedure has been shown to reduce the risk of regional occurrence.[4]

Although only 5% of patients present with metastatic disease, the majority of patients who ultimately die from melanoma will have developed recurrent and/or distant disease. About 1/3 of patients with early stage melanoma will develop metastasis; however, 1/2 of the patients with nodal disease will recur and likely die from metastatic disease.[5] Brain metastases are common and occur in up to 75% of patients with overt metastatic disease.
In highly selected patients with metastatic disease, clinical benefit may occur from surgical resection of known sites of disease and may result in long term survival.

Unfortunately, most metastatic patients are not candidates for surgical resection and systemic treatment is the only alternative. The prognosis for these patients remains poor. The median survival has been 6-9 months with 5 year survival of approximately 6%.[6] With the more recent introduction of new and effective treatments, a significant improvement in survival is being realized.

Over the past 30 years, standard first-line systemic treatment has been dacarbazine.[4,7] Although this alkylating agent is generally well tolerated, response rates are low (7-15%) and complete responses are rare.[8] In comparative studies the use of dacarbazine has not been shown to improve survival in metastatic melanoma.[9-13] Temozolomide, an oral imidazole tetrazene derivative of dacarbazine, is activated to the active metabolite of dacarbazine, and has also been commonly used. In phase III trials comparing temozolomide directly to dacarbazine, similar progression free and overall survival rates were observed.[14-16]

In the early 1990s the FDA approved the use of high dose Interleukin-2 based on phase II data showing a response rate of 16% and a durable complete response of 5%.[17,18] Unfortunately, high dose Interleukin-2 is associated with severe toxicity and requires intense cardiac monitoring and hemodynamic support. Interleukin-2 is largely unavailable in Canada.

A wide spectrum of chemotherapeutic and immunological treatments has been explored in patients with metastatic melanoma. Until recently limited to no success has been achieved. It has become increasingly apparent that melanoma represents a heterogeneous group of diseases. A variety of genetic abnormalities exists within primary melanomas and their respective metastases and influence both cellular proliferation and ultimately response to therapy.[19-21]

The MAP kinase signaling pathway appears to be a key regulatory mechanism for cell growth and differentiation in melanoma.[22] Mutations in the BRAF protein within this pathway can result in uncontrolled cellular proliferation and increased potential for metastatic spread.[23] Approximately 50% of human melanomas appear to have an activated mutation in BRAF which has become a key target for inhibition and potential therapeutic site[24]. Vemurafenib and Dabrafenib are BRAF inhibitors that targets the V600 mutation and are approved by Health Canada based on studies showing improvements in risk of death and risk of tumor progression. [25-32] Compared to single agent BRAF inhibitors, dual inhibition of the MAP kinase pathway by combination BRAF and MEK inhibitors have shown improvements in RR, PFS, and OS.[33,34] Unfortunately, for those patients who are BRAF positive, resistance to the BRAF and MEK inhibitors ultimately develops and patients experience rapid and often unrelenting disease progression. In the 50% of the patients who do not have BRAF mutation, the BRAF inhibitors are uniformly ineffective.

More recently antibodies to immune checkpoint inhibitors (Ipilimumab, Nivolumab, Pembrolizumab) have shown improved outcomes, independent of BRAF status, in metastatic melanoma. Ipilimumab is a monoclonal antibody that binds to and blocks the cytotoxic T-lymphocyte associated antigen 4 (CTLA4) located on cytotoxic T-lymphocytes has been shown to improve survival in first and second line settings in the treatment of metastatic melanoma.[35,36] Response rates to ipilimumab are low (11-15%), and median OS is modest at 10-11 mos. Of major importance however, is that even though the median OS is modest, a proportion of patients treated with immune checkpoint inhibitors will experience prolonged disease control lasting many years, and the hope is that they are cured of metastatic melanoma. With ipilimumab 15-20% of patients experience prolonged disease control and may not require further treatment.[35] In 2012, ipilimumab was initially approved by Health Canada for the treatment of unresectable or metastatic melanoma in patients who have failed or do not tolerate other systemic therapy for advanced disease.[1] In September 2014, it was further approved as first line therapy of unresectable or metastatic melanoma.[37] The Health Canada-recommended dose for ipilimumab, in both previously treated and untreated patients, is 3 mg/kg administered intravenously over a 90-minute period every 3 weeks for a total of four doses.[38] The pCODR Expert Review Committee (pERC) recommended funding ipilimumab, conditional on the cost-effectiveness being improved to an acceptable level, in good performance status patients in first or second line setting for patients with unresectable Stage III or Stage IV melanoma.[40,41] Adverse events are significant and potentially life threatening with ipilimumab therapy, approximately 15% of patients experience grade 3 or 4 immune mediated side effects that require management and monitoring, including risks for severe and fatal events (ie colitis).

Nivolumab and Pembrolizumab are antibodies to programmed death 1 (PD-1) immune-checkpoint inhibitors. In previously untreated patients, nivolumab was superior to dacarbazine with higher ORR (40.0% vs 13.9%), mPFS (5.1mos vs 2.2 mos HR 0.43, $p<0.001$), and OS at 1 year (72.9% vs 42.1% HR 0.42, $p<0.001$).[46] Grade 3 or 4 adverse events occurred in 11.7% of the nivolumab treated patients and 17.6% of the dacarbazine treated patients. In the KEYNOTE-006 trial Pembrolizumab has recently been compared directly to Ipilimumab in 1st or 2nd line therapy for

advanced melanoma[41] with improvements in RR (34% vs 12%), 6 months PFS (47% vs 26% HR 0.58 p<0.001), estimated 12 mos OS (74% vs 58% HR 0.63 p=0.0005) and lower grade 3 to 5 treatment related adverse events (13.3% vs 19.9%). However, only minority of patients respond to ipilimumab used in the first or second line setting, and treatment options for ipilimumab refractory patients are very limited and patients typically have short survival.

3.3 Evidence-Based Considerations for a Funding Population

The KEYNOTE-006 trial[41] was a 3 arm, phase 3, 1st or 2nd line trial in metastatic melanoma that enrolled 834 patients to receive either pembrolizumab (10mg/kg) q 2 weeks vs pembrolizumab (10m/gk) q 3 weeks vs ipilimumab (3mg/kg) q 3weeks. Approximately 65% of patients received the therapy as 1st line therapy and 35% as 2nd line. Of note 35% of patients were BRAF mutation positive and 50% had received prior BRAF targeted therapy. The primary endpoint of the trail was PFS and OS. Patients were accrued from September 2013 to March 2014 and at the protocol specified second interim analysis March 3, 2015 the data and safety monitoring committee recommended that the study be unblinded.

Ipilimumab is considered a standard of care for first or second line treatment of metastatic melanoma. Pembrolizumab is submitted for consideration of funding for ipilimumab naïve and ipilimumab refractory patients based on the KEYNOTE-006 trial which showed clinically significant improvements in RR, PFS, OS associated with pembrolizumab as compared with ipilimumab and clinically significant lower rates of treatment-related adverse events including immune related adverse events.

Unmet Needs: Long term disease control is relatively uncommon with available therapies for metastatic melanoma. Only 50% of patients have BRAF mutations and in those patients resistance invariably develops to BRAF and MEK inhibitors. Standard chemotherapy with dacarbazine has a low response rate and there are no studies to demonstrate improved survival as compared to best supportive care or placebo. High dose IL2 therapy is very toxic and not available in most provinces in Canada and there is no phase 3 data supporting its use. Ipilimumab is a standard of care for first or second line therapy however response rates are low, side effects are significant and can be severe, and long term disease control occurs only in a minority of patients (15-20%). Thus, the majority of patients with metastatic melanoma have disease that quickly becomes resistant to the available therapies (dacarbazine/ipilimumab/BRAF-MEK) and survival at that point is typically very short. As a result there is a huge unmet need in the treatment of melanoma for patients with both ipilimumab naïve and ipilimumab refractory. The KEYNOTE-006 trial of pembrolizumab in melanoma showed clinically significant improvements in RR, PFS, and OS compared to ipilimumab in both ipilimumab naïve and refractory patients and importantly clinically significant side effects were less frequent as compared to ipilimumab and is thus submitted for consideration of funding to help meet this large unmet need.

Additionally, the optimal sequencing of BRAF/MEK drugs and immune checkpoint inhibitors is unknown and will hopefully be clarified in future clinical trials.

3.4 Other Patient Populations in Whom the Drug May Be Used

Ocular melanoma was excluded from the KEYNOTE-006; these patients typically have a poor prognosis and limited treatment options and clinicians will likely wish to use pembrolizumab in this patient group.

4 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

The following three patient advocacy groups, (1) Canadian Skin Patient Alliance (CSPA), (2) Melanoma Network of Canada (MNC) and (3) Save Your Skin Foundation (SYSF), provided input on pembrolizumab (Keytruda) for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab therapy and, if BRAF V600 mutation positive, following a BRAF or MEK inhibitor, and their input is summarized below.

CSPA conducted one-on-one interviews with 3 patients with metastatic melanoma, of which 2 have gone through the treatment under review, and 3 caregivers.

MNC conducted a confidential on-line survey of patients from across Canada (104 respondents), the US (42 respondents) and Australia (14 respondents) as well as four from three other countries. Patients were recruited through a generic letter and email and an on-line website posting requesting input from patients that had been treated with pembrolizumab, patients who had been treated with other drugs and patients who may see a need for this therapy in the future. MNC received a total of 164 patients responded of which 52 respondents (32%) had been treated with pembrolizumab. The survey had a combination of multiple choice and open ended questions, as well as rating and options for comment. MNC has provided selected commentary of respondents that are reflective of various perspectives.

SYSF conducted one-on-one interviews, focus groups, and surveys with 50 patients with metastatic melanoma, of which 20 have gone through the treatment under review, and 5 caregivers. SYSF reported 60% of interviewees were female, with an average age between 40 – 49 and ranged from across Canada.

From a patient perspective, there are both mental and physical impact for patients with metastatic melanoma. Respondents commonly experience pain, scarring, fatigue, disrupted sleep and fear, depression and anxiety. Patient Advocacy Groups 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. Respondents believe that this new therapy will give them hope. With pembrolizumab, there is the expectation that they may live longer, with few side effects and have a good quality of life or potential lasting response. The majority of respondents who have experienced with pembrolizumab indicated the drug was well tolerated with few side effects. These side-effects include skin rash, fatigue, weakness, diarrhea, colitis, headaches. A small number of respondents indicated having experienced no side effects with the treatment. All respondents stated that side-effects to treatment were manageable, and that pembrolizumab improved their quality of life. Respondents also reported tumour shrinkage and for some full disappearance of growth. Respondents also reported liking the dosing profile for pembrolizumab and feel that it is more palatable than other treatments. They expect that the 21-day dosing period will provide some stability in their lives, knowing that they will feel lousy for 21 days and then feel normal afterwards; and the treatment time is also easier to handle – three hours in the clinic versus four-five hours for other treatments.

Please see below for a summary of specific input received from the patient advocacy groups. Quotes are reproduced as they appeared in the survey, with no modifications made for spelling, punctuation or grammar. The statistical data that was reported have also been reproduced as is according to the submission and have not been corrected.

4.1 Condition and Current Therapy Information

4.1.1 Experiences Patients have with Metastatic Melanoma

According to CSPA, melanoma is like no other cancer that is often invisible; there is no pain and usually with minimal physical effects. Yet it is never far away from the patients' and caregivers' minds. For example, making plans for the next family vacation, celebrating a significant anniversary or dreaming of retirement are just not possible given the uncertainty of the disease. The following statements were reported by respondents to help contextualize the worry and anxiety that patients and caregivers experience:

> "*You have no idea what anxiety I have four weeks before the scans are coming. It's the worst, because I've been there. I've had scans that have come back and said I'm a stage IV, and it turned my life upside down. I've had a scan that has come back and said you have a brain met, which was my greatest fear I ever had, was to have a brain met. So the anxiety of coming up to scans could turn your life upside down. You're only as good as your last scan.*"

> "*There's this loss of dreams you had about what the future holds. That makes me sad because it is not the way normal people live.*"

SYSF reported key impact on patients with this disease, include the inability to mentally and physically return to work, the inability to return to "normal" daily life, and anxiety and depression due to their prognosis. Some patients have also suffered from loss of mobility due to muscle and tissue removal of surgery or treatment.

CSPA noted that the physical limitations experienced by patients are often linked to current therapies rather than the advanced melanoma itself.

SYSF reported that the ongoing symptoms from respondents include loss of energy, fear, anxiety and depression. All of the respondents experienced moderate to severe emotional distress. Some respondents suffered fatigue, mood swings, loss of vitality and low energy levels.

MNC asked respondents to identify as many symptoms as they had experienced from a list of common adverse effects associated with the disease and treatments. According to MNC, patients commonly experienced pain, scarring, fatigue, disrupted sleep and fear, depression and anxiety. Below is a list of the key findings from the survey on symptoms and issues that respondents reported.

Cancer and the different stages of cancer affect people in different ways. What issues have you experienced with the cancer itself? Please select as many responses as appropriate.

Answer Options (patients could select as many options as were applicable)	Response Percent (of those that responded)	Response Count
Pain	57.9%	66
Scarring or disfigurement	66.7%	76
Edema or fluid retention	19.3%	22
Lymphedema	35.1%	40
Mobility issues (unable to walk or impaired movement)	21.1%	24
Gastrointestinal issues	31.6%	36
Breathing problems	15.8%	18

Headaches	31.6%	36
Peripheral neuropathy (nerve pain or damage)	26.3%	30
Disrupted sleep	54.4%	62
Appetite loss or weight gain	43.9%	50
Fear or anxiety	73.7%	84
Fatigue	61.4%	70
Depression	50.9%	58
Post-traumatic stress	7.0%	8
Cognitive Impairment	15.8%	18
Nausea or vomiting	24.6%	28
Damage to organs, such a lungs, liver, brain	21.1%	24
Negative Impact to family or social life	49.1%	56
Financial loss or job loss	42.1%	48

To help illustrate the impact of this cancer, CSPA and MNC reported the following comments obtained from respondents:

> *"I was a sun worshipper. I can even remember sitting in the sun in high school. That was in the 60s. The only thing I could say is you have no idea how many nights I wake up wishing I could do it over again."*
>
> *Inability to make long term plans. Don't know if I will be alive or physically able to do anything.*
>
> *The resulting PTSD and lymphedema have left my life a shell of what it was prior to melanoma. My mobility is permanently damaged, my career is over, I have given up my house as a result of physical limitations.*
>
> *Gastrointestinal issues, nausea and vomiting daily from the cancer. Pain from the bone metastasis is constant.*
>
> *I am scared to have another child. I am constantly worried I have another spot I am unaware of. I avoid situations where I will be in the sun even though I could go and protect myself.*
>
> *Loss of income due to sick time, sleep deprivation, nausea, lack of interest in life at times, lasting post treatment side effects.*
>
> *Large tumors on legs have led to neuropathic pain, which has made walking and driving difficult. Lack of breath. Unable to walk or do normal things like wash, dress or go to the bathroom. Pain in many forms.*
>
> *A lot of nerve damage and continuing edema from original surgery. Our emotions are on a roller coaster ride. The original surgery to take out 68 lymph nodes in my neck left scaring, nerve damage and some mobility issues.*
>
> *I have had to take periods of unpaid leave from work which has wiped out my savings and increased my debt levels. The first few months were also difficult emotionally but counselling helped with that.*

Fatigue, anxiety about my family's future. Not being able to work or plan for the future.

Depression and anxiety are fairly constant. It cost me my work - I really couldn't go back as I couldn't handle the stress anymore without breaking down in tears.

PT weekly for lymphedema, compression garments for arm and trunk. Pain and swelling at surgical sites.

4.1.2 Patients' Experiences with Current Therapy for Metastatic Melanoma

CSPA 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. Current therapies cited in the interviews included ipilimumab, interferon and granulocyte-macrophage colony-stimulating factor (GM-CSF). Respondents reported a myriad of symptoms attributed to these treatments including fatigue, insomnia, irritability, flu-like symptoms (chills, sweats, diarrhea, vomiting), headaches and weight loss.

Although all of the respondents reported their individual experiences and symptoms, the most common statements were expressed by respondents on their experiences were as follows:

> "*It's treatment every day. Its like, having the worst flu you can possibly have for a month, even longer than that. You get the chills, you get the sweats, diarrhea, vomiting, I didn't lose my hair but I lost chunks of it. Headache like a railway spike through the brain. It was probably a good five, six months until I felt better. I lost weight, I lost energy, and I lost fitness. I remember trying to walk around our parking lot and having to stop and take a rest.*"

> "*Tremendous tingling and pain sensation in my face and head and hands. It feels like every nerve ending was exploding.*"

> "*The steroid I was on created insomnia. Let me say this also. It's hard to differentiate the difference between brain surgery, gamma knife radiation, and steroid. The best thing I can say to you is I had a perfect storm in my brain.*"

As a result of the significant and devastating side effects, CSPA reported that some respondents are deciding not to use the available treatments:

> "*My local oncologist said ... you're going to be sick for an entire year (with interferon.) You have to be on it for an entire year and you're going to be sick for the entire year. The advantage of being on this drug is it'll give you an additional 4% advantage. We decided that being sick for an entire year and possibly having very significant side effects, for only a 4% advantage, we turned it down. After we conveyed our decision, the oncologist said, well, we read between the lines in our ongoing conversation with him, that he would probably do the same thing.*"

SYSF reported that current drugs used to treat melanoma include interferon, surgery, dacarbazine (dacarbazine), temozolomide, stereotactic radiation (used on brainstem tumours), vemurafenib, ipilumumab, trametinib and dabrafenib.

According to SYSF, 10% of respondents interviewed reported positive results with interferon, dacarbazine, temozolomide. These respondents experienced fatigue and pain from the cancer while undergoing treatment. Respondents felt that the treatments may have slowed the spread of disease, but were not effective in preventing metastasis. SYSF noted that 40% of respondents interviewed reported positive results with vemurafenib, ipilimumab, trametinib and dabrafenib.
Of the respondents who responded to the question about their current treatments, 75% of respondents reported adverse side-effects that were most difficult to tolerate included: fever, hair loss, extreme fatigue, diarrhea, skin issues, nausea, rash, joint pain, colitis. Notwithstanding, all respondents agreed symptoms were manageable with medications and would undergo these treatments again if necessary.

It was reported that 50% of respondents interviewed experienced with either no response or temporary response with current treatments. While side effects could be difficult to tolerate, but respondents found it to be manageable if watched closely. It was reported that these respondents would undergo treatment for as long as is needed despite the side effects.

SYSF found that 90% of respondents responded “yes” that they would “try anything” to win their fight with this cancer. The other 10% of respondents responded, “yes” depending on the severity of the side of effects.

MNC reported that respondents were treated with a variety of therapies, most commonly interferon (19%), ipilimumab (36%), and approximately 19% of respondents had received a targeted therapy such as vemurafenib, dabrafenib or trametinib. Other drugs mentioned were temozolomide and IL-2. 16 respondents did not know which therapies they had received.

According to MNC, those who received interferon indicated that it was difficult to tolerate and the majority experienced, headaches, rigours, flu like symptoms, extreme fatigue, low blood counts, vomiting, diarrhea, cognitive impairment, hair loss, depression. With respect to temozolomide, side effects reported were virtually the same as with interferon, with the addition of numbness, insomnia and weakness or loss of coordination. The majority of respondents indicated that interferon wore them down and the length of time they had to be on the drug (generally 1 year) was too much. The fatigue, depression and constantly feeling sick were most common and what patients indicated they could not tolerate well. For respondents on temozolomide, it was not taken as long so it did not seem to pose long lasting side effects. Many respondents could not work through this course of treatment, resulting in more negative impacts emotionally (depression and anxiety) and financially as well as with the family.

For respondents treated with targeted therapies, they had indicated a variety of side effects including rash, additional skin cancers, fatigue, sun sensitivity, abdominal pain and diarrhea, headaches, edema. Most indicated it was tolerated, but two respondents had dose reductions and then removed from treatment for side effects. Of the 146 respondents that responded to this question, 36% of respondents had been treated with ipilimumab. Respondents on ipilimumab indicated side effects were commonly diarrhea (2 had severe colitis that required steroids), headaches, chills, rashes, stomach cramps, fatigue, nausea and vomiting. 87% of respondents indicated that the side effects were tolerable and short lived, once therapy ceased. When asked if respondents would be willing to put up with side effects if there was a possibility of a better quality of life or overall survival, all but one indicated that they were willing to have these side effects if it meant a longer life or improved quality of life.

MNC reported that the symptoms that were most important to control for patients were:

- Progression of disease, death.
- Cognitive impairment, fatigue
- Pain everyday associated with disease progression or treatment
- Anxiety, fear, depression
- Gastrointestinal issues, including vomiting and diarrhea

1. SYSF noted that while newer therapies are becoming more readily available, they do not work for all patients and is not easily accessible. As such, patients feel frustrated as time is very important when dealing with melanoma and access to treatment.
2.
3. According to SYSF, over 60% of respondents were able to access treatment through their oncologist at a centre close to them; while 40% of respondents found it difficult to find a centre close to their home. Respondents reported having difficulty getting on a trial as they only accept a small number of participants.

4. CSPA also found that patients and caregivers expressed frustration in trying to access better drugs due to eligibility stipulations which requires patients to try these ineffective treatments with many side effects before being able to be prescribed more effective drugs. Their physicians understand this frustration and would try to find loopholes to get their patients on more effective drugs. The current treatment options often offer little results with the significant side effects. One respondent stated: "*Even when [my spouse] was first diagnosed in 2013, for stage 3 the only option that they gave was interferon which was a completely useless drug that had no impact on overall survival. And people were taking it, and it's very toxic, and people were taking it because it's all that was offered, and I think that's a crying shame*."

MNC indicated that there were no access issues reported other than the length of time it took to get on the therapy. 22 respondents reported that they had to travel to receive treatment on a regular basis, which had a financial impact. One respondent said: "*I had to travel 250km once every three weeks, staying over about two or three days (sometimes longer). We finally decided to sell our home and move closer to the centre for the treatments. We waited about two months for the drug to be available to me - lots of paperwork for my oncologist*."

At least 7 respondents indicated a financial impact due to loss of income from work as a result of treatment.' One respondent said: "*We sold the house and moved away from our friends and church (our strong support group!). It affects our travel time to see friends and family and to take holidays. According to my treatment schedule I am on a three week intravenous schedule - I have to be close to a cancer centre for those treatments*."

When asked about unmet need, the responses tended to reflect a common theme of a need for a cure or effective treatment. Seven (7) respondents also indicated it would be easier if they could receive treatment closer to home or if the drug was oral versus intravenous. Comments also included being thankful that there is something else to try. If they had been on one therapy and it stopped working, at least they had something else to go to that may work permanently or get them to the next therapy that may work.

4.1.3 Impact of Metastatic Melanoma and Current Therapy on Caregivers

MNC reported that caregivers generally face a number of challenges, including time lost from work and financial impact, increased burden of caregiving and responsibilities for the

family, anxiety and depression, physical challenges of assistance and lifting as well as travelling to appointments. Challenges were the same with pembrolizumab.

Below are some key statements from caregivers that MNC has highlighted to help provide context on the outcome with the treatment:

> *I am all thrilled he is happy and healthy and still here. Still working full-time and living a basically normal life*
>
> *spouse isn't planning my funeral anymore*
>
> *I have my husband back and he can help around the house on his own or run out and buy things we need.*
>
> *Huge positive impact. Gave me another year to spend with him.*
>
> *This drug has had a very positive impact on myself and all members of my family.*
>
> *My wife says my survival has had a very positive impact on her daily life (thank goodness!).*
>
> *His family live overseas and having a treatment with mild side effects meant that I didn't need anyone to come out as a caregiver - which has saved them a lot of trouble and expense. He has also been able to go back and visit them while on treatment.*

According to CSPA, caregivers stated that a diagnosis of advanced melanoma compromises their emotional well-being as the disease is constantly on their minds, even after a clear scan. The stress and anxiety leading up to the next scan can be just as unbearable for the caregivers as is it for the patient. One respondent stated: "*It's pretty much a chronic state of either worrying about the scan approaching or dealing with the bad news of what the scan revealed.*"

Given the common prognosis of advanced melanoma, there is a lot of anticipatory grief for the caregivers, which is compounded by the day to day stress and worry of caregiving. Caregivers begin to anticipate what life will be like without the family member and worry about the impending death itself. Respondents reported the following:

> "*It's almost like there's a sense of grieving now that he's still alive because the prognosis is not great, and so, it makes me sad….It impacts my sleep. I have bad dreams sometimes.*"
>
> "*And I also worry about, you know, if (my spouse) dies, then he would be experiencing a painful death, I worry a fair bit about that because that's traumatic…I've read people's stories, about going through that…spouses of people with melanoma or their loved ones with melanoma and it can be a really painful process, and I don't want to have to see that.*"

SYSF reported the emotional distress due to an uncertain prognosis and unknown treatment plan, cancellation of any long-term plans, and time away from work to assist the patient all impacted the routine of the caregiver. The challenge for the caregiver was confusion over the effects related to the current therapy. The caregivers respondents interviewed found it difficult to know if the symptoms were treatment or cancer related.

Respondents also reported on lack of information about the side effects resulted in confusion and distress.

According to SYSF, the main challenge for some caregivers was finding treatments that might work for the loved one. They cost to the family to travel to centers for treatment is very difficult.

One respondent stated: "*My spouse is thrilled with the effect the drug has had on the cancer and with the minimal side effects. Mentally this drug has given him the most positive impact since diagnosis.*"

4.2 Information about the Drug Being Reviewed

4.2.1 Patient Expectations for and Experiences To Date with pembrolizumab

CSPA, MNC and SYSF reported that pembrolizumab has given the patients and caregivers hope and empowerment. They believe in this new clinical approach to beat melanoma. Respondents feel that approval of this treatment as an early line treatment for those with advanced melanoma would be very beneficial since there are currently such limited options without devastating side effects.

> "*I think [having this drug approved] will have a great emotional impact, first of all. […] I can feel that the oncologists and surgeons sometimes follow the protocol knowing that maybe there is another answer. They are stuck. So I think the impact will be first of all emotional, having more choices. Having more choices gives you a sense of being more in control. You feel more empowered. You feel that you have a voice in a situation where you feel completely powerless.*"
>
> "[…] *the mood of the melanoma communities that I'm in, how the mood has become really much more hopeful with the advent of this drug, almost like a real sense of finally we have something that actually does some good. And while nobody is saying that this is the cure, it's certainly the best thing that's been around for a long time.*"

Respondents who were interviewed by CSPA believe that this new therapy will keep them alive, with less side-effects, until new options are available to them, so that advanced melanoma will become a chronic illness much like HIV.

Respondents to the MNC survey indicated that if and when they stopped responding to ipilimumab, that it was the end of the line. With pembrolizumab, there is the expectation that they may live longer, with few side effects and have a good quality of life or potential lasting response. From the responses provided, the side effects seem manageable and in many cases were minimal. The unmet need is to find a drug that provides a durable response or that can give a good quality of life until another is available.

Respondents who were interviewed by SYSF reported the benefits outweighing the risks of treatment, and that symptoms seem to be much more tolerable than current therapies and it may increase the overall survival rate for patients with melanoma.

MNC reported that 52 respondents had experienced with pembrolizumab. 100% of respondents that responded to the question and had been treated with pembrolizumab

indicated the side effects were worth the treatment. The majority indicated the drug was well tolerated with few side effects. Below were the key side effects that were reported:

If you are or have been treated with the medication Pembrolizumab (Keytruda, MK3475) to control or eliminate your disease, what side effects (if any) of the treatment did you or are you experiencing?	
Answer Options	**Response Count**
Pain	0
Skin rash	12
Shortness of breath, cough or chest pain (pneumonitis)	4
Fatigue or weakness	12
Diarrhea or colitis	8
Constipation	6
Muscle or Joint pain	6
Fever or flu like symptoms	4
Headaches	2
Hormone or thyroid problems	3
Stomach pain	0
Liver problems	0
Kidney problems	0
Bleeding or bruising more easily	2
Weight loss or Loss of appetite	0
Weight gain	0
Cognitive Impairment	0
None	2

SYSF reported that 20 respondents have experienced with pembrolizumab. According to SYSF, side effects of the treatment included:

- Diarrhea/colitis (over 60% of respondents)
- Headaches (over 30% of respondents)

It was reported by SYSF that 30% of respondents reported no side effects. All respondents stated that side-effects to treatment were manageable, and that pembrolizumab improved their quality of life. Respondents also reported tumour shrinkage and for some full disappearance of growth. One respondent stated: "*My tumours have mostly disappeared and the remainder have shrunk significantly. Treatments are very easy to manage*"

CSPA reported that two respondents have experienced with pembrolizumab. Respondents indicated that while there were side effects with pembrolizumab but they were not as debilitating as the side effects from other drugs. Respondents feel that they can live with them, compared to what they have been used to. One respondent stated: "*My biggest complaint has been tiredness. [Compared to interferon and Ipi], no, no, not nearly, if I'm comparing, so far this drug is a walk in the park... I'm tired, I have a little bit of headache, a couple of days ago I had a bit of fever and chills, but they're not long lasting.*"

Respondents interviewed by CSPA like the dosing profile for pembrolizumab and feel that it is more palatable than other treatments. They expect that the 21-day dosing period will provide some stability in their lives, knowing that they will feel lousy for 21 days and then feel normal afterwards. And the treatment time is also easier to handle – three hours in the clinic versus four-five hours for other treatments. One respondent stated: "*Very easy.*

It's a quick infusion, 15 minutes, with a little bit of fluids afterwards. So total time at the doctor's office including the blood draws and everything was probably about 3 hours…versus Ipi which was four or five hours easily. So a quick infusion is nice. It's a 21 day cycle and that's also very nice…I mean if I've got to be on a leash, I want it as long as possible!"

SYSF noted that all of but one of the respondents interviewed are still undergoing treatment. The one respondent that has completed treatment was treated in the US and has been clear for over 3 years.

MNC reported that approximately 64% of respondents treated with pembrolizumab indicated a slowing of progression of disease, and a further 36% of respondents indicated that there is currently no evidence of disease.

Below were some of the key comments obtained from respondents on their experience with pembrolizumab:

> *I had a pleural effusion one month after beginning the Pembrolizumab which was resolved quickly with a chest drain. Fatigue was common for about 4 months and the colitis began at the 2 yrs mark (I was in Phase 1 of 2mg, every 3 weeks). This is still ongoing.*
>
> *Without the treatment I would have died, so it was definitely worth it.*
>
> *Well, I am right in the middle of whether I can continue the Pembrolizumab because of the pancreatic issues and have already had one treatment cancelled but I suffer no pain from it. However since my stomach is now more sensitive I have learned what triggers the nausea and acid reflux and thus practise avoidance.*
>
> *None of my symptoms have been serious enough to need other medication to resolve*
>
> *My thyroid was destroyed as a result of the treatment. The resulting hypothyroidism can be treated easily and inexpensively with synthetic thyroxine. Without the MK-3475 treatment I would be dead. The loss of my thyroid gland is a small price to pay.*
>
> *Fatigue was minimal. I get my injections and schedule them for a Friday afternoon so that I have the weekend to relax. I have been able to work throughout treatment.*

4.3 Additional Information

CSPA found that it is not always clear the difference between the sections 3.1 and 3.2 of the template, as patient expectations and experiences are intertwined.

SYSF report that many melanoma patients indicated their concerns that there are still not enough treatment options available in a timely fashion. Some had to find this treatment on their own and most had to travel outside of their province to get the treatment. This added emotional and financial stress to an already very stressful diagnosis. But all patients were extremely grateful that there are now treatment options available to them.

MNC submits that coverage be made available for this drug as MNC believes it brings a good quality of life for patients after treatment.

5 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

The Provincial Advisory Group includes representatives from provincial cancer agencies and provincial and territorial Ministries of Health participating in pCODR. The complete list of PAG members is available on the pCODR website (www.cadth.ca/pcodr). PAG identifies factors that could affect the feasibility of implementing a funding recommendation.

Overall Summary

Input was obtained from eight of the nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation of pembrolizumab for metastatic melanoma. Due to the scope expansion, PAG was provided the opportunity to revise input accordingly.

Clinical factors:

- Therapeutic gap for patients who are ipilimumab refractory and/or resistant to treatment with BRAF inhibitors +/- MEK inhibitors
- Treatment algorithm and/or sequencing with recently available drugs
- Long-term safety and efficacy compared to other treatments available

Economic factors:

- Drug wastage
- Cost-effectiveness compared to other treatments available

Please see below for more details.

5.1 Factors Related to Comparators

PAG identified that the current standard of practice in the first-line treatment of patients with metastatic melanoma is ipilimumab or BRAF inhibitors +/- MEK inhibitors. As dacarbazine is not very effective nor well tolerated, it is no longer the appropriate comparator.

Ipilimumab is second-line treatment for patients who have not received ipilimumab in the first-line. For patients who are ipilimumab refractory or have BRAF mutations but are resistant to treatment with BRAF inhibitors +/- MEK inhibitors, there are no effective options and there is a therapeutic gap.

PAG is seeking direct comparison data comparing pembrolizumab to ipilimumab, nivolumab, BRAF inhibitors and MEK inhibitors in all lines of therapy.

5.2 Factors Related to Patient Population

Pembrolizumab may be an alternate to ipilimumab for ipilimumab-naïve patients and would provide an option for patients who have progressed on ipilimumab. PAG is seeking clarity on the place in therapy and/or line of therapy for pembrolizumab with respect to ipilimumab and other treatments for metastatic melanoma.

Given the many new treatments recently available and possibly more upcoming new treatments, PAG noted that dacarbazine would no longer be used and is seeking guidance from tumour groups for a national treatment algorithm for metastatic melanoma.

5.3 Factors Related to Accessibility

The dose in the funding request is 2mg/kg administered every three weeks. PAG noted that there are ongoing trials evaluating a 10mg/kg dose and an administration frequency of every two weeks. This could have relevance for both the clinical and economic reviews as it raises the potential for dose creep.

5.4 Factors Related to Dosing

PAG has concerns for incremental costs due to drug wastage, specifically in centers where vial sharing would be difficult because there could only be one patient in the day. As dose is based on weight and there is only one vial size (50mg), a dose of 140mg (2mg/kg x 70kg) would result in wastage given that any unused portion would be discarded as the stability of reconstituted drug is poor.

Pembrolizumab is a new class of drug and health care professionals would need to become familiar with the preparation, administration and monitoring upon implementation.

Pembrolizumab is to be used until progression and the PAG is seeking information on the range in duration of treatment with pembrolizumab, if available.

PAG noted that recent data indicates that ipilimumab could safely be infused over 30 minutes instead of 90 minutes (Momtaz et al. Safety of Infusing Ipilimumab Over 30 Minutes. J Clin Onco 2015 June 29. http://jco.ascopubs.org/content/early/2015/06/24/JCO.2015.61.0030.abstract). Pembrolizumab is infused over 30 minutes, which could be a shorter than or same infusion time as ipilimumab, depending on the infusion time being used for ipilimumab in the cancer centres.

PAG is requesting clarity whether testing for PD1 ligand is required.

5.5 Factors Related to Implementation Costs

Pembrolizumab, being an intravenous drug, would be administered in an outpatient chemotherapy center for appropriate administration and monitoring of toxicities. Intravenous chemotherapy drugs would be fully funded (i.e. no co-payments for patients) in all jurisdictions for eligible patients, which is an enabler for patients.

As pembrolizumab is a high cost drug and requires monitoring of immune-mediated reactions post-infusion, PAG noted that smaller outpatient cancer centres may not have the expertise and resources to administer pembrolizumab. This is a barrier for those patients who will need to travel to larger cancer centres that have the resources and expertise to administer pembrolizumab.

PAG noted that the expertise and resources may be required to monitor and treat infusion related reaction and serious adverse events. PAG noted that there is a lack of long-term data on the safety of pembrolizumab.

Based on the prescribing information in the United States, PAG noted that the pharmacy preparation time appears to be longer than the majority of other chemotherapy drugs, which could impact resources and be a barrier to implementation.

5.6 Other Factors

The high cost of pembrolizumab would be a barrier to implementation. PAG noted that the one vial size is appropriate to minimize drug wastage but that multiple vials are required to prepare the dose.

6 SYSTEMATIC REVIEW

6.1 Objectives

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

Note: Supplemental Questions most relevant to the pCODR review and to the Provincial Advisory Group were identified while developing the review protocol and are outlined in section 7.

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the Clinical Guidance Panel and the pCODR Methods Team. Studies were chosen for inclusion in the review based on the criteria in the table below. Outcomes considered most relevant to patients, based on input from patient advocacy groups are those in bold.

[Table 6.1] Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
First-line therapy (ipilimumab naïve)				
Published or unpublished RCTs	Patients with unresectable or metastatic melanoma (stage III or IV)	Pembrolizumab (various dosing regimens)	• Chemotherapy • Best supportive care • Ipilimumab • BRAF inhibitors: Vemurafenib or Dabrafenib • MEK inhibitors: Trametinib	• Overall survival (All cause mortality) • Progression free survival • Quality of life • Response rate • Grade 3 and 4 adverse events • Withdrawal due to adverse effects • Adverse effects
Second-line therapy (ipilimumab refractory)				

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Published or unpublished RCTs	Patients with unresectable or metastatic melanoma and disease progression following ipilimumab therapy. <u>Subgroups:</u> BRAF mutation or wild type.	Pembrolizumab (various dosing regimens)	• Standard chemotherapy (dacarbazine, temozolomide, carboplatin and paclitaxel) • Standard immunotherapy (Interferon-alpha, interleukin-2) • Best supportive care[1] • BRAF inhibitors: Vemurafenib or Dabrafenib[2] • MEK inhibitors: Trametinib[2]	• Overall survival (All cause mortality) • Progression free survival • Quality of life • Response rate • Grade 3 and 4 adverse events • Withdrawal due to adverse effects • Adverse effects

RCT: randomized controlled trial; IV: intravenous.

1. Best supportive care is defined according to the National Cancer Institute in the U.S. as care given to improve the quality of life of patients who have life-threatening diseases. The goal of best supportive care is to prevent or treat as early as possible the symptoms of disease or side effect of treatment and the psychological, social or spiritual problem related to the disease or its treatment [insert reference].
2. BRAF and MEK inhibitors were not included in the first search in May 2015. The protocol was amended after the first literature search and BRAF/MEK inhibitors were included in later literature search.

** Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions)*

6.2.2 Literature Search Methods

The literature search was performed by the pCODR Methods Team using the search strategy provided in Appendix A.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-2015) with in-process records & daily updates via Ovid; EMBASE (1980-May 04, 2015) via Ovid; The Cochrane Central Register of Controlled Trials (issue April 2015) via Wiley; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were pembrolizumab-Keytruda.

No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year. Retrieval was limited to the English language.

The search is considered up to date as of October 6th, 2015.

Grey literature (literature that is not commercially published) was identified by searching the websites of regulatory agencies (Food and Drug Administration and European Medicines Agency), clinical trial registries (U.S. National Institutes of Health – clinicatrials.gov and Ontario Institute for Cancer Research – Ontario Cancer Trials) and relevant conference abstracts. Searches of conference abstracts of the American Society of Clinical Oncology (ASCO) were limited to the last five years. Searches were

supplemented by reviewing the bibliographies of key papers and through contacts with the Clinical Guidance Panel. In addition, the manufacturer of the drug was contacted for information as required by the pCODR Review Team.

6.2.3 Study Selection

One member of the pCODR Methods Team selected studies for inclusion in the review according to the predetermined protocol. All articles considered potentially relevant were acquired from library sources. Two members of the pCODR Methods Team independently made the final selection of studies to be included in the review and differences were resolved through discussion.

Included and excluded studies (with reasons for exclusion) are identified in section 6.3.1.

6.2.4 Quality Assessment

Assessment of study bias was performed by one member of the pCODR Methods Team with input provided by the Clinical Guidance Panel and other members of the pCODR Review Team. SIGN-50 Checklists were applied as a minimum standard. Additional limitations and sources of bias were identified by the pCODR Review Team.

6.2.5 Data Analysis

No additional data analyses were conducted as part of the pCODR review.

6.2.6 Writing of the Review Report

This report was written by the Methods Team, the Clinical Guidance Panel and the pCODR Secretariat:

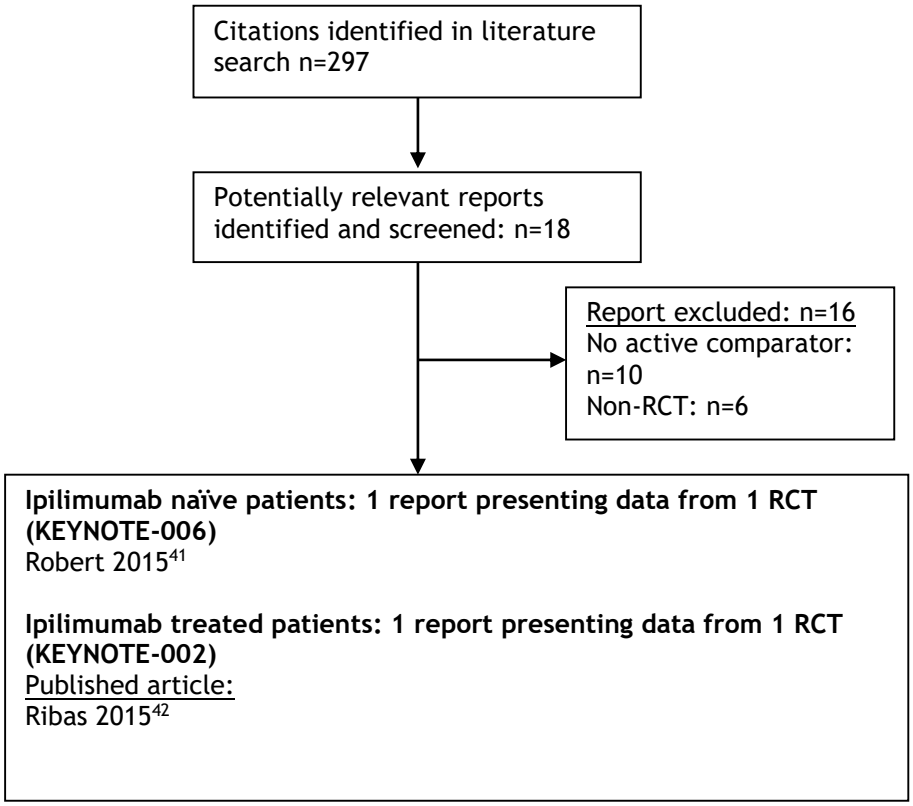
- The Methods Team wrote a systematic review of the evidence and summaries of evidence for supplemental questions.
- The pCODR Clinical Guidance Panel wrote a summary of background clinical information and the interpretation of the systematic review. The Panel provided guidance and developed conclusions on the net overall clinical benefit of the drug.
- The pCODR Secretariat wrote summaries of the input provided by patient advocacy groups and by the Provincial Advisory Group (PAG).

6.3 Results

6.3.1 Literature Search Results

Of the 18 potentially relevant reports identified, one study (KEYNOTE-006)[41] was included in the first line systematic review and one study (KEYNOTE-002)[42] was included in the second line systematic review.

Figure 6.1 QUOROM Flow Diagram for Inclusion and Exclusion of studies



Note: Additional data related to the KEYNOTE-002 and KEYNOTE-006 studies was also obtained through requests to the Submitter by pCODR[45]

6.3.2A Summary of Included Studies (ipilimumab naïve patients)

6.3.2.1A Detailed Trial Characteristics

Table 6.2 Summary of Trial characteristics of the included Study

Trial Design	Key Inclusion Criteria	Intervention and Comparator	Outcomes
KEYNOTE-006[41] (NCT01866319) Multicenter international active control phase III trial Enrollment: Sept 2013 to March 2014 n=834 1st interim analysis cut-off date: Sept 3, 2014 2nd interim analysis cut-off date: March 3, 2015 Median follow-up: 7.9 months Randomization ratio 1:1:1 stratified by • ECOG-PS (0 vs 1) • Line of therapy (1st vs 2nd) • PD-L1 expression (positive vs negative) Funded by: Merck Sharp & Dohme Corp.	• Patients who were 18 years of age or older were eligible for enrollment if they had histologically confirmed, unresectable stage III or IV melanoma • Received no more than one previous systemic therapy for advanced disease • Known BRAF V600 mutational status • Previous BRAF inhibitor therapy was not required for patients with normal LDH levels • No clinically significant tumor-related symptoms or evidence of rapidly progressive disease. • ECOG 0 or 1 • Assessing PD-L1 expression **Exclusion criteria** • Previous therapy with CTLA-4, PD-1 or PD-L1 inhibitors • Ocular melanoma • Active brain metastases • History of autoimmune disease	Pembrolizumab 10 mg/kg every 2 weeks Pembrolizumab 10 mg/kg every 3 weeks Ipilimumab 3 mg/kg every 3 weeks for 4 cycles	Primary outcomes: • Overall survival • Progression-free survival (PFS) Secondary outcomes: • Overall response rate • Duration of response • Safety

RECIST= Response Evaluation Criteria in Solid Tumours; **ECOG-PS** = Eastern Cooperation Oncology Group performance status; **LDH** = lactate dehydrogenase; **RCT**= randomized controlled trial; **PFS**= Progression free survival; **PD-L1**: programmed death legend 1; **PD-1**: Programmed cell death protein 1; **CTLA-4**: cytotoxic T-lymphocyte-associated protein 4.

a) Trials

One randomized controlled trial (KEYNOTE-006)[41] met the inclusion criteria of the first-line review (Table 6.2A). KEYNOTE-006 was a randomized open label clinical trial. Although the investigators and patients were not blinded, the independent review panel, which assessed the effect of treatment, were blinded to the allocation of treatment.

KEYNOTE-006 was sponsored by Merck Sharp & Dohme Corp. The study enrolled 834 patients with histologically confirmed stage III or IV melanoma in 16 countries. Patients were randomized in a 1:1:1 ratio to receive either pembrolizumab 10 mg/kg every 2 weeks, pembrolizumab 10 mg/kg every 3 weeks or four cycles of ipilimumab at 3 mg/kg every 3 weeks. Randomization was stratified by ECOG-PS, PD-L1 expression (positive or negative) and line of therapy (first versus second).

The primary outcomes of KEYNOTE-006 were overall survival and progression-free survival (PFS). These two outcomes were assessed during the two interim analyses. The first interim analysis was performed after the data cut-off date of Sept 3, 2014. The purpose of the first interim analysis was to evaluate the effect of pembrolizumab on PFS when compared with ipilimumab. The second interim analysis was performed after the data cut-off date of March 3, 2015. The purpose of the second interim analysis was to evaluate the effect of pembrolizumab and ipilimumab in terms of overall survival. Secondary outcomes included overall response rate, duration of response and safety.

Tumor response was assessed at week 12 and every 6 weeks thereafter. A blinded central radiologic review panel assessed the tumor response according to RECIST v1.1 criteria. Survival was assessed every 3 months after the discontinuation of treatment. Adverse events, lab value and vital signs were assessed regularly. Adverse events were graded according to the National Cancer institute CTCAE version 4.0. Quality of life (QoL) was assessed by the European Organization for Research and Treatment of Cancer QLQ-C30 (EORTC QLQ-30) at week 12. EORTC QLQ-30 is a questionnaire developed to assess cancer specific QoL. It assesses the QoL based on symptom, functional and social aspect. A decrease from baseline score would indicate a decrease of quality of life. The use of EORTC QLQ-30 in melanoma is not yet validated[43].

This study was not completed yet. The information in this review came from two interim analyses of the trial.

b) Populations

KEYNOTE-006 randomized 834 patients to receive either 10 mg/kg pembrolizumab every 2 week, or every 3 weeks or 4 cycles of 3 mg/kg ipilimumab. The median age of patients was 62 years. Male patients contributed to 60% of the population. Over 80% of patient had been classified as positive for PD-1 expression. BRAF mutation was found in 36% of the patients and 18% of patients had been treatment with BRAF or MEK inhibitors. Details of baseline characteristic are listed in table 6.3A.

Table 6.3 Baseline characteristics (KEYNOTE-006)[41]			
	Pembro every 2 weeks (n=279)	Pembro every 3 weeks (n=277)	Ipilimumab (n=278)
Age, median (range), year	61 (18-89)	63 (22-89)	62 (18-88)
Gender, n of Male (%)	161 (58%)	174 (63%)	162 (58%)
ECOG PS= 0	196 (70%)	189 (68%)	188 (68%)
ECOG PS= 1	83 (30%)	88 (32%)	90 (32%)
BRAF mutant	98 (35%)	97 (35%)	107 (39%)
PD-1 positive tumor	225 (81%)	221 (80%)	225 (81%)
Elevated LDH level	81 (29%)	98 (35%)	91 (33%)
M stage M0	9 (3%)	9 (3%)	14 (5%)
M stage M1[1]	6 (2%)	4 (1%)	5 (2%)
M stage M1a	21 (8%)	34 (12%)	30 (11%)
M stage M1b	64 (23%)	41 (15%)	52 (19%)
M stage M1c	179 (64%)	189 (68%)	177 (64%)
Brain metastasis	23 (8%)	27 (10%)	28 (10%)
No previous systemic therapy	183 (66%)	185 (67%)	181 (65%)
Tried one type of systemic therapy	96 (34%)	91 (33%)	97 (35%)
Type of previous therapy[2]			
Chemotherapy	36 (13%)	41 (15%)	29 (10%)
Immunotherapy	8 (3%)	7 (3%)	12 (4%)
BRAF or MEK inhibitor or both	50 (18%)	45 (16%)	56 (20%)

ECOG-PS = Eastern Cooperation Oncology Group performance status; **LDH** = lactate dehydrogenase; **PD-1**: Programmed cell death protein 1.

1. Further classification of the M stage was not provided.
2. List included only treatment for advance or metastatic disease.

c) Interventions

Patients were randomized to 10 mg/kg IV pembrolizumab once every 2 weeks or 3 weeks or 3 mg/kg IV ipilimumab every 3 weeks for 4 cycles. Patients would continue on pembrolizumab treatment for 24 months or until disease progression, unacceptable toxicity, investigator decision to discontinue or withdrawal of patient consent. Patients with confirmed complete response who received pembrolizumab for at least 6 months could discontinue therapy after receiving at least two doses beyond the determination of complete response. These patients should continue to undergo disease evaluations, and in the event of disease recurrence, pembrolizumab may be resumed in these patients. Patients who completed 24 months of treatment were monitored for an additional 24 months and could be eligible for re-induction with pembrolizumab until a maximum of 12 months upon progression. No information was provided on whether any patients received pembrolizumab as an induction treatment after completion of 2 years treatment followed by disease progression. Ipilimumab was taken for 4 cycles or until disease progression, the

onset of unacceptable toxicity, an investigator's decision to discontinue or withdrawal of patient consent.

KEYNOTE-006 was an open-label trial. However, the radiologists on the independent review panel were blinded to the allocation of treatment.

As for July 2015, pembrolizumab was not approved by Health Canada for first-line treatment of unresectable or metastatic melanoma. Therefore, recommended dose for this indication was not available.

d) Patient Disposition

Patient disposition is listed in table 6.4.

Table 6.4 Patient disposition (N)

	Pembro 10 mg/kg every 2 weeks	Pembro 10 mg/kg every 3 weeks	Ipilimumab
Screened	1106		
Randomized	279	277	278
Received treatment	278	277	256
Withdrawal due to disease progression	111	103	41
Withdrawal due to adverse effects	20	29	37
Withdrawal due to death	2	1	6
Withdrawal due to other reasons	17	19	16
Total number of withdrawal	150	152	100
Patients remain on treatment	128	125	144[1]
ITT analysis for efficacy	279	277	278
ITT analysis for safety	278	277	258

Footnote
1. Number of patients completed 4 cycle of ipilimumab treatment as assigned.

e) Limitations/Sources of Bias

The study was not yet completed. Critical appraisal of the trial was based on information from the interim analyses:

1. Randomization and allocation concealment (assessment the risk of selection bias)

   The study utilized the IVRS/IXRS system for centralized randomization. Once a patient passed through the screening process and met all the inclusion criteria, an allocation number was assigned through the IVRS/IXRS system. Each patient could only have one allocation number and it could not be changed. Treatment was given according to the allocation number. This procedure was adequate to minimize the risk of selection bias. In

addition, the baseline characteristics were well balanced. Therefore, the risk of selection bias was low in KEYNOTE-006

2. Blinding (assessment of performance and detection bias)

   KEYNOTE-006 was an open label study. However, the analysis team and reporting team were blinded to the treatment assignment. The radiologists on the central imaging review panel were also blinded to the treatment allocation. Therefore, the risk of performance bias was low.

3. Attrition (assessment of attrition bias)

   The primary reason for discontinuation of treatment in KEYNOTE-006 was due to disease progression (primary end-point). The number of patients drop-out due to other reason was between 14% in the group taking pembrolizumab every 2 weeks, 18% in the group taking pembrolizumab every 3 weeks and 21% in the ipilimumab arm.
   The efficacy outcomes were analyzed according to the intention to treat principle. Safety outcomes analysis used the as-treated population, which included 97% of the randomized patients. The risk of attrition bias was low.

4. Reporting of outcomes (assessment of reporting bias)

   The most common adverse effect was reported as treatment-related. However, the reporting team was blinded to the allocation of the treatment. In addition, the kind of adverse effect and the severity reported were similar to other pembrolizumab studies. Other than that, all the relevant outcomes were reported. We found no evidence to raise concern about the outcome reporting of KEYNOTE-006. The risk of reporting bias was low.

5. Other limitations

   Pembrolizumab does not have Health Canada approval to treatment ipilimumab naïve patients. Currently, there is not an approved dosage or duration of treatment for pembrolizumab in ipilimumab naïve patients either.

6.3.2.2A Detailed Outcome Data and Summary of Outcomes (Ipilimumab naïve patients)

The efficacy outcomes were analyzed according to the intent-to-treat principle. Safety population included only patients who had received at least one treatment after randomization. Table 6.5 summarizes the key outcome in KEYNOTE-006.

Table 6.5 Summary of key outcomes in KEYNOTE-006[41]

	Pembrolizumab every 2 weeks	Pembrolizumab every 3 weeks	Ipilimumab
1-year overall survival (n/N)	207/279 (74.1%)	189/277 (68.4%)	162/278 (58.2%)
Hazard ratio (95%CI) for death comparing pembrolizumab and ipilimumab	0.63 (0.47, 0.83) p<0.0005	0.69 (0.52, 0.9) p=0.0036	---
6-month progression free survival (n/N)	132/279 (47.3%)	129/277 (46.4%)	74/278 (26.5%)
Hazard ratio for disease progression comparing pembrolizumab and ipilimumab	0.58 (0.46, 0.72) p<0.001	0.58 (0.47, 0.72) p<0.001	---
Quality of life (EORTC QLQ-C30, least square mean of overall score change from baseline (95% CI)	-2.3 (-5.21, 0.62)	-2.6 (-5.44, 0.23)	-9.9 (-13.01, -6.72)
Difference of LS mean score between pembrolizumab and ipilimumab	7.6 (3.40, 11.75) p=0.0004	7.3 (3.15, 11.38) p=0.0006	---
Overall response rate (n/N)	94/279 (33.7%)	91/277 (32.9%)	33/278 (11.9%)
Estimated percentage difference in overall response rate between pembrolizumab and ipilimumab	16.1% (7.8, 24.5) p<0.001	17.2% (9.5-25.6) p<0.001	---
Withdrawal due to adverse effects (n/N)	20/278 (7.2%)	29/277 (10.5%)	37/256 (14.5%)
Statistic comparing pembrolizumab and ipilimumab in withdrawal due to AE	NR	NR	---
Number of patients experiencing at least one all cause grade 3-5 adverse event	105/278 (37.8%)	92/277 (33.2%)	94/256 (36.7%)
Hazard ratio for all cause grade 3-5 adverse event comparing pembrolizumab and ipilimumab	0.59 (0.43, 0.80) p<0.001	0.52 (0.38, 0.72) p<0.001	---
Number of patients with at least one drug related adverse effect	211/278 (79.5%)	202/277 (72.9%)	187/256 (73.0%)

Efficacy outcomes

Overall survival

The overall survival analysis was performed after 289 patients had died and the minimum follow-up duration was 12 months for all patients. The data cut-off date for the overall survival analysis was March 3, 2015. It was conducted in an un-blinded manner by a statistician employed by Merck.

The overall survival was defined as the time from randomization to death from any cause. The one-year overall survival rate was 74.1% for patients taking pembrolizumab every 2 weeks, 68.4% for patients taking pembrolizumab every 3 weeks and 58.2% for patients taking ipilimumab. The hazard ratio (95% CI) for death compared with ipilimumab was 0.63 (0.47 – 0.83, p<0.0005) for pembrolizumab every 2 weeks, 0.69 (0.52-0.90, p=0.0036) for pembrolizumab every 3 weeks. A second database lock occurred May 2015 from which OS was subsequently assessed as a sensitivity analysis. There was no difference in the OS and results were essentially identical to the March 3, 2015 OS results. The submitter confirmed that the OS results from the May 2015 analysis will not be published separately.[45]

Similar effect was observed for OS in most subgroups with the exception for PD-L1 negative patients. In this subgroup, the hazard ratio for death when compared with ipilimumab was 0.91 (0.49-1.69) for patients taking pembrolizumab every 2 weeks and 1.02 (0.56-1.85) for patients taking pembrolizumab every 3 weeks. The study was stopped early after the overall survival analysis. Median overall survival was not reached in any study group.

Progression free survival

Progression-free survival was defined as time from randomization to documented disease progression according to RESIST by blinded independent review or death from any cause. Progression-free survival (PFS) analysis was performed after 502 PFS events had occurred. The data cut-off date was September 3, 2014. It was conducted by an independent statistician who was not blinded to the treatment assignment.

Median PFS were 5.5 months, 4.1 months, 2.8 months respectively. The hazard ratio for disease progression (95% CI) when compared with ipilimumab was 0.58 (0.46-0.72, p<0.001) for 2-week regimen and 0.58 (0.47-0.72, p<0.001) for 3-week regimen. The 6-month PFS rate was 47.3% for patients taking pembrolizumab every 2 weeks, 46.4% for patients taking pembrolizumab every 3 weeks and 26.5% for patients taking ipilimumab. As of March 5, 2015, the pre-specified second interim analysis, approximately 34% of patients were still in the PFS state in the pembrolizumab arms compared to approximately 15% in the ipilimumab arm.

Subgroups analysis showed similar effect in most of the pre-specified subgroups. (See Figure 2A and B in Robert et al 2015, NEJM Publication for KEYNOTE-006 Study)

Quality of life

Quality of life was assessed by the European Organization for Research and Treatment of Cancer QLQ-C30 (EORTC QLQ-30) at week 12. Only 458 (54.9%) patients among 834 randomized patients participated in the quality of life assessment at both baseline and week 12. Results showed that QoL decreased in all three arms, although less of a decline was measured in the pembrolizumab arms compared to the ipilimumab arm. The least square mean (95% CI) of score change from baseline was -2.3 (-5.21, 0.62) in the pembrolizumab Q2W arm, -2.6 (-5.44, 0.23) in the pembrolizumab Q3W arm and -9.9 (-13.01, -6.72) in the ipilimumab arm. The difference of least square mean was 7.6 (3.40, 11.75) (p=0.0004) between pembrolizumab Q2W and ipilimumab, 7.3 (3.15, 11.38) (p=0.0006) between pembrolizumab Q3W and ipilimumab. A melanoma specific QoL module is still being developed[47]. However, the minimum clinically important differences (MCIDs) for EORTC QLQ-C30 have been established in other types of cancer[48]. A mean difference of 5 to 10 in global health score was considered as small change.

Overall response rate

The overall response rate was assessed by the independent review panel according to RECIST v 1.1 criteria. The overall response rate was 33.7% in patients taking pembrolizumab every 2 weeks, 32.9% in patients taking pembrolizumab every 3 weeks and 11.9% in patients taking ipilimumab. The overall response rate were significantly higher in both pembrolizumab arms when compared with ipilimumab (both p<0.001). Rate of complete response were 5.0%, 6.1% and 1.4% respectively. The median times to response were 86 days, 85 days and 87 days respectively.

Harm outcomes

Withdrawal due adverse effects

Among the 811 patients in the safety population, the rate of withdrawal due to adverse effect was 20/278 (7.2%) in patients taking pembrolizumab every 2 weeks, 29/277 (10.5%) in patients taking pembrolizumab every 3 weeks and 37/256 (14.5%) in patients taking ipilimumab.

Grade 3 and 4 adverse events

Number of patients who experience at least one grade 3-5 adverse event regardless of the cause was reported. The rate of grade 3-5 adverse event was 105/278 (37.8%) in patients taking pembrolizumab every 2 weeks, 92/277 (33.2%) in patients taking pembrolizumab every 3 weeks and 94/256 (36.7%) in patients taking ipilimumab. Among grade 3-5 AE attributed to a study drug by investigators, 13.3%, 10.1%, and 19.9% occurred in patients in the 2-week regimen, 3-week regimen and ipilimumab arms, respectively). The median time to the first onset of grade 3-5 adverse event were 59 days, 64 days and 39.5 days respectively. The hazard ratio (95% CI) of grade 3-5 adverse event when compared with ipilimumab was 0.59 (0.43-0.80, p<0.001) for patients taking pembrolizumab every 2 weeks and 0.52 (0.38-0.72, p<0.001) for patients taking pembrolizumab every 3 weeks.

Immune-mediated adverse effects

The most common immune-mediated adverse effects were hypothyroidism, hyperthyroidism and colitis. Generally around 1% of patients experienced immune-mediated adverse effect at grade 3-5 severity except for colitis, which was found in 2.5% of patients in pembrolizumab Q3W arm and 7% of patients in ipilimumab arm.

Most common adverse effects

The rate of treatment-related adverse effect was reported in the article. The investigators, who were not blinded, attributed the relationship between an adverse effect and the study

drugs. The number of patients who experience at least one adverse effect was 211/278 (79.5%) in patients taking pembrolizumab every 2 weeks, 202/277 (72.9%) in patients taking pembrolizumab every 3 weeks and 187/256 (73.0%) in patients taking ipilimumab. Table 6.6 and 6.7 summarizes the most common treatment related adverse effect and adverse effect of special interest.

Table 6.6 Most common treatment-related adverse effects

	Pembrolizumab 10 mg/kg every 2 weeks (n=278)		Pembrolizumab 10 mg/kg every 3 weeks (n=277)		Ipilimumab (n=256)	
Adverse effects observed in more than 10% of patients	Grade 1-2	Grade 3-5	Grade 1-2	Grade 3-5	Grade 1-2	Grade 3-5
Any	221 (79.5%)	37 (13.3%)	202 (72.9%)	28 (10.1%)	187 (73.0%)	51 (19.9%)
Fatigue	58 (20.9%)	0	53 (19.1%)	1 (0.4%)	39 (15.2%)	3 (1.2%)
Pruritus	40 (14.4%)	0	39 (14.1%)	0	65 (25.4%0	1 (0.4%)
Nausea	28 (10.1%)	0	31 (11.2%)	1 (0.4%)	22 (8.6%)	1 (0.4%)
Diarrhea	47 (16.9%)	7 (2.5%)	40 (14.4%)	3 (1.1%)	58 (22.7%)	8 (3.1%)
Rash	41 (14.7%)	0	37 (13.4%)	0	37 (14.5%)	2 (0.8%)
Arthralgia	26 (9.4%)	0	32 (11.6%)	1 (0.4%)	13 (5.1%)	2 (0.8%)
Asthenia	32 (11.5%)	1 (0.4%)	31 (11.2%)	0	16 (6.3%)	2 (0.8%)
Vitiligo	25 (9.0%)	0	31 (11.2%)	0	4 (1.6%)	0

Table 6.7 Adverse effect of special interest (all cause)

	Pembrolizumab 10 mg/kg every 2 weeks (n=278)		Pembrolizumab 10 mg/kg every 3 weeks (n=277)		Ipilimumab (n=256)	
All cause adverse event of special interest	Grade 1-2	Grade 3-5	Grade 1-2	Grade 3-5	Grade 1-2	Grade 3-5
Hypothyroidism	28 (10.1%)	1 (0.4%)	24 (8.7%)	0	5 (2.0%)	0
Hyperthyroidism	18 (6.5%)	0	9 (3.2%)	0	6 (2.3%)	1 (0.4%)
Colitis	5 (1.8%)	4 (1.4%)	10 (3.6%)	7 (2.5%)	21 (8.2%)	18 (7.0%)
Hepatitis	3 (1.1%)	3 (1.1%)	5 (1.8%)	5 (1.8%)	3 (1.2%)	1 (0.4%)
Hypophysitis	1 (0.4%)	1 (0.4%)	2 (0.7%)	1 (0.4%)	6 (2.3%)	4 (1.6%)
Pneumonitis	1 (0.4%)	0	5 (1.8%)	1 (0.4%)	1 (0.4%)	1 (0.4%)
Type 1 diabetes mellitus	1 (0.4%)	1 (0.4%)	1 (0.4%)	1 (0.4%)	0	0
Uveitis	1 (0.4%)	0	3 (1.1%)	0	0	0
Myositis	0	0	2 (0.7%)	0	1 (0.4%)	0
Nephritis	0	0	1 (0.4%)	0	1 (0.4%)	1 (0.4%)

6.3.2B Summary of Included Studies (Previously treated with Ipilimumab and, if BRAF mutation positive, a BRAF inhibitor)

6.3.2.1B Detailed Trial Characteristics

Table 6.8 Summary of Trial characteristics of the included Study

Trial Design	Key Inclusion Criteria	Intervention and Comparator	Outcomes
KEYNOTE-002[42] (NCT01704287) Multicenter international DBRCT active control phase II trial Enrollment: Nov 2012 to Nov 2013 Interim analysis cut off date: May 12, 2014 Median follow-up: 10 months Randomization ratio 1:1:1 stratified by • ECOG-PS (0 vs 1) • LDH (normal vs elevated) • BRAF status (mutant vs wild type) n=540 Funded by: Merck Sharp & Dohme Corp.	• Patient with advance melanoma • Disease progression within 24 weeks after ≥ 2 ipilimumab doses • Patient previously BRAF or MEK inhibitor if they have BRAF mutant gene. • ECOG-PS 0 or 1 • Resolution of ipilimumab adverse effects. **Exclusion criteria** • Chronic systemic steroid therapy (>10 mg/day prednisone or equivalent). • Active autoimmune disease. • Expected to require any other form of systemic or localized antineoplastic therapy while on study. • Known active central nervous system (CNS) metastases and/or carcinomatous meningitis. • Prior treatment with any other anti-programmed cell death (PD) agent • Active infection requiring systemic therapy • Known history of Human Immunodeficiency Virus (HIV) • Active Hepatitis B or C • Regular user (including recreational use of) illicit drugs or had a recent history (within the last year) of substance abuse (including alcohol) • Pregnant, breastfeeding or expecting to conceive or father children within the projected duration of the study	1. Pembrolizumab 2 mg/kg once every 3 weeks 2. Pembrolizumab 10 mg/kg once every 3 weeks 3. Standard chemotherapy (Carbo-texol, paclitaxel, carboplatin, dacarbazine or temozolomide)	Primary outcomes: • Overall survival • Progression-free survival (PFS) Secondary outcomes: • Overall response rate • Duration of response • Safety • HRQoL at week 12

CR= complete response; **DB**= double-blind; **PC**= placebo controlled; **PR**= partial response; **RECIST**= Response Evaluation Criteria in Solid Tumours; **ECOG-PS** = Eastern Cooperation Oncology Group performance status; **LDH** = lactate dehydrogenase; **RCT**= randomized controlled trial; **PFS**= Progression free survival; **HRQoL**: Health Related Quality of Life.

a) Trials

One randomized controlled trial (KEYNOTE-002)[42] met the inclusion criteria of the second-line review (Table 6.8). The investigators and patients were blinded to the assignment of pembrolizumab dosage. The allocation of whether patients were assigned into pembrolizumab or standard chemotherapy was not blinded. A blinded, central review panel assessed the patients' response to treatment.

KEYNOTE-002 was sponsored by Merck Sharp & Dohme Corp. It was being conducted in 12 countries including the U.S., Europe, Israel and Argentina. The study enrolled patients with ipilimumab refractory melanoma, defined by confirmed disease progression in 24 weeks following more than 2 doses of ipilimumab. If a BRAF mutation was present, patient had to have previously been treated with BRAF inhibitor or MEK inhibitor when eligible. A total of 540 patients were randomized in a 1:1:1 ratio to receive either pembrolizumab 2 mg/kg once every 3 weeks, pembrolizumab 10 mg/kg once every 3 weeks or investigators' choice standard chemotherapy. Randomization was stratified by ECOG-PS, LDH and BRAF status.

The primary outcomes of KEYNOTE-002 were overall survival and progression free survival (PFS). The interim analysis was performed pre-specifically after 270 PFS events had occurred. The analysis cut-off date was May 12, 2014. Median follow-up time at the interim analysis was 10 months.

Secondary outcomes included overall response rate, duration of response and safety. Response was assessed at week 12 then every 6 weeks up to week 48, then every 12 weeks thereafter, using RECIST v1.1 by a blinded independent central review panel. Supportive analyses by investigator review used RECIST v1.1 and modified RECIST v1.1. Modified RECIST v1.1 was required to confirm progression of disease. The study was powered to evaluate superiority of either pembrolizumab doses over control at $\alpha = 0.25\%$ (one-sided), the estimated hazard ratio was 0.66. The estimated enrollment was 510 patients.

This study was not completed yet. The outcome data came from an interim analysis of the trial.

b) Populations

KEYNOTE-002 randomized 540 patients to receive either 2 mg/kg pembrolizumab every 3 weeks, 10 mg/kg pembrolizumab every 3 weeks or standard chemotherapy. The overall median age was 61.5 years (range 18 to 89 years). Male patients contributed to 61% of the population. ECOG performance status was similar between treatment arms, which 55% of all patients having performance status of zero and 45% having performance status of one. BRAF mutation was found in 23% of all patients. There was no significant difference in the percentages of patient having BRAF mutation between treatment arms. The study reported that 25% of all patients had previously been treated with a BRAF or MEK inhibitor. No explanation was given why 2% of non-BRAF mutated patients received BARF/MEK inhibitor. Details of baseline characteristic are listed in table 6.9.

Table 6.9 Baseline characteristics				
	Standard chemotherapy (n= 179)	Pembro 2 mg/kg every 3 weeks (n= 180)	Pembro 10 mg/kg every 3 weeks (n= 181)	Overall total (n=540)
Age, median (range), year	63.0 (27-87)	62.0 (15-87)	60.0 (27-89)	61.5 (15-89)
Gender, n of Male (%)	114 (63.7%)	104 (57.8%)	109 (60.2%)	327 (60.6%)
ECOG PS= 0	99 (55%)	98 (54%)	98 (54%)	295 (55%)
ECOG PS= 1	80 (45%)	80 (44%)	83 (46%)	243 (45%)
BRAF mutant	41 (23%)	44 (24%)	40 (22%)	125 (23%)
BRAF wild type	138 (77%)	136 (76%)	141 (78%)	415 (77%)
Tumor size mean (SD)	n=165 126.1 mm (96.6)	n=165 121.9 mm (89.2)	n=163 122.6 mm (99.6)	n=493 123.5 mm (95.1)
Normal LDH level	107 (60%)	99 (55%)	105 (58%)	311 (58%)
Elevated LDH level (≥110% ULN)	68 (38%)	77 (43%)	73 (40%)	218 (40%)
Unknown or missing LDH level	4 (2%)	4 (2%)	3 (2%)	11 (2%)
M stage M0	2 (1%)	1 (<1%)	1 (<1%)	4 (<1%)
M stage M1a	15 (8%)	9 (5%)	13 (7%)	37 (7%)
M stage M1b	15 (8%)	22 (12%)	17 (9%)	54 (10%)
M stage M1c	147 (82%)	148 (82%)	150 (83%)	445 (82%)
No. of previous therapy[1]				
0	0 (0%)	1 (<1%)	0 (0%)	1 (<1%)
1	47 (26%)	40 (22%)	56 (31%)	143 (26%)
2	78 (44%)	79 (44%)	66 (37%)	223 (41%)
≥3	54 (30%)	60 (33%)	59 (33%)	173 (32%)
Types of previous therapy				
Ipilimumab	179 (100%)	180 (100%)	181 (100%)	540 (100%)
Interleukin-2	12/179 (7%)	21/ 180 (12%)	16/181 (9%)	49/540 (9%)
Other immunotherapy	23/179 (13%)	25/180 (14%)	18/181 (10%)	66/540 (12%)
Chemotherapy	86/179 (48%)	90/180 (50%)	84/181 (46%)	260/540 (48%)
BRAF or MEK inhibitor	43/179 (24%)	46/180 (26%)	45/181 (25%)	134/540 (25%)

ECOG-PS = Eastern Cooperation Oncology Group performance status; **LDH** = lactate dehydrogenase.
Footnote:

- Number of prior lines of therapies equal to 0 indicates patients only received adjuvant/ neoadjuvant therapies.

c) Interventions

Patients received either 2 mg/kg IV pembrolizumab for 30 minutes every 3 weeks, 10 mg/kg IV pembrolizumab for 30 minutes every 3 weeks or investigators' choice chemotherapy. Four different chemotherapy regimens were used by the investigators, which included carboplatin + paclitaxel, paclitaxel alone, dacarbazine, or temozolomide. If patients were assigned to pembrolizumab, both patients and investigators were blinded to the dosage of pembrolizumab. The allocation of pembrolizumab or chemotherapy was not blinded.

Among the 2 pembrolizumab dosages used in this study, only 2 mg/kg pembrolizumab is the recommended dose in product monograph approved by Health Canada[49]. It is also the only recommended dose approved by the FDA[50].

d) Patient Disposition

Patient disposition is listed in table 6.10.

Table 6.10 Patient disposition (N)

	Pembro 2 mg/kg	Pembro 10 mg/kg	Chemotherapy
Screened	672		
Randomized	180	181	179
Received treatment	178	179	171
Withdrawal due to disease progression	89	76	128
Withdrawal due to adverse effects	21	24	18
Withdrawal due to death	0	1	1
Withdrawal due to other reasons	16	17	10
Total withdrawal	126	118	157
Patients remain on treatment	52	61	14
ITT analysis for efficacy	180	181	179
ITT analysis for safety	178	179	171

e) Limitations/Sources of Bias

The study was not yet completed. Critical appraisal of the trial was based on information from the interim analysis:

- Randomization and allocation concealment (assessment of selection bias)

  The study utilized the IVRS/IXRS system for centralized randomization. Once a patient passed through the screening process and met all the inclusion criteria, an allocation number was assigned through the IVRS/IXRS system. Prior to randomization, the physician chose the chemotherapy regimen in the case when the patient was randomized to chemotherapy. After the investigator entered the information of the patient into the IVRS/IXRS system, an allocation number would be assigned to the patient. Each patient could only have one allocation number and it could not be changed. Treatment was given

according to the allocation number. This procedure was adequate to minimize the risk of selection bias. In addition, the baseline characteristics were well balanced. The risk of selection bias in KEYNOTE-002 was low.

- Blinding (assessment of performance and detection bias)

  Patients and investigators were blinded to the dosage of pembrolizumab, but the allocation between pembrolizumab and chemotherapy was not blinded. The independent radiologic review panel was blinded to the treatment assignment. Information on treatment allocation was never sent to the vendor for central imaging review. Images were saved in a digital imaging and communications in medicine (DICOM) file format. All electronic header information (e.g., subject identifiers) was blinded within the digital data set. Therefore, the risk of performance bias was low for KEYNOTE-002.

- Attrition (assessment of attrition bias)

  The efficacy outcomes in this study were analyzed according to the intention-to-treat principle for the interim analysis. All the patients were accounted for in the report. The safety population included only the patients who received at least one treatment. Twelve of the randomized 540 patients (2%) did not receive treatment and thus not included in the safety population. Therefore, the risk of attrition bias was low.

- Reporting of outcomes (assessment of reporting bias)

  Until the 25th of August, 2015, the analysis for overall survival was not performed because the number of deaths had not yet reached the pre-specified 370 deaths. PFS was reported with median follow-up of 10 months. Secondary outcomes were reported in this review. The risk of reporting bias was low.

- Other limitation

  Forty eight percents of patients in chemotherapy group crossed over to receive pembrolizumab after confirmed disease progression on chemotherapy. Since these patients were still being followed for overall survival, the high crossover rate could potentially underestimate the difference between pembrolizumab and chemotherapy in overall survival. The reviewers should be aware of this potential effect when interpreting the overall survival analysis.

6.3.2.2B Detailed Outcome Data and Summary of Outcomes

Patients were evaluated every 6 weeks from week 12 to week 48, then every 12 week thereafter. All patients had a minimum follow-up of 24 weeks. The median duration of follow-up was 10 months at the time of the interim analysis. The cut-off date for the interim analysis was May 12, 2014. Table 6.11 summarizes the key outcome in KEYNOTE-002.

Table 6.11 Summary of key outcomes in KEYNOTE-002[42]

	Pembrolizumab 2 mg/kg	Pembrolizumab 10 mg/kg	Chemotherapy
6-month progression free proportion	34%	38%	16%
9-month progression free proportion	24%	29%	8%
Hazard ratio (95% CI) of death or disease progression comparing pembrolizumab and chemotherapy	0.57 (0.45, 0.73) p<0.0001	0.50 (0.39, 0.64) p<0.0001	---
Quality of life (EORTC QLQ-C30, least square mean of overall score change from baseline (95% CI)	-2.6 (-6.15, 0.96)	-2.55 (-5.99, 0.89)	-9.13 (-12.86, -5.39)
Difference of LS mean score between pembrolizumab and chemotherapy	6.53 (1.53, 11.53) p=0.011	6.57 (1.65, 11.50) p=0.009	---
Overall response rate (n/N)	38/180 (21%)	46/181 (25%)	8/179 (4%)
Difference in overall response between pembrolizumab and chemotherapy (95% CI)	13% (7%, 21%) p<0.0001	18% (11%, 27%) p<0.0001	---
Withdrawal due to adverse effects (n/N)	21/178 (12%)	25/179 (14%)	19/171 (11%)
Withdrawal due to grade 3-5 adverse event	16/178 (9%)	25/179 (14%)	13/171 (8%)
Odds ratio for withdrawal due to grade 3-5 adverse event comparing pembrolizumab and chemotherapy	1.20 (0.56, 2.58)	1.97 (0.97, 4.00)	---
Number of patients experiencing at least one all cause grade 3-5 adverse event	83/178 (46.6%)	79/179 (44.1%)	88/171 (51.5%)
Relative risk for all cause grade 3-5 adverse event	0.91 (0.73, 1.12) p=0.3669	0.86 (0.69, 1.07) p=0.1709	---
Number of patients experiencing at least one adverse effect	122/178 (68.5%)	133/179 (74.3%)	138/171 (80.7%)

The efficacy outcomes were analyzed according to the intent-to-treat principle. Safety population included only patients who had received at least one treatment after randomization.

Efficacy outcomes

Overall survival

The final overall survival analysis was planned to occur after 370 deaths. As of August 25th of 2015, the pre-specified number of deaths required for overall survival analysis had not been reached yet. Therefore, no overall survival analysis was conducted at this point.

Progression free survival

Progression-free survival (PFS) was the primary end point of KEYNOTE-002. It was defined as the time from randomization to confirmed disease progression by independent central review according to RECIST v1.1 criteria. The median time of progression-free survival was 2.9 months (range 2.8-3.8) for 2 mg/kg pembrolizumab, 2.9 months (range 2.8-4.7) in 10 mg/kg pembrolizumab and 2.7 months (range 2.5-2.8) for chemotherapy group.

After 6 months, 34% of patients in the 2 mg/kg pembrolizumab arm and 38% of patients in the 10 mg/kg pembrolizumab arm remained progression-free compared with 16% of patients in the chemotherapy arm. At 9 month, the progression-free rate was 24% for the 2 mg/kg pembrolizumab arm, 29% for the 10 mg/kg pembrolizumab arm and 8% for chemotherapy group. The restricted mean PFS time, based on data from 12 months of follow-up, was 5.4 months for the 2 mg/kg pembrolizumab arm, 5.8 months for the 10 mg/kg pembrolizumab arm and 3.6 months for the chemotherapy arm.

The hazard ratio for death or disease progression (95% CI) was 0.57 (0.45-0.73, p<0.0001) for 2 mg/kg pembrolizumab and 0.50 (0.39-0.64, p<0.0001) for 10 mg/kg pembrolizumab compared with chemotherapy group. The PFS hazard ratio (95% CI) comparing the two pembrolizumab arms was 0.91 (0.71-1.16, p=0.44).

Subgroup analysis was done on various pre-specified subgroups (See Figure 3, Ribas et al 2015, Lancet Publication). In BRAF wild type subgroups, both doses of pembrolizumab showed significant differences compared to chemotherapy. However, in patients with BRAF mutation, only 10 mg/kg pembrolizumab showed significant when compared to chemotherapy. Interaction analysis between BRAF status and treatment arms was not significant in any of the subgroup.

Quality of life

Quality of life was assessed by the European Organization for Research and Treatment of Cancer QLQ-C30 (EORTC QLQ-30) at week 12. A negative change in score from baseline would indicate a decrease in the quality of life. The least squares mean change (95% CI) from baseline at week 12 was -2.60 (-6.15, 0.96) in the 2 mg/kg pembrolizumab arm, -2.55 (-5.99, 0.89) in 10 mg/kg pembrolizumab arm and -9.13 (-12.86, -5.39) in the chemotherapy arm. The difference in least squares mean change from baseline was 6.53 (1.53, 11.53; p=0.011) between 2 mg/kg pembrolizumab and chemotherapy, and 6.57 (1.65, 11.50; p=0.009) between 10 mg/kg pembrolizumab and chemotherapy. The difference in the least square mean change of score between the two pembrolizumab group was 0.04 (p=0.986).The decrease in quality of life during treatment was significantly less in pembrolizumab arms compared with chemotherapy arms. A melanoma specific QoL module is still being developed47. However, the minimum clinically important differences (MCIDs) for EORTC QLQ-C30 have been established in

other types of cancer48. A mean difference of 5 to 10 in global health score was considered as small change.

Overall response rate

The overall response rate (ORR) was assessed by the independent central review panel according to RECIST v1.1 criteria. Patients were evaluated every 6 weeks from week 12 to week 48, then every 12 weeks thereafter. The ORR was 38/180 (21%) in patients taking 2 mg/kg pembrolizumab, 46/181 (25%) in patients taking 10 mg/kg pembrolizumab and 8/179 (4%) in chemotherapy group. When compared with chemotherapy in ORR, the p value was less than 0.0001 in both 2 mg/kg and 10 mg/kg pembrolizumab group. Four (2%) patients taking 2 mg/kg pembrolizumab, 5 (3%) patients taking 10 mg/kg pembrolizumab showed completed response, compared with none of the patients taking chemotherapy showed complete response.

Harm outcomes

Withdrawal due adverse effects

Withdrawal due to adverse effect is defined as the adverse effect serious enough to cause discontinuation of the respective treatment. Among the 528 patients in the safety population, 21/178 (12%) patients in 2 mg/kg pembrolizumab, 25/179 (13%) patients in 10 mg/kg pembrolizumab arm discontinued their treatment due to adverse effect compared with 19/171 (11%) patients in chemotherapy arm.

The rate of grade 3-5 adverse events that lead to withdrawal from treatment was 16/178 (9%) in 2 mg/kg pembrolizumab, 25/179 (14%) in 10 mg/kg pembrolizumab and 13/171 (8%) in the chemotherapy arm. The odds ratio (95% CI) for withdrawal due to grade 3-5 adverse event in pembrolizumab arms compared with chemotherapy was 1.20 (0.56, 2.58) in 2 mg/kg pembrolizumab arm and 1.97 (0.97, 4.00) in 10 mg/kg pembrolizumab arm.

Grade 3 to 5 adverse events

The definition of grade 3 adverse event according to the U.S. National Cancer Institute is severe or medically significant but not immediately life-threatening adverse event, resulting in hospitalization, prolongation of hospitalization or disabling, limiting self-care activities of daily living. Grade 4 adverse event is defined as life-threatening consequences or when urgent intervention indicated. Grade 5 adverse event is defined as death[44].

The authors reported the results for treatment related grade 3-4 adverse event. Rates of treatment related grade 3-4 adverse events were similar between the three arms [20/178 (11%) vs. 25/179 (14%) vs. 45/171 (26%) respectively, in the 2mg, 10mg and chemotherapy arms]. The Methods team requested information on all cause grade 3-5 AE's from the submitter. While the actual proportions of patients experiencing all cause grade 3-5 AE's was not made disclosable, the proportion of patients experiencing all cause grade 3-5 AE's was numerically higher in all three arms (by approximately 20% per arm). No significant difference was however identified for 'all-cause' Grade 3-5 AEs between treatment arms. There were no 'treatment-related' deaths.[45]

Most common adverse effects

One hundred twenty one of 178 (68.5%) patients in 2 mg/kg pembrolizumab, 133 of 179 (74.3%) patients in 10 mg/kg pembrolizumab experienced at least 1 treatment-related adverse effect of any grade compared with 138 of 171 (80.7%) patients in chemotherapy arm. Table 6.11 summarizes the most common treatment-related adverse effects.

Table 6.11 Most common treatment-related adverse effects						
	Pembrolizumab 2 mg/kg (n=178)		Pembrolizumab 10 mg/kg (n=179)		Chemotherapy (n=171)	
Adverse effects observed in more than 5% of patients	Grade 1-2	Grade 3-4	Grade 1-2	Grade 3-4	Grade 1-2	Grade 3-4
Any	101 (57%)	19 (11%)	107 (60%)	25 (14%)	93 (54%)	45 (26%)
Fatigue	38 (21%)	2 (1%)	51 (28%)	1 (<1%)	54 (32%)	8 (5%)
Pruritus	37 (21%)	0	42 (23%)	0	6 (4%)	0
Nausea	8 (4%)	0	15 (8%)	1 (<1%)	52 (30%)	4 (2%)
Decreased appetite	8 (4%)	0	15 (8%)	2 (1%)	26 (15%)	0
Anemia	4 (2%)	1 (<1%)	7 (4%)	0	26 (15%)	9 (5%)
Diarrhea	15 (8%)	0	17 (9%)	2 (1%)	11 (6%)	3 (2%)
Rash	21 (12%)	0	18 (10%)	0	8 (5%)	0
Alopecia	5 (3%)	0	1 (<1%)	0	24 (20%)	1 (<1%)
Vomiting	1 (<1%)	1 (<1%)	9 (5%)	1 (<1%)	22 (13%)	4 (2%)
Arthralgia	12 (7%)	1 (<1%)	10 (6%)	1 (<1%)	8 (5%)	1 (<1%)
Constipation	5 (3%)	0	9 (5%)	0	14 (8%)	0
Myalgia	7 (4%)	2 (1%)	7 (4%)	0	9 (5%)	1 (<1%)
Asthenia	5 (3%)	1 (<1%)	7 (4%)	1 (<1%)	9 (5%)	1 (<1%)
Hypothyroidism	9 (5%)	0	13 (7%)	0	0	0
Vitiligo	10 (6%)	0	9 (5%)	0	2 (1%)	0
Dry skin	9 (5%)	0	9 (5%)	0	2 (1%)	0
Thrombocytopenia	2 (1%)	0	0	1 (<1%)	12 (7%)	4 (2%)
Neutropenia	1 (<1%)	0	1 (<1%)	0	8 (5%)	6 (3%)
Peripheral neuropathy	2 (1%)	0	0	0	12 (7%)	2 (1%)
Maculopapular rash	4 (2%)	1 (<1%)	9 (5%)	1 (<1%)	0	0
Leucopenia	0	0	0	0	8 (5%)	6 (3%)
Paraesthesia	1 (<1%)	0	2 (1%)	0	11 (6%)	0
Decreased platelet count	0	0	1 (<1%)	0	8 (5%)	5 (3%)

6.4 Ongoing Trials

No ongoing and/or unreported trials were identified that would have met the inclusion criteria for the systematic review.

7 SUPPLEMENTAL QUESTIONS

The following supplemental questions were identified during development of the review protocol as relevant to the pCODR review of pembrolizumab (Keytruda) for metastatic melanoma

- Critical appraisal of a network meta-analysis of treatments for advance melanoma

Topics considered in this section are provided as supporting information. The information has not been systematically reviewed.

7.1 Critical appraisal of a Network Meta-Analysis

7.1.1 Objective

The manufacturer provided a 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. The interventions included in this NMA were pembrolizumab 2 mg/kg every 3 weeks, ipilimumab 3 mg/kg, dacarbazine, vemurafenib and dabrafenib. Table 7.1 describes the PICOS of the NMA.

7.1.2 Findings

Table 7.1 PICOS

Criteria	Inclusion	Exclusion
Population	Patients with unresectable stage III or IV melanoma, naïve to treatment with ipilimumab	Patients with non-cutaneous melanoma (i.e. ocular or mucosal melanoma) and with unknown primary site
Interventions	The following treatments as monotherapy or as combination therapy:* • pembrolizumab • ipilimumab 3mg/kg • dacarbazine/dacarbazine • vemurafenib • dabrafenib	Any other intervention
Comparisons	Any of the interventions listed above, other interventions that have been compared to at least two of the interventions above	Any other comparison
Outcomes	At least one of the two outcomes:** • Progression-free survival (PFS) • Overall survival (OS) • Overall response (OR)	Other efficacy and safety outcomes are considered for analysis, but each study must include at least one of those presented to the left
Study Design	Randomized controlled trials	Non-randomized clinical trials, prospective and retrospective observational studies, case studies

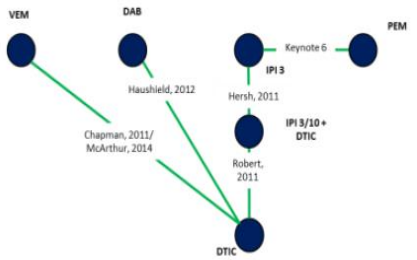
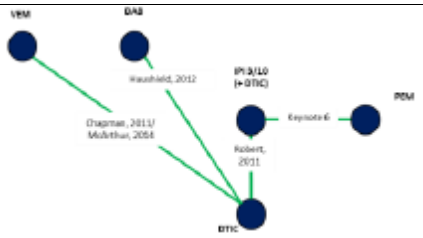
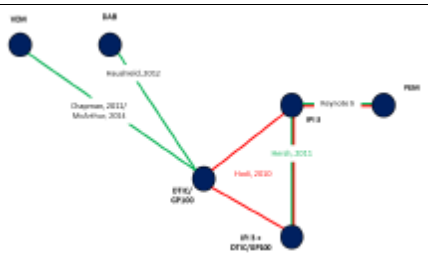
Six RCTs were included in the NMA. Table 7.2 summarizes the study design of included studies.

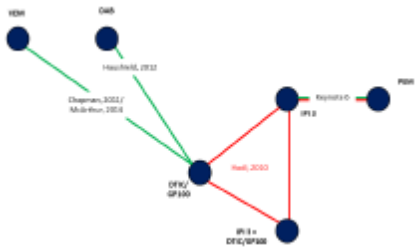
Table 7.2 Trial design

Trial	Treatments	Treatment crossover	Double blinded?
Robert et al 2015 (Keynote 006) (NCT01866319) 32-34	Pembrolizumab 10 mg/kg q2w	None	No
	Pembrolizumab 10 mg/kg q3w		
	Ipilimumab 3 mg/kg q3w		
Hauschild et al 2012 (BREAK-3) (NCT01227889) 35,36	Dabrafenib 150 mg bid	dacarbazine crossed over to dabrafenib if evidence of disease progression	No
	dacarbazine 1000 mg/m2 q3w		
Chapman et al 2011/ McArthur et al 2014 (BRIM-3) (NCT01006980) 14,16,37	Vemurafenib 960 mg bid	dacarbazine cross over to vemurafenib recommended by safety monitoring board	No
	dacarbazine 1000 mg/m2 q3w		
Hersh et al 2011 (NCT00050102) 15,17	Ipilimumab 3 mg/kg q4w	Ipilimumab crossed over to combination therapy if evidence of disease progression	No
	dacarbazine 250 mg/m2 5 days/3 weeks + Ipilimumab 3 mg/kg q4w		
Robert et al 2011 (NCT00324155) 10,38	dacarbazine 850 mg/m2 q3w+ Ipilimumab 10 mg/kg weeks 1, 4, 7, and 10	None	Yes
	dacarbazine 850 mg/m2 q3w		
Hodi et al 2010 (NCT00094653) 9,17	Ipilimumab 3 mg/kg q3w + gp100 q3w	None	Yes
	Ipilimumab 3 mg/kg q3w		
	gp100 q3w		

Baseline characteristics were similar across the included studies in terms of age, sex, race, ECOG score. Some variation was found in disease stage, LDH level but did not raise any concern. Only 3 studies (KEYNOTE-006, BREAK-3, BRIM-3) tested the BRAF status of patients. The number of BRAF mutated patients was not known in other studies.

Network diagram and assumptions

Scenario	Network diagram	Limitations and assumptions
1		1. Ipilimumab 3 mg/kg + dacarbazine assumed similar as ipilimumab 10 mg/kg + dacarbazine 2. Hersh et al 2011 had crossover affecting OS HRs 3. Hersh et al 2011 had no PFS requiring use of OS data and relationship between HR PFS and HR OS based on Flaherty et al 2014 4. In Hersh et al 2011 patients were chemotherapy naïve but 45.8% had previous immune therapy 5. BREAK-3 had crossover affecting OS HRs; HR OS based on PFS data and relationship between HR PFS and HR OS based on Flaherty et al 2014 6. BREAK-3 patients were chemotherapy naïve but 26.8% had previous immune therapy 7. BRIM-3 has crossover but HR with and without crossover adjustment was similar. As such reported OS KM curves without crossover adjustment were assumed to represent relative treatment effects without crossover.
2		1. Ipilimumab 3 mg/kg assumed similar as ipilimumab 10 mg/kg + dacarbazine 2. BREAK-3 had crossover affecting OS HRs; HR OS based on PFS data and relationship between HR PFS and HR OS based on Flaherty et al 2014 3. In BREAK-3 patients were chemotherapy naïve but 26.8% had previous immune therapy 4. BRIM-3 has crossover but HR with and without crossover adjustment was similar. As such reported OS KM curves without crossover adjustment were assumed to represent relative treatment effects without crossover.
3A		1. Ipilimumab 3 mg/kg + dacarbazine assumed similar as ipilimumab 3 mg/kg + gp100 2. dacarbazine assumed similar as gp100 3. Hersh et al 2011 had crossover affecting OS HRs 4. BREAK-3 had crossover affecting OS HRs; HR OS based on PFS data and relationship between HR PFS and HR OS based on Flaherty et al 2014

Scenario	Network diagram	Limitations and assumptions
		5. BRIM-3 had crossover but HR with and without crossover adjustment was similar. As such reported OS KM curves without crossover adjustment were assumed to represent relative treatment effects without crossover. 6. Covariate in model to adjust for between-trial differences in proportion 2L (i.e. proportion previous systemic treatment: Keynote 006 1L covariate=0; Keynote 006 1L covariate=1; Hodi 2010 covariate =1; Hersh et al 2011 covariate =0.458; BRIM-3 covariate = 0; BREAK-3 covariate =0.268) 7. The relative difference in relative treatment effects between 1L and 2L is the same for all interventions relative to IPI 3. In other words, the covariate estimate is treatment independent.
3B		1. Ipilimumab 3 mg/kg + dacarbazine assumed similar as ipilimumab 3 mg/kg + gp100 2. dacarbazine assumed similar as gp100 3. BREAK-3 has crossover affecting OS HRs; HR OS based on PFS data and relationship between HR PFS and HR OS based on Flaherty et al 2014 4. BRIM-3 has crossover but HR with and without crossover adjustment was similar. As such reported OS KM curves without crossover adjustment were assumed to represent relative treatment effects without crossover. 5. Covariate in model to adjust for between-trial differences in proportion 2L (i.e. proportion previous systemic treatment: Keynote 006 1L covariate=0; Keynote 006 1L covariate=1; Hodi et al 2010 covariate =1; Hersh et al 2011 covariate =0.458; BRIM-3 covariate = 0; BREAK-3 covariate =0.268) 6. The relative difference in relative treatment effects between 1L and 2L is the same for all interventions relative to ipilimumab 3 mg/kg. In other words, the covariate estimate is treatment independent.

7.1.3 Summary

Since direct comparison data comparing pembrolizumab to ipilimumab (KEYNOTE-006) and chemotherapy (KEYNOTE-002) was available, the only relevant comparison in this NMA that might have contributed to our review was between pembrolizumab and the BRAF inhibitors. After evaluating the evidence presented in this NMA, the methods team concluded that the evidence did not provide any addition information that might impact the results of our review. The reasons are listed below.

1. The quality of evidence comparing pembrolizumab to BRAF inhibitors in this NMA seems to be low for several reasons:
2. The network was relatively linear, that indirect comparison between pembrolizumab and the BRAF inhibitors had to gone through as much as 4 generations of direct comparisons (see scenario 1). Indirect comparisons that are far from each other are usually more prone to biases and contain more limitations as more assumptions have to be made.
3. In some cases, certain assumption or limitation might be difficult to accept. For example, in scenario one, one of the intermediate comparisons found that ipilimumab was not better than dacarbazine which was not support by the most current evidence. Other scenarios assumed that dacarbazine is similar to gp100 vaccine. The validity of these assumptions and limitations must be taken into account when interpreting the result.
4. All the connection in the network included only one trial, which raised concern about the strength of evidence. Connections that included only one trial could be prone to biases and limitations within that single trial.
5. Since each connection within the network included only one trial, it was not possible to test for heterogeneity, which prompted caution during interpretation.

Due to the various limitations in this NMA, it is difficult to draw any definitive conclusion from this NMA.

8 ABOUT THIS DOCUMENT

This Clinical Guidance Report was prepared by the pCODR Endocrine Clinical Guidance Panel and supported by the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding the clinical evidence available on pembrolizumab (Keytruda) for metastatic melanoma. Issues regarding resource implications are beyond the scope of this report and are addressed by the relevant pCODR Economic Guidance Report. Details of the pCODR review process can be found on the pCODR website (www.cadth.ca/pcodr).

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Clinical Guidance Report was handled in accordance with the pCODR Disclosure of Information Guidelines.

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

The Melanoma Clinical Guidance Panel is comprised of three medical oncologists. The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/ Application Information Package, which is available on the pCODR website (www.cadth.ca/pcodr). Final selection of the Clinical Guidance Panels was made by the pERC Chair in consultation with the pCODR Executive Director. The Panel and the pCODR Methods Team are editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

APPENDIX A: LITERATURE SEARCH STRATEGY

See section 6.2.2 for more details on literature search methods.

1. **Literature search via OVID platform (accessed Oct 6th, 2015)**

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present

#	Search terms	Result
1	(pembrolizumab* or lambrolizumab* or Keytruda* or MK-3475* or MK3475* or DPT0O3T46P* or 1374853-91-4).ti,ab,rn,nm,sh,hw,ot.	141

Embase 1980 to 2015 May 04 (accessed May 4, 2015)

#	Search terms	Result
1	(pembrolizumab* or lambrolizumab* or Keytruda* or MK-3475* or MK3475*).ti,ab.	241

EBM Reviews - Cochrane Central Register of Controlled Trials April 2015 (accessed May 4, 2015)

#	Search terms	Result
1	(pembrolizumab* or lambrolizumab* or Keytruda* or MK-3475* or MK3475*).ti,ab,sh,hw,ot.	10

2. Grey literature search

U.S. NIH ClinicalTrials.gov <www.clinicaltrials.gov>
Ontario Institute for Cancer. Ontario Cancer trials
<www.ontariocancertrials.ca>

Search terms: pembrolizumab or lambrolizumab or Keytruda or MK-3475 or MK3475
Condition: Melanoma

Conference abstracts:
American Society of Clinical Oncology (ASCO)
http://www.asco.org/
Search terms: pembrolizumab or lambrolizumab or MK-3475 or MK3475

Select international agencies including:
Food and Drug Administration (FDA):
http://www.accessdata.fda.gov/scripts/cder/drugsatfda/
Search terms: pembrolizumab or lambrolizumab

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