pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Nivolumab (Opdivo) for Metastatic Melanoma

April 1, 2016

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FUNDING

The pan-Canadian Oncology Drug Review is funded collectively by the provinces and territories, with the exception of Quebec, which does not participate in pCODR at this time.

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1 GUIDANCE IN BRIEF

1.1 Background

The purpose of this review is to evaluate the safety and efficacy of nivolumab for the treatment of adult patients with:

- Previously untreated advanced (unresectable or metastatic) melanoma, regardless of BRAF status.
- Previously treated advanced (unresectable or metastatic) melanoma, regardless of BRAF status.

The review of nivolumab was first initiated in patients with previously untreated advanced melanoma. Based upon a request from the pCODR Provincial Advisory Group (PAG) expressing a need for nivolumab in the second- and third-line setting (i.e., previously treated with ipilimumab), an assessment was made for the expansion of scope to include the second- and third-line indication. This assessment resulted in the scope of the review being expanded to include patients with previously treated advanced melanoma. Of note, the use of nivolumab in combination with ipilimumab was outside of the scope of this review.

Nivolumab is an immunotherapy that targets the programmed cell death-1 receptor (PD-1) and inhibits the PD-1 pathway. Nivolumab has received Health Canada approval for the treatment of previously untreated unresectable or metastatic BRAF V600 wild-type melanoma at a recommended dose of 3 mg/kg administered intravenously over 60 minutes every 2 weeks. Treatment is continued as long as clinical benefit is observed or until it is no longer tolerated by the patient.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

1.2.1 A) Previously Untreated Advanced Melanoma

Two randomized controlled trials (RCTs) were identified that investigated the use of nivolumab in patients with previously untreated advanced melanoma: CheckMate 067, which randomized patients to receive nivolumab, ipilimumab, or nivolumab plus ipilimumab; and, CheckMate 066, which randomized patients to receive nivolumab or dacarbazine.

CheckMate 067 was a three arm double-blinded phase 3 RCT that was designed to determine the efficacy and safety of nivolumab alone (n=316) or nivolumab plus ipilimumab (n=314) compared with ipilimumab alone (n=315) in patients with previously untreated advanced melanoma, regardless of BRAF status. The study was not designed to compare the nivolumab alone arm with the nivolumab plus ipilimumab arm. Patients were randomized equally to all three arms. Patients with an Eastern Cooperative Oncology Group (ECOG) performance status of 2 or higher and those with active brain metastases or ocular melanoma were excluded. Crossover of patients was not permitted. Baseline patient characteristics were well balanced between the three treatment arms. Of note, over 30% of patients had a BRAF V600 mutation.

CheckMate 066 was a double-blinded phase 3 RCT that was designed to compare the efficacy and safety of nivolumab alone (n=210) with dacarbazine (n=208) in patients with previously untreated BRAF wildtype advanced melanoma. Patients with an ECOG performance status of 2 or higher and active brain metastases or ocular melanoma were excluded. Baseline characteristics were balanced between the two treatment arms, with the exception of ECOG performance status, where 70.5% of patients in the nivolumab group had a score of 0 compared with 58.2% of patients in the dacarbazine group.

Efficacy

CheckMate 067 demonstrated statistically significant improvements in progression-free survival and objective response rates in favour of nivolumab compared with ipilimumab (hazard ratio [HR] for death or disease progression, 0.57, [99.5% confidence interval (CI), 0.43 to 0.76; p<0.001]; odds ratio for objective response, 6.11 [95% CI, 3.59 to 10.38; p<0.001]). Median PFS was 6.9 months for the nivolumab group and 2.9 months for the ipilimumab group. In a subgroup analysis by BRAF mutation status, there was a statistically significant and clinically meaningful difference in progression-free survival in favour of nivolumab (median 7.89 months) compared with ipilimumab (median 2.83 months; HR 0.50, 95% CI 0.39 to 0.63) in patients with BRAF wild-type disease. In patients with BRAF mutation-positive disease, no statistically significant difference was demonstrated (HR 0.77, 95% CI 0.54 to 1.09 in favour of nivolumab). However, while patients were stratified by BRAF mutation status at randomization, the subgroup analysis of patients with BRAF mutation-positive disease may not have been adequately powered to detect a difference in effect. The objective response rate was 43.7% for the nivolumab group and 19.0% for the ipilimumab group. Overall survival data were not available as the data are immature and no interim analysis is planned. The study is ongoing and remains blinded with respect to overall survival. Health-related quality of life (HRQoL) was assessed using the European Organization for the Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-C30. A difference in scores of 10 or more points was considered the minimum important difference (MID). The EORTC QLQ-C30 completion rates at baseline and at one or more post-baseline visits was 85.1% in the nivolumab arm and 82.2% in the ipilimumab arm. EORTC QLQ-C30 global health mean change scores appeared stable over time (never equivalent or exceeding the MID from baseline to week 67) for patients in the nivolumab arm. In the ipilimumab arm, mean change scores were also stable from baseline to week 61. Similar results were noted for most EORTC QLQ-C30 scales over time. Additionally, an exploratory analysis assessing general health status using the EQ-5D utility index and visual analogue scale indicates that quality of life was stable over time between arms.

CheckMate 066 demonstrated a statistically significant improvement in overall survival at 1 year in favour of nivolumab (72.9% alive) compared with dacarbazine (42.1% alive; HR 0.42, 99.79% CI 0.25 to 0.73; data cut-off of June 2014). Progression-free survival was also statistically significantly improved in favour of nivolumab (median 5.1 months) compared with dacarbazine (median 2.2 months; HR 0.43, 95% CI 0.34 to 0.56) as was the difference in objective response rates (40.0% for nivolumab versus 13.9% for dacarbazine; odds ratio 4.06, 95% CI 2.52 to 6.54). Of note, the study was terminated early for efficacy by the data safety monitoring committee after an unplanned interim safety analysis. Following early termination, the study was unblinded and patients receiving dacarbazine were permitted to crossover to receive nivolumab. Health-related quality of life was assessed using the EORTC QLQ-C30 with an MID of 10 points. Additionally, the EQ-5D utility index and visual analogue scale were used to determine general health status, with MIDs of ≥ 0.08 points, and ≥ 7 points respectively. No data on completion rates at baseline or at post-baseline visits were reported. It was noted in a poster presentation at the American Society of Clinical Oncology (ASCO) that baseline completion rates were high in both arms;

however, a higher proportion of patients were available for assessment in the nivolumab arm than in the dacarbazine arm as a result of high attrition in the dacarbazine arm. The authors of that poster noted that nivolumab was less likely to lead to deterioration before dacarbazine in the EORTC QLQ-C30 global health status (rate of deterioration reached 50% at 276 days in the nivolumab arm compared with 179 days in the dacarbazine arm; HR for time to first decline, 0.66; 95% CI 0.47 to 0.94; p=0.021) and the EQ-5D utility index score (HR for time to first decline, 0.55; 95% CI 0.38 to 0.80; p=0.002).

Harms

In CheckMate 067, less frequent grade 3 or 4 treatment-related adverse events were reported for patients who received nivolumab (16.3%) compared with those who received ipilimumab (27.3%). A total of 7.7% of patients who received nivolumab alone discontinued therapy due to any treatment-related adverse event compared with 14.8% of patients who received ipilimumab alone. Two deaths were attributed to study drug toxicity: one death in a patient treated with nivolumab (neutropenia) and the other death in a patient treated with ipilimumab (cardiac arrest).

In CheckMate 066, less frequent grade 3 or 4 treatment-related adverse events occurred in patients who received nivolumab (11.7%) compared with those who received dacarbazine (17.6%). A total of 6.8% of patients who received nivolumab discontinued therapy due to any adverse event compared with 11.7% of patients who received dacarbazine. No deaths were attributed to study drug toxicity in either group.

1.2.1 B) Previously Treated Advanced Melanoma

One RCT was identified that investigated the use of nivolumab in patients with advanced melanoma that was previously treated with ipilimumab: CheckMate 037.

CheckMate 037 was an open-label phase 3 RCT that was designed to determine the efficacy and safety of nivolumab alone (n=272) with investigator's choice of chemotherapy (ICC [dacarbazine alone or paclitaxel plus carboplatin]; n=133) in patients with previously treated advanced melanoma. Patients with BRAF wild-type must have had disease progression after anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) treatment (i.e., ipilimumab), while patients with BRAF V600 mutation-positive disease must have had disease progression after treatment with anti-CTLA-4 and a BRAF inhibitor. Patients were randomized 2:1 to nivolumab or to ICC. Patients with an Eastern Cooperative Oncology Group (ECOG) performance status of 2 or higher, active brain metastases, or ocular melanoma or patients who had experienced grade 4 toxic effects or used infliximab to manage adverse events from previous ipilimumab treatment were excluded. Crossover of patients was not permitted. Baseline patient characteristics were balanced between the treatment arms, with the exception of high lactate dehydrogenase and history of brain metastases (both were more commonly reported in patients in the nivolumab arm), which has the potential to bias the study as both are risk factors known to negatively affect the outcome of melanoma patients.

Efficacy

The analysis of objective response rate was conducted on the first 120 patients treated with nivolumab with a minimum follow-up of 24 weeks (per-protocol analysis). The rate of objective response was 31.7% (95% CI 23.5% to 40.8%) in the nivolumab arm and 10.6% (95% CI 3.5% to 23.1%) in the ICC arm. In an intention-to-treat analysis available in the European Public Assessment Report, the objective response rate was 25.4% in the nivolumab arm and 8.3% in the ICC arm. At the time of the analysis for objective response rate (data cut-off May, 2014), the PFS data were not mature; however, the European

Public Assessment Report provided a descriptive analysis. Median PFS was 4.7 months in the nivolumab arm compared with 4.2 months in the ICC arm, with a HR of 0.74 (95% CI 0.47 to 1.16). At the time of the interim analysis for OS (data cut-off November 2014), no statistically significant improvement in overall survival was demonstrated (HR for death, 0.93; 95% CI, 0.68 to 1.26). The median overall survival was 15.5 months in the nivolumab arm compared with 13.7 months in the ICC arm. Health-related quality of life was assessed using the EORTC QLQ-C30 and general health status using the EQ-5D; however, no data are yet available as the analysis of quality of life data is planned to be conducted at the time of the final overall survival analysis.

Harms

In CheckMate 037, less frequent grade 3 or 4 treatment-related adverse events were reported within 30 days of the last dose of study drug for patients who received nivolumab (9.0%) compared with those who received ICC (31.4%). Increased lipase and alanine aminotransferase, fatigue, and anemia were the most commonly reported grade 3 or 4 treatment-related adverse events for patients who received nivolumab (<2%). Neutropenia, thrombocytopenia, and anemia were the most commonly reported grade 3 or 4 treatment-related adverse events for patients who received ICC (13.7%, 5.9%, and 4.9%, respectively). A total of 2.6% of patients treated with nivolumab withdrew due to the study drug toxicity compared with 6.9% of patients treated with ICC. No deaths were attributed to study drug toxicity in either treatment arm.

1.2.2 Additional Evidence

pCODR received input on nivolumab as a first-line treatment for advanced adult melanoma patients, regardless of BRAF status from one patient advocacy group [Melanoma Network of Canada (MNC)]. Provincial Advisory Group (PAG) input was obtained from eight of the nine provinces participating in pCODR.

No supplemental issues were identified during the development of the review process.

1.2.3 Interpretation and Guidance

Burden of Illness and Need

It is estimated that 6,500 Canadians will be diagnosed with melanoma in 2015, and that approximately 1,050 will die of melanoma in 2015. 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 aged 25 to 35 years, and therefore, is the cause of a disproportionate number of years of life lost. Historically, unresectable stage III or stage IV melanoma carries a poor prognosis with a median survival of 6-9 months and only 25.5% of patients surviving to one year. However, since the emergence of immune checkpoint inhibitors (e.g., ipilimumab) and targeted therapies (e.g., BRAF inhibitors, MEK inhibitors), the prognosis of these patients has improved dramatically. While five-year data for patients treated with ipilimumab alone has shown that overall survival plateaus at 20% alive at around 3 years and continues through the follow-up period (5 years total), it is important to note that 80% of melanoma patients will eventually succumb to their disease. Therefore more effective treatments are needed.

Efficacy

In the first-line treatment (i.e., previously untreated) of patients with advanced melanoma, the double-blind CheckMate 066 RCT demonstrated statistically significant and clinically meaningful improvements in overall survival and progression-free survival in favour of nivolumab compared with dacarbazine. Furthermore, the trial also

demonstrated that treatment with nivolumab may be associated with a longer time to deterioration in global health status, based on the EORTC QLQ-C30 than dacarbazine.

The double-blind CheckMate 067 RCT, also conducted in previously untreated advanced melanoma, demonstrated that nivolumab alone had a statistically significant and clinically meaningful improvement in progression-free survival compared with ipilimumab alone as well as improved rates of objective response. However, longer follow-up is required to determine if the difference in progression-free survival translates into a difference in overall survival. HRQoL data for this trial, collected using the EORTC QLQ-C30 and EQ-5D, indicate that global health status were mostly stable over time for patients treated with nivolumab and for those treated with ipilimumab.

The open-label CheckMate 037 RCT was conducted in patients with advanced melanoma who previously received ipilimumab (BRAF wild-type patients) or ipilimumab and a BRAF inhibitor (BRAF mutation-positive patients). The primary outcomes were objective response and overall survival. A non-comparative analysis of objective response by the per-protocol analysis demonstrated a rate of 31.7% (95% CI, 23.5% to 40.8%) for the nivolumab arm and 10.6% (95% CI 3.5% to 23.1%) for the chemotherapy arm and by the intent-to-treat analysis a rate of 25.4% for nivolumab and 8.3% for chemotherapy. Median progression-free survival was 4.7 months for nivolumab and 4.2 months for chemotherapy, which, in an exploratory analysis, was not statistically significant (HR 0.74, 95% CI 0.47 to 1.16). Median overall survival was 15.5 months in the nivolumab arm and 13.7 months in the chemotherapy arm, but not statistically significant in an interim analysis (HR 0.93, 95% CI 0.68 to 1.26). While the response rate results have not translated into similar improvements in progression-free survival or overall survival, the trial is ongoing and the collection of data for these outcomes continues.

Safety

Serious and life threatening immune related adverse events are a major concern with immune checkpoint inhibitors and ipilimumab is no exception. The most common grade 3 or 4 toxicities are diarrhea and colitis, which generally range from 3% to 10%. The incidence of diarrhea with nivolumab alone ranged from 1% to 2.2% in the two trials with previously untreated patients and 0.4% in the trial of previously treated patients. The most common toxicities associated with PD-1 inhibitors such as nivolumab are endocrine disorders, of which the majority are thyroid (hypo- or hyperthyroidism). Of note, there are well developed algorithms in place to manage immune-related adverse events. In general, nivolumab is well tolerated with a low incidence of grade 3 or 4 adverse events.

1.3 Conclusions

Patients with Previously Untreated Advanced Melanoma

The Clinical Guidance Panel concluded that there is an overall net clinical benefit to nivolumab monotherapy in the treatment of patients with previously untreated unresectable stage III or IV melanoma compared with chemotherapy. This conclusion is based on one well-conducted randomized controlled trial that demonstrated a clear statistically significant and clinically meaningful benefit in overall survival, progression-free survival, and response rate in favour of nivolumab compared with chemotherapy in patients with BRAF wild-type advanced melanoma.

Furthermore, the Clinical Guidance Panel concluded that there is an overall net clinical benefit to nivolumab monotherapy in the treatment of patients with previously untreated

unresectable stage III or IV melanoma, regardless of BRAF mutation status, compared with ipilimumab. This conclusion is based on one well-conducted randomized controlled trial that demonstrated a clear statistically significant and clinically meaningful benefit in progression-free survival in favour of nivolumab monotherapy compared with ipilimumab monotherapy in patients with advanced melanoma.

Advanced Melanoma that was Previously Treated with Ipilimumab

The Clinical Guidance Panel concluded that there is a net overall clinical benefit to nivolumab monotherapy in the treatment of patients with unresectable stage III or IV melanoma that was previously treated with ipilimumab compared with chemotherapy. This conclusion is based on one randomized controlled trial that demonstrated a difference in response rates in favour of nivolumab monotherapy compared with chemotherapy in patients with advanced melanoma that was previously treated with ipilimumab and on the unmet clinical need and significant burden of this illness on patients.

The progression-free survival data and overall survival data from the CheckMate 037 trial are immature; however, due to the high clinical burden that this illness poses to patients and based on the higher response rates observed with nivolumab monotherapy compared with chemotherapy, the Panel concluded that nivolumab has a net clinical benefit in this patient population.

For previously untreated patients and patients who were previously treated with ipilimumab, 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 are generally low on nivolumab with lower rates of diarrhea/colitis than ipilimumab.
- In general, the side profile shows that nivolumab 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 important to patients and clinicians.
- The Clinical Guidance Panel is unaware of any trials directly comparing nivolumab with pembrolizumab. Therefore the Clinical Guidance Panel could not offer an opinion on the relative efficacy of these two agents.
- There is insufficient evidence to recommend the measurement of PD-L1 to guide the use of nivolumab. In addition, there is a lack of consistency in the assays and cut-offs used to assess PD-L1.
- The Clinical Guidance Panel 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 depending on the clinical situation, and prior BRAF drug use should not preclude the use of nivolumab in ipilimumab naïve or refractory patients.

2 CLINICAL GUIDANCE

This Clinical Guidance Report was prepared to assist the pan-Canadian Oncology Drug Review (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 nivolumab 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 CADTH website (www.cadth.ca/pcodr).

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

The systematic review and any 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 nivolumab and a summary of submitted PAG Input on nivolumab are provided in Sections 3, 4 and 5 respectively.

2.1 Context for the Clinical Guidance

2.1.1 Introduction

Surgery is the cornerstone treatment for early stages of melanoma. However, when surgery is not sufficient (i.e., when treating unresectable or metastatic melanoma), treatment options may include chemotherapy (dacarbazine), immunotherapy (ipilimumab), and targeted therapy (BRAF or MEK inhibitors). Availability of these treatment options varies across Canada. Moreover, treatment options are limited for patients who show progression after immunotherapy and/or targeted therapy.

Nivolumab is another immunotherapy (a fully human IgG4 monoclonal antibody) that targets the programmed cell death-1 receptor (PD-1) and is often referred to as a PD-1 inhibitor.

On September 25, 2015, nivolumab was approved by Health Canada for the treatment of unresectable or metastatic BRAF V600 wild-type melanoma in previously untreated adults.[1] The recommended dose, as it appears in the Product Monograph, is 3 mg/kg administered intravenously over 60 minutes every 2 weeks. Treatment is continued as long as clinical benefit is observed or until it is no longer tolerated by the patient. Dose escalation or reduction is not recommended. Dosing delay or discontinuation may be required (based on individual safety and tolerability).[2]

Initially, the review for nivolumab was intended for the previous untreated population: an assessment of the effectiveness and safety of nivolumab for the treatment of advanced (unresectable or metastatic) melanoma in previously untreated adult patients, regardless of BRAF status. However, input was received from PAG expressing an interest in understanding the evidence for nivolumab in the previously treated population given the availability of evidence and possible pressure from clinicians and patients in light of its approval in the United States. As a result, the pCODR Secretariat conducted an assessment in consultation with a three-person panel of pERC (consisting of the pCODR Expert Review Committee (pERC) Chair, the pERC Vice-Chair, and one additional pERC member), the PAG, and the submitter to determine the clinical need, jurisdictional need and feasibility of expanding the scope of the review into the previously treated population. This assessment resulted in the scope of the review being expanded to include the previously treated population.

Nivolumab has yet to be approved by Health Canada for the treatment of advanced (unresectable or metastatic) melanoma in previously treated patients.

2.1.2 Objectives and Scope of pCODR Review

i. To evaluate the effectiveness and safety of nivolumab (OPDIVO™) for the treatment of advanced (unresectable or metastatic) melanoma in previously untreated adult patients, regardless of BRAF status.

ii. To evaluate the effectiveness and safety of nivolumab (OPDIVO™) for the treatment of advanced (unresectable or metastatic) melanoma in previously treated adult patients, regardless of BRAF status.

See section 6.2.1 for details on PICO question and review protocol.

2.1.3 Highlights of Evidence in the Systematic Review

Previously Untreated Unresectable or Metastatic Melanoma

In the previously untreated population, two trials sponsored by Bristol-Meyers Squibb were identified: CheckMate 067 and CheckMate 066.

CheckMate 067

In CheckMate 067, a three arm double-blinded phase 3 randomized controlled trial (RCT) was conducted to evaluate the safety and efficacy of nivolumab alone or nivolumab combined with ipilimumab in comparison with ipilimumab alone in patients with previously untreated metastatic melanoma. The study was not designed to compare nivolumab alone to nivolumab plus ipilimumab. Patients were randomly assigned in a 1:1:1 ratio to receive, (1) 3mg/kg nivolumab every 2 weeks plus ipilimumab-matched placebo (n=316); (2) 1mg/kg nivolumab every 3 weeks plus 3mg/kg ipilimumab every 3 weeks for 4 doses, followed by 3mg/kg nivolumab every 2 weeks for cycle 3 and beyond (n=314); or (3) 3mg/kg ipilimumab every 3 weeks for 4 doses, plus nivolumab-matched placebo (n=315) by means of intravenous infusion. Key inclusion criteria were: previously untreated stage III or IV melanoma, age 18 years or older, Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1, and available tumour tissues from metastatic or unresectable site. Key exclusion criteria were: ECOG performance status score of 2 or higher, and the presence of active brain metastases, ocular melanoma, or autoimmune disease. Crossover was not permitted.[3]

The patients were well-balanced between treatment arms. The trial enrolled only patients with an ECOG performance status of 0 or 1. Most patients had an ECOG performance status of 0 and over 30% had a BRAF V600 mutation. Key study outcomes can be found in Table 2.1. Statistically significant improvements in progression-free survival (PFS) and objective response were found in favour of nivolumab compared to ipilimumab [HR for death or disease progression: 0.57 (99.5% CI, 0.43 to 0.76; *P*<0.001); odds ratio for objective response: 3.40 (95% CI, 2.02 to 5.72; *P*<0.001)] and in favour of nivolumab plus ipilimumab compared to ipilimumab alone [HR for death or disease progression: 0.42 (99.5% CI, 0.31 to 0.57; *P*<0.001); odds ratio for objective response: 6.11 (95% CI, 3.59 to 10.38; *P*<0.001)]. Estimates of median PFS were 6.9 months for the nivolumab monotherapy group, 11.5 months for the nivolumab plus ipilimumab group, and 2.9 months for the ipilimumab monotherapy group. Objective response rate (ORR) was 43.7% for the nivolumab arm, 57.6% for the nivolumab plus ipilimumab arm, and 19.0% for the ipilimumab arm. For those who achieved a response, the duration of response was not reached in any arm.

Overall survival (OS) data were immature and therefore, no OS analysis has been conducted yet. No OS interim analysis was planned. This study is ongoing and remains blinded with respect to overall survival.

Subgroup: BRAF wildtype (n=645)

A PFS benefit was observed in nivolumab compared to ipilimumab for BRAF wildtype patients [HR for death or disease progression in BRAF wildtype patients: 0.50 (95% CI, 0.39 to 0.63; *P* not reported)]; however, PFS was not statistically significant for patients with BRAF V600 [HR for death or disease progression in BRAF V600 patients: 0.77 (95% CI, 0.54 to 1.09; *P* not reported)]. Of note, while patients were stratified by BRAF mutation status at randomization, the subgroup analysis of patients with BRAF mutation-positive disease may not have been adequately powered to detect a difference in effect. For BRAF wildtype patients, the median PFS was 7.89 months for the nivolumab monotherapy group and 2.83 months for the ipilimumab monotherapy group. For BRAF V600 patients, the median PFS was 5.62 months for the nivolumab monotherapy group and 4.04 months for the ipilimumab monotherapy group. The ORR results from the BRAF status subgroup analysis were not reported.[4]

The assessment of health-related quality of life using the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 was a secondary objective, while the assessment of the general health status using the EQ-5D utility index and VAS were exploratory objectives. A presentation from the 2015 Society for Melanoma Research International Congress summarized the health-related quality of life data assessed in CheckMate 067. Results are presented below.[5]

The minimum important difference (MID) used for assessing health-related quality of life using the EORTC QLQ-C30 was greater than or equal to 10 points. At baseline, EORTC QLQ-C30 completion rates were 89.9% (n=284 out of 316) in the nivolumab arm, 92.4% (n= 290 out of 314) in the nivolumab plus ipilimumab arm, and 88.6% (n=279 out of 315) in the ipilimumab arm. The EORTC QLQ-C30 completion rates at baseline and one or more post-baseline visits were 85.1% (n=269 out of 316) in the nivolumab arm, 87.3% (n=274 out of 314) in the nivolumab plus ipilimumab arm, and 82.2% (n=259 out of 315) in the ipilimumab arm. It appears that quality of life was maintained over time (from baseline to week 67) for the nivolumab and nivolumab plus ipilimumab arms since the EORTC QLQ-C30 Global Health mean change scores appeared stable over time (never equivalent or exceeding the MID from baseline to week 67). In the ipilimumab arm, it appears that quality of life was maintained from baseline to week 61 (at week 61, 5.4%, n=17 out of 315) since the EORTC QLQ-C30 Global Health mean change scores appeared stable, after which it appears that quality of life may have worsened, where EORTC QLQ-C30 Global Health mean change scores appears to be equivalent to the MID (at week 67, 2.9%, n=9 out of 315). Similar results were noted for most EORTC QLQ-C30 scales over time.[5]

In the exploratory analysis, the MID used for assessing the general health status using the EQ-5D utility index was greater than or equal to 0.08 points. At baseline, EQ-5D completion rates were 89.2% (n=282 out of 316) in the nivolumab arm, 92.4% (n= 290 out of 314) in the nivolumab plus ipilimumab arm, and 88.3% (n=278 out of 315) in the ipilimumab arm. The EQ-5D completion rates at baseline and one or more post-baseline visits were 84.5% (n=267 out of 316) in the nivolumab arm, 87.3% (n=274 out of 314) in the nivolumab plus ipilimumab arm, and 81.9% (n=258 out of 315) in the ipilimumab arm. Using the EQ-5D utility index, it appears that quality of life may be trending to clinical improvement at week 67 (4.1%, n=13 out of 316) for the nivolumab arm (exceeding the MID at week 67). The minimum important difference used for assessing the general health status using the EQ-5D VAS was greater than or equal to 7 points. Using the EQ-5D VAS, it appears that quality of life was maintained over time for the nivolumab, nivolumab plus ipilimumab, and ipilimumab arms (never equivalent or exceeding the MID from baseline to week 67).[5]

In CheckMate 067, less frequent grade 3 or 4 treatment-related adverse events (TRAE) were reported for nivolumab treated patients (16.3%) compared to nivolumab-plus-ipilimumab treated patients (55.0%) and ipilimumab treated patients (27.3%).[6] A total of 7.7% of patients discontinued therapy with nivolumab due to any TRAE compared with 36.4% of patients treated with nivolumab-

plus-ipilimumab and 14.8% of patients treated with ipilimumab alone. Two deaths were attributed to study-drug toxicity: one death in patients treated with nivolumab (neutropenia) and one other death in patients treated with ipilimumab (cardiac arrest).[6]

CheckMate 066

In CheckMate 066 (BRAF wildtype population), a double-blinded phase 3 RCT was conducted to determine whether nivolumab, as compared with dacarbazine, improves OS among previously untreated patients who have advanced melanoma without a BRAF mutation. Patients were randomly assigned in a 1:1 ratio to receive, (1) 3mg/kg nivolumab every 2 weeks plus a dacarbazine-matched placebo every 3 weeks (n=210); or (2) 1000 mg/m^2 dacarbazine every 3 weeks plus a nivolumab-matched placebo every 2 weeks (n=208) by means of intravenous infusion. Key inclusion criteria were: previously untreated stage III or IV melanoma without a BRAF mutation, age 18 years or older, ECOG performance status score of 0 or 1, and available tumour tissues from metastatic or unresectable site. Key exclusion criteria were: active brain metastases, uveal melanoma, and history of serious autoimmune disease.

The patients were balanced between the two treatment arms, with the exception of ECOG performance status where 70.5% of patients in the nivolumab group had an ECOG performance status of 0, compared with 58.2% of patients in the dacarbazine arm.

Key study outcomes can be found in Table 2.1. Refer to Figure 2.2 for a Kaplan-Meier plot of OS and Figure 2.3 for a Kaplan-Meier plot of PFS. Statistically significant improvements in OS at 1 year, PFS and objective response were found in favour of nivolumab [hazard ratio for death (N=418): 0.42 (99.79% CI, 0.25 to 0.73); hazard ratio for death or disease progression: 0.43 (95%CI, 0.34 to 0.56); odds ratio for objective response: 4.06 (95% CI, 2.52 to 6.54)] The overall survival rate at 1 year was 72.9% in the nivolumab group compared with 42.1% in the dacarbazine group. (Data cut-off of June 24, 2014) The data safety monitoring committee stopped the study for superior efficacy reasons (data showed a significant difference in OS in favour of nivolumab) during an earlier safety review (in an unplanned interim analysis); they recommended that the study be unblinded and amended to allow patients who had initially received dacarbazine and had disease progression to crossover and receive nivolumab. Prior to the amendment, crossover was not permitted.[3]

Refer to Table 2.2 for updated overall survival data (database lock of July 15, 2015). Updated overall survival data indicate the overall survival rate at 12 months and 24 months was 70.7% and 57.7%, respectively in the nivolumab group.[7]

For those who achieved a response, the duration of response was not reached (range: 0.0-12.5 months; n=84) in the nivolumab arm and was 6.0 months (range: 1.1 -10.0 months, n=29) in the dacarbazine arm (data were censored for the range values since observations were ongoing**).**

The assessment of health-related quality of life using the EORTC QLQ-C30 was a secondary objective, while the assessment of the general health status using the EQ-5D utility index and VAS were exploratory objectives. A poster presented at the American Society of Clinical Oncology summarized the health-related quality of life data assessed in CheckMate 066.

Completion rates at baseline or baseline and at least one post-baseline visit were not reported. The author indicated that although baseline completion rates were high in both arms, a higher proportion of patients were available for assessment in the nivolumab arm compared to the dacarbazine arm as a result of high attrition in the dacarbazine arm. In Checkmate 066, EORTC QLQ-C30 was a secondary endpoint, while the EQ-5D index and VAS were exploratory endpoints. For EORTC QLQ-C30, the minimal important difference was ≥ 10 points, while for EQ-5D utility index and EQ-5D VAS, the minimal important difference were ≥ 0.08 points, and ≥ 7 points respectively.

In a cross-sectional analysis, the authors stated that EORTC QLQ-C30 subscale scores did not change over time for either arm, however, some clinically meaningful changes were observed in patients treated with nivolumab for EORTC QLQ-C30 emotional and social functioning scales at certain time points (data not shown in poster). For EQ-5D utility index score, some clinically meaningful improvement was observed in patients treated with nivolumab at week at week 37 (25.7%, n=53 out of 210), 61 (6.7%, n=14 out of 210) and 67 (2.9%, n=6 out of 210). The authors concluded that health-related quality of life in patients treated with nivolumab generally showed no deterioration over the course of treatment.[8] The authors stated that nivolumab was significantly less likely to lead to deterioration before dacarbazine for EORTC QLQ-C30 global health status (where the rate of deterioration reached 50% at 276 days for nivolumab arm compared with 179 days for the dacarbazine arm) and EQ-5D utility index score. The authors also concluded that nivolumab was significantly more likely to lead to improvement in the EORTC QLQ-C30 global health status score and the EQ-5D utility index score compared with dacarbazine.[8]

Utility data from Long et al were calculated using UK weights.[8] An abstract from Harrison and Kim highlighted utility data calculated using Australian weights.[9] Harrison et al. described that utility data were collected during the CheckMate 066 study every 6 weeks via the EQ-5D-3L instrument and questionnaires scored using Australian specific weights within Microsoft Excel. Details of mean utility scores at baseline, prior to the development of progressive disease, and following the development of progressive disease are listed in Table 2.3.[9]

According to Harrison and Kim, for patients randomised to nivolumab, the development of progressive disease per RECIST v1.1 criteria did not significantly impact utility (mean change = 0.01, P=0.4618); however, for patients randomise to dacarbazine, the development of progressive disease per RECIST v1.1 criteria did significantly impact utility (mean change = 0.08, P=0.0005). [9]

In CheckMate 066, less frequent grade 3 or 4 TRAEs were reported for nivolumab treated patients (11.7%) compared to dacarbazine treated patients (17.6%).[10] 6.8% of patients discontinued therapy with nivolumab due to any adverse events compared with 11.7% of patients treated with dacarbazine.[10] No deaths were attributed to study-drug toxicity in either group.[10]

Table 2.1 Summary of Key Outcomes (Previously Untreated Population)

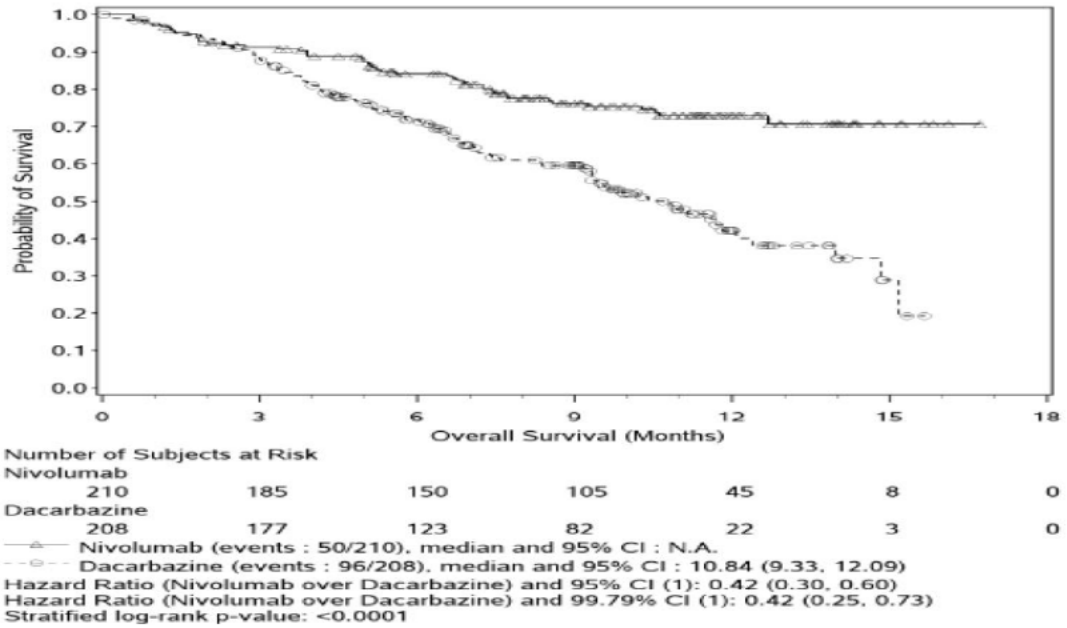
	CheckMate 067[6,11] Data cut-off: February 17, 2015			CheckMate 066[10] Data cut-off: June 24, 2014	
	Nivolumab (n=316)	Nivolumab plus ipilimumab (n=314)	Ipilimumab (n=315)	Nivolumab (n=210)	Dacarbazine (n=208)
Median OS months (95%CI)	NA	NA	NA	Not reached	10.8 (9.3-12.1)
Hazard ratio (99.79%CI),p<0.001	NA	NA	-	0.42 (0.25-0.73)	
OS rate at 1 year	NA	NA	NA	72.9%	42.1%
Median PFS months (95%CI)	6.9 (4.3-9.5)	11.5 (8.9-16.7)	2.9 (2.8-3.4)	5.1 (3.5-10.8)	2.2 (2.1-2.4)
Hazard ratio (95%CI),p<0.001 (99.5%CI),p<0.001	- 0.57(0.43-0.76)	- 0.42(0.31-0.57)	- -	0.43 (0.34-0.56) -	
Objective response N (%)	138 (43.7%)	181 (57.6%)	60 (19.0%)	84 (40.0%)	29 (13.9%)
Odds Ratio (95%CI),p<0.001	3.40 (2.02-5.72)	6.11 (3.59-10.38)	-	4.06 (2.52-6.54)	

CI = confidence interval; NA = not available; OS = overall survival; PFS = progression-free survival.

Table 2.2 CheckMate 066 Updated Overall Survival Data (After Amendment)[7]		
Data cut-off: July 15, 2015	Nivolumab (n=210)	Dacarbazine (n=208)
OS rate 12 months 24 months	 70.7% 57.7%	 46.3% 26.7%
Hazard ratio, (95%CI),p<0.0001	0.43(0.33-0.57)	

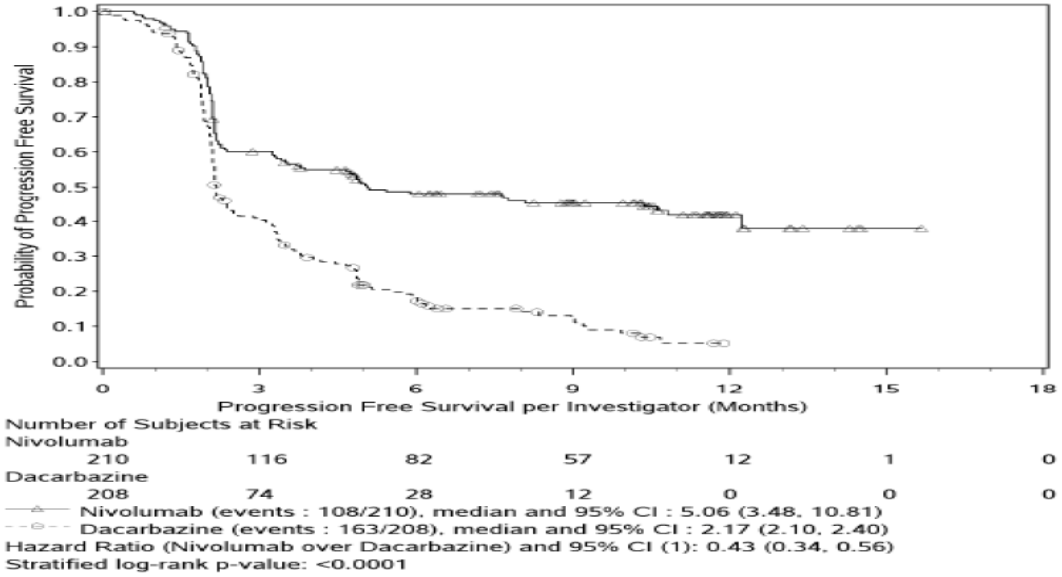
Table 2.3 CheckMate 066 - Mean utility scores using Australian weights[9]		
HRQoL Assessment using EQ-5D-3L	Nivolumab Mean Utility(95%CI)	Dacarbazine Mean Utility(95%CI)
At Baseline	0.78(0.75-0.81)	0.71(0.67-0.75)
Prior to the development of progressive disease	0.84(0.83-0.85)	0.78(0.76-0.81)
Following the development of progressive disease	0.83(0.80-0.86)	0.70(0.66-0.74)
CI = confidence interval; HRQoL = health related quality of life.		

Figure 2.2 CheckMate 066 – Kaplan-Meier plot of overall survival[11]



Source: Opdivo assessment report. European Medicines Agency; 2015 Apr 23. p.64[11] (Database locked on May 27, 2014)

Figure 2.3 CheckMate 066 – Kaplan-Meier plot of progression-free survival[11]



Source: Opdivo assessment report. European Medicines Agency; 2015 Apr 23. p.65[11] (Database locked on May 27, 2014)

Previously Treated Unresectable or Metastatic Melanoma

In the previously treated population, one trial sponsored by Bristol-Meyers Squibb was identified: CheckMate 037.

In CheckMate 037, an open label phase 3 RCT was conducted to assess the efficacy and safety of nivolumab compared with investigator's choice of chemotherapy (ICC) in patients who progressed during or after anti-CTLA-4 treatment for advanced melanoma, or during or after anti-CTLA-4 treatment and a BRAF inhibitor if they were BRAF V600 mutation positive. Patients were randomly assigned in a 2:1 ratio to receive, (1) nivolumab 3mg/kg every 2 weeks (n=272) or (2) ICC (dacarbazine 1000mg/m² or paclitaxel 175mg/m² combined with carboplatin area under the curve [AUC] 6) every 3 weeks (n=133) by means of intravenous infusion. Key inclusion criteria were: stage III or IV melanoma; age 18 years or older; ECOG performance status score of 0 or 1; patients with BRAF wild-type must have had disease progression after anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) treatment (i.e., ipilimumab), while patients with BRAFv600 positive mutation must have had disease progression with anti-CTLA-4 treatment and a BRAF inhibitor. Key exclusion criteria included: active brain metastases; ocular melanoma; previous treatment with anti-PD-1, anti-PD-L1, or anti-PD-L2 antibodies; experienced grade 4 toxic effects or used infliximab to manage adverse events from previous ipilimumab treatment; active, known or suspected autoimmune disease; prior systemic melanoma therapy with both dacarbazine and carboplatin and paclitaxel. Crossover was not permitted in this trial.[12]

The patients were balanced between the two arms, with the exception of high lactate dehydrogenase and history of brain metastases. There were a higher proportion of patients in the nivolumab arm with an elevated lactate dehydrogenase and a history of brain metastases.[11] This may have a potential to affect the internal validity of the study, as a result of confounding since history of brain metastases and elevated lactate dehydrogenase are risk factors known to negatively affect the outcome of melanoma patients.[11]

Data for key outcomes of the Checkmate 037 trial can be found in Table 2.4. In the primary study publication, Weber et al. reported that the objective response rate (ORR) analysis was conducted

on the first 120 patients treated with nivolumab with a minimum follow-up of 24 weeks (per-protocol analysis).[13] The publication reported that the ORR was 31.7% for patients in the nivolumab arm and 10.6% for patients in the ICC arm.[13] Among those who achieved a response, the median duration of response was not reached (range: 1.4+ to 10.0+ months, n=38) in the nivolumab arm and was 3.5 months (range: 1.3+ to 3.5 months, n=5) in the ICC arm.[13] An intent-to-treat ORR analysis [provided by the European Medicines Agency (EMA)], which included all randomized patients, reported that the ORR was 25.4% for patients in the nivolumab group and 8.3% for patients in the ICC group.[11]

At the time of the ORR analysis (database locked on May 30, 2014), PFS data were not mature, and therefore presented in a descriptive analysis by the EMA.[11] No statistically significant PFS difference was found [hazard ratio for death or disease progression: 0.74 (95%CI, 0.47 to 1.16)]. Estimates of the median PFS were 4.7 months for the nivolumab arm and 4.2 months for the ICC arm.[11,12] Among the patients that received at least one dose of treatment, objective responses were observed in nivolumab regardless of BRAF status.[11]

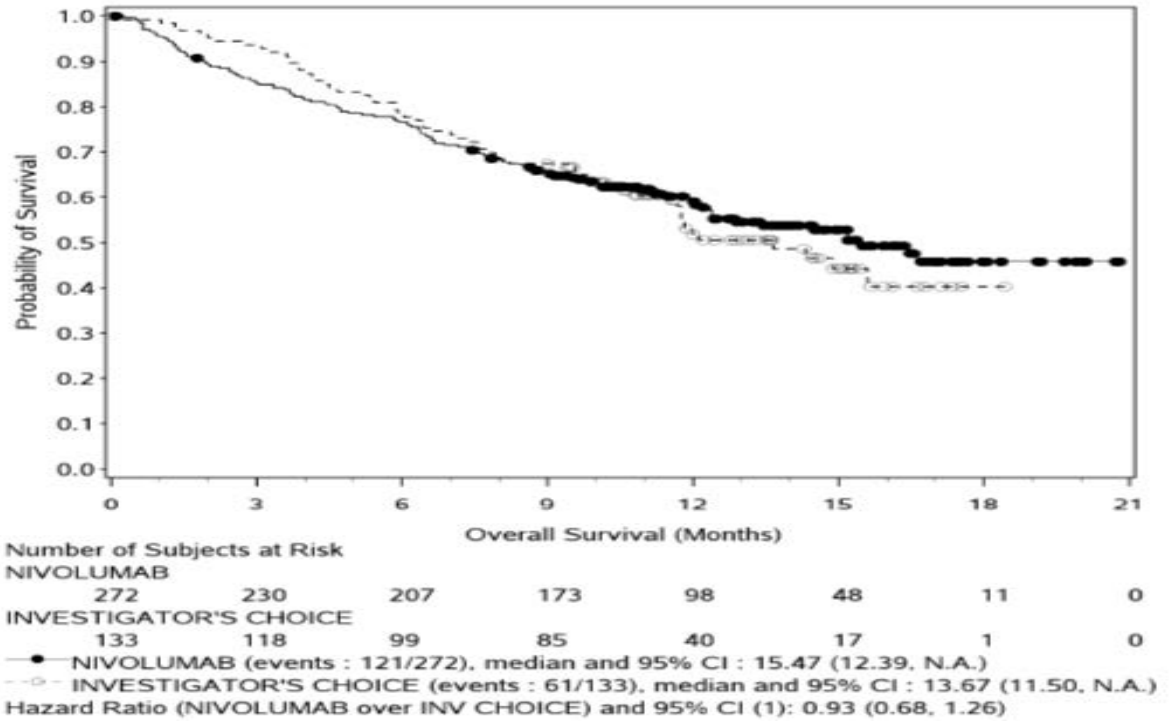
At the time of the interim OS analysis (database locked on November 12, 2014), no statistically significant improvement in OS was found [hazard ratio for death: 0.93(95%CI, 0.68 to 1.26)]. The median OS was 15.5 months for the nivolumab group compared to 13.7 months for the ICC group (Refer to Figure 2.4 for Kaplan-Meier plot of overall survival).[11] The OS results from the BRAF status subgroup analysis were not reported.

Table 2.4 CheckMate 037 - Summary of Key Outcomes (Second-line and Later Setting)[11]

All randomized patients (N=405)	**Nivolumab (n=272)**	**ICC (n=133)**
Median OS (interim analysis) months (95%CI)	15.5 (12.39-NA)	13.7 (11.5-NA)
6 months OS rate (%) no. at risk	76.7% 207	78.6% 99
Hazard ratio (95%CI),p=NR	0.93 (0.68-1.26)	
1 year OS rate* (%) no. at risk	58.9% 98	52.1% 40
Objective response n (%)	69 (25.4%)	11 (8.3%)
Odds Ratio (95%CI),p=NA	NA	
ORR Population† (N=182)	**Nivolumab (n=122)**	**ICC (n=60)**
Median PFS‡ (descriptive analysis) months (95%CI) p=NR	4.7 (2.3-6.5)	4.2 (2.1-6.3)
Hazard ratio (95%CI), p=NR (99.99%CI), p=NR	0.74(0.47-1.16) 0.82(0.32-2.05)	

CI = confidence interval; ICC = investigator's choice of chemotherapy; NA = not applicable; NR= not reported; OS = overall survival; PFS = progression-free survival.
*estimated from published Kaplan-Meier plot of overall survival
†all randomized subjects to either treatment group with at least 6 months of follow-up at the time of the objective response rate analysis
‡data not mature

Figure 2.4 CheckMate 037 – Kaplan-Meier plot of overall survival (Interim analysis)[11]



Source: Opdivo assessment report. European Medicines Agency; 2015 Apr 23. p.88[11] (Database locked on Nov 12, 2014)

Less frequent grade 3 or 4 TRAEs were reported within 30 days of the last dose of study therapy for nivolumab treated patients compared to ICC treated patients (9.0% versus 31.4%).[13] Increased lipase, increased alanine aminotransferase, fatigue, and anemia were the most commonly reported grade 3 or 4 TRAEs among nivolumab treated patients (<2%).[13] Neutropenia, thrombocytopenia and anemia were the most commonly reported grade 3 or 4 TRAEs among ICC treated patients (13.7%, 5.9%, 4.9%).[13] A total of 2.6% of patients treated with nivolumab withdrawal due to study drug toxicity compared to 6.9% of patients treated with ICC.[11,13] No deaths were attributed to study-drug toxicity were reported in either group.[11,13]

See Section 6.3.2 for details on the included studies. Table 2.5 addresses the generalizability of the evidence and an assessment of the limitations and sources of bias can be found in in Sections 6.3.2.1a and 6.3.2.1b (regarding internal validity).

2.1.4 Comparison with Other Literature

There was a single-arm, phase 1 trial (NCT00730639) identified through the systematic review literature search that did not meet the inclusion criteria for the systemic review, however, CGP felt that the results of the study may provide context for long term outcomes with nivolumab. Therefore, the study details are summarized briefly in this section.

The study was a dose-escalation, cohort expansion study used to evaluate the anti-tumour activity and safety of nivolumab in patients with advanced cancers such as melanoma, non-small cell lung cancer, kidney, colorectal, and castration-resistant prostate cancer. The study was expanded to accrue additional patients with melanoma and amended to evaluated overall survival. A total of 107 patients with previously treated advanced melanoma were enrolled from US centres to receive 0.1, 0.3, 1.0, 3.0, or 10 mg/kg of nivolumab every two weeks for up to 96 weeks.[14] Patients must have received at least one, but no more than five prior systemic cancer therapies.[14] Patients with a history of autoimmune disease, prior therapy with T-cell modulating antibodies [i.e., anti-PD-1 or anti-PDL-1 (e.g., nivolumab and pembrolizumab), or anti-CTLA-4 (e.g., ipilimumab)], conditions which required immunosuppression, chronic infections, or history of other invasive cancers within the last two years were excluded.[14]

The median age of patients included in the study was 61 years; patients ranged from 29 to 85 years of age.[15] Most patients were male (67%), received at least two prior treatments for melanoma (62%), and had an ECOG performance status of 0 (64%).[14,15] A smaller proportion of patients had an ECOG status of 1 (34%); and 3% of patients had an ECOG performance status of 2.[15] A total of 17 out of 107 patients received nivolumab at the recommended dose, as per the product monograph (3mg/kg).[14]

A presentation from the Society for Melanoma Research 2014 Congress described the long-term survival of all 107 patients with melanoma. Overall survival rates for all doses (N=107) at 1, 2, 3 and 4 years were 63%, 48%, 42% and 32%, respectively.[16] Similar overall survival rates for patients who received the recommended dose (n=17) were found (65%, 47%, 41%, and 35% respectively).[16] The median OS among all doses (N=107) was 17.3 months compared to the median OS for patients who received the recommended dose (n=17) was 20.3 months.[16] There were 3 three deaths following treatment-related adverse events, all from pneumonitis (two patients with non–small-cell lung cancer and one patient with colorectal cancer).[14]

It is important to highlight that this trial is a non-comparative study, with no active control. As a result, it is difficult to assess the true treatment effect compared to standard of care and other available relevant therapies. Moreover, the small sample size overall (N=107) increases the uncertainty in the OS estimates. Furthermore, the small number of patients treated with recommended dose (n=17) increases the uncertainty in the dose-response relationship and impact on OS estimates.

Overall, the results of the trial should be interpreted with caution, given the absence of comparative evidence, small sample size and small number of patients treated with the recommended dose.

2.1.5 Summary of Supplemental Questions

No supplemental questions were addressed in this review.

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 a number of symptoms associated with advanced melanoma, which include pain, scarring, fatigue or disrupted sleep, fear, depression and anxiety. Patients reported about the impact of advanced melanoma on their lives which included an inability to make long term plans and limited normal day to day activities. The most common side effects in these patients included fatigue or weakness (86.4%), headaches (40.9%), and weight loss or loss of appetite (36.6%).

MNC also reported that 71.4% of patients indicated an improvement in quality of life while on nivolumab, 25% have not responded to treatment, 25% reported they are cancer-free, and 50% reported that they had a slowing of their disease. All patients with the exception of two indicated that they are willing to tolerate certain side effects, particularly if these side effects meant a longer or improved quality of life.

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 Nivolumab for metastatic melanoma. Due to the scope expansion, PAG was provided the opportunity to revise input accordingly.

Clinical factors:

- Dacarbazine is no longer the appropriate comparator; Ipilimumab and BRAF inhibitors +/- MEK inhibitors are now the standard of care in first-line setting
- Lack of direct comparison to all other treatments now available for metastatic melanoma
- Use in second-line setting

Economic factors:

- Drug wastage
- Cost-effectiveness compared to other treatments available
- Treatment algorithm and/or sequencing with recently available therapies

2.2 Interpretation and Guidance

Patients with metastatic melanoma have currently obtained marked improvement in their treatment options over the past 5-10 years with the development of immune modulated treatment specifically checkpoint inhibitors including a CTLA-4 agent (ipilimumab) and currently 2 programmed death inhibitors (pembrolizumab and nivolumab). Pembrolizumab was recently recommended (conditional on cost-effectiveness being improved) by the pCODR Expert Review Committee (pERC) because they found it offered an overall net clinical benefit to patients with metastatic melanoma. However, it is not yet funded in the provinces that participate in the pCODR process. Furthermore, the CGP is unaware of any trials directly comparing nivolumab with pembrolizumab in patients with metastatic melanoma. Therefore, the CGP could not comment on the relative efficacy and safety of nivolumab compared with pembrolizumab.

The current Health Canada indication for nivolumab is for the first line treatment of metastatic melanoma or unresectable stage 3 disease. The CGP was also requested to review the indication of nivolumab as second line treatment as many patients will have been exposed over the course of their illness to chemotherapy agents and ipilimumab.

Effectiveness

Nivolumab is a fully humanized IgG4 antibody that is an expanded Phase I trial has shown high response rates and durable. Until recently Ipilimumab has only had a second line indication in Canada and Europe and therefore first-line treatment of melanoma often consisted of chemotherapy despite the paucity of evidence that chemotherapy improved either quality of life or overall survival. The BMS Checkmate 066 trial randomized patients with unresectable Stage III or Stage IV BRAF wild-type melanoma in a double blind, 1:1 randomization to receive either dacarbazine or nivolumab at a dose of 3 mg/kg. The study only included BRAF wild-type patients as it was felt to be unethical to include BRAF mutant patients as previous studies had shown clear survival benefits of BRAF inhibitors over dacarbazine The study was closed after an unplanned interim analysis as there was a 30% improvement in one year survival compared to dacarbazine. The median overall survival for nivolumab was not yet been reached and for dacarbazine it was 10.5 months, with a median follow-up at time of 8.9 months for the nivolumab group and 6.8 months for the dacarbazine group. A total of 54.8% of patients in the chemotherapy arm went on to second line treatment which was most commonly ipilimumab. The overall survival at one year for the nivolumab was 72.9% vs. 42.1% in the chemotherapy arm with $p<0.001$. Median progression free survival was 5.1 months for nivolumab versus 2.2 months for dacarbazine (HR 0.43, 95% CI, 0.34 to 0.56) and overall response for the group 40.0% for nivolumab versus 13.9% for dacarbazine.

The CheckMate 067 trial randomized patients with previously untreated advanced melanoma, regardless of BRAF mutation status, to receive nivolumab, nivolumab plus ipilimumab or to ipilimumab. The primary endpoints were progression-free survival and overall survival. The trial did not plan to directly compare the nivolumab plus ipilimumab arm with the nivolumab monotherapy arm; however, that comparison was outside of the scope of this review and was not considered further by the CGP. Median progression-free survival was statistically significantly longer in the nivolumab monotherapy arm (6.9 months) compared with the ipilimumab arm (2.9 months; HR 0.57, 95% CI 0.43 to 0.76). The trial is ongoing and remains blinded as overall survival data continue to be collected. Objective response rates were also statistically significantly higher in the nivolumab monotherapy group compared with the ipilimumab monotherapy group (43.7% versus 19.0%; odds ratio, 3.40, 95% CI 2.02 to 5.72). In a subgroup analysis by BRAF status, a statistically significant improvement in progression-free survival for patients with BRAF wild-type disease in favour of nivolumab monotherapy (median 7.89 months) compared with ipilimumab monotherapy (median 2.83 months) was demonstrated (HR 0.50, 95% CI 0.39 to 0.63, p=NR). In the BRAF mutation-positive subgroup, progression-free survival was not statistically significantly different for the nivolumab monotherapy arm compared with the ipilimumab monotherapy arm (HR 0.77, 95% CI 0.54 to 1.09, p=NR). Of note, while the randomization was stratified by BRAF mutation status, the subgroup analyses were not powered to detect differences in this outcome. Furthermore, it is the opinion of the CGP that nivolumab would offer a clinical benefit to patients with BRAF mutated disease and those with BRAF wild-type disease, based on the biology of metastatic melanoma and the mechanism of action of nivolumab.

Recently Health Canada and the EMA have approved ipilimumab for the treatment of previously untreated metastatic melanoma. Ipilimumab is associated with long term survival and is now accepted by the FDA as a potentially curative treatment in advanced melanoma with a 22% 3 year survival and 20% 5 year survival. Prognostic factors such as high LDH, poor performance status and bulky disease are associated with low response rates. In addition responses are slower and may take months and therefore patients with rapidly progressive disease are unlikely to respond.

CheckMate 037 randomized previously treated advanced melanoma patients, who previously received ipilimumab (BRAF wild-type patients) or ipilimumab and a BRAF inhibitor (BRAF mutation-positive patients), to nivolumab versus investigator's choice of chemotherapy. The trial was open-label had two primary endpoints: objective response and overall survival. The first interim analysis that was preplanned looking at when 120 patients had been randomized to nivolumab out of 272, and followed for 24 weeks. The median follow-up for the data presented was for 8.4 months. The planned analysis for overall response rate was subsequently modified to allow non-comparative estimation of overall response rate in the Nivolumab arm. The objective response rate, by the per-protocol analysis, for the nivolumab arm was 31.7% (95% CI 23.5% to 40.8%), compared with 10.6% (95% CI 3.5% to 23.1%) in the chemotherapy arm. An intent to treat analysis provided to the EMA, which included all randomized patients to any treatment group, objective response rate was 25.4% for nivolumab, and 8.3% for chemotherapy. The results of a subgroup analysis of objective response rates by BRAF mutation status were similar. The median duration of response for nivolumab was not reached and for chemotherapy it was 3.5 months. The median progression-free survival was 4.7 months for nivolumab and 4.2 months for chemotherapy, which was not statistically significantly different (HR 0.74, 95% CI 0.47 to 1.16). Three explanations for this result were offered: 1) a possible imbalance of adverse prognostic features; 2) immaturity of the data; 3) false positive disease progression based on immune modulated reactions. Overall survival at 6 months was 76.7% for nivolumab and 78.6% for chemotherapy, with median overall survival of 15.5 months for nivolumab and 13.7 months for chemotherapy; however, this difference was not statistically significantly different (HR 0.93, 95% CI 0.68 to 1.26). While the response rate results have not translated into similar improvements in progression-free survival or overall survival, the trial is ongoing and the collection of these data continues.

PD-1 inhibitors such as nivolumab have shown quicker response times and improved response rates to ipilimumab. In 2 randomized studies PD-1 inhibitors when compared in randomized studies with ipilimumab as the control arm have shown superior response rates and improved progression free survival. Longer follow up is required to see if this translates to improvements in overall survival.

Immune checkpoint blockade has revolutionized the treatment of melanoma and is a potential cure in some patients with a 20% long term survival. These drugs are however expensive and as such much research has focused on predictive biomarkers such as PD-1 ligand status. Multiple studies have failed to confirm PD-1 as a predictive biomarker, and further research such as immune profiles are needed to select those patients likely to respond versus those who do not. Predictive biomarkers have the potential of saving thousands of dollars in treatment costs.

Safety

Nivolumab has an excellent safety profile, particularly when compared to ipilimumab. The unique toxicity profile of immune checkpoint inhibitors is called immune related adverse events (irAEs). Ipilimumab is associated with significant irAEs. The most common grade III or IV toxicity is diarrhea and colitis, ranging from 3 to 10%. The incidence of grade III/IV diarrhea is less than 2% with nivolumab. In the first Phase I trial reported by Topalian et al there were 3 deaths, all from pneumonitis, which is reported to be more frequent in the lung cancer population, likely due to chronic lung inflammation. Since the recognition of pneumonitis the incidence of Grade III/IV events has decreased as it is being diagnosed earlier and will rapidly resolve on steroids. The incidence of all Grade III/IV drug toxicities is less than 2%. The most common toxicity associated with PD-1 inhibitors such as nivolumab is endocrine disorders, of which almost all is thyroid. Patients can develop Hypo or hyperthyroidism. There are well developed algorithms in place to deal with irAEs.

Likewise the Checkmate 066 second line trial comparing chemotherapy to nivolumab demonstrated a more favourable toxicity profile (or less frequent serious adverse events) in favor of the nivolumab. In summary nivolumab is well tolerated with a low incidence of Grade III/IV events.

Burden of Illness

It is estimated that 6,500 Canadians will be diagnosed with melanoma in 2015, and approximately 1050 patients will die of melanoma in 2015. The majority of patients will present with early stage disease and be cured by surgery but for 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. Historically, unresectable stage III or stage IV melanoma carries a poor prognosis with a median survival of 6.2 months and only 25.5% of patients surviving to one year, although recently new therapies have improved the prognosis and a small proportion are experiencing long term survival.

Need

The prognosis of melanoma had remained poor with a median survival of 6.7 months. The survival of metastatic melanoma had not changed in the preceding 5 decades, and it was recognized by the NCI that no significant advances had been made in this disease and it was mandated as a priority to encourage more active trials in melanoma. Since the emergence of immune check point inhibitors and targeted therapies the prognosis of these patients has improved dramatically. 5 year survival rates with Ipilimumab alone have shown that the curve plateaus at about 3 years with a 20% five year survival rate. Those patients who remain in complete response are likely cured, and in fact the FDA has just recently allowed BMS to state that this treatment is potentially curative. Still approximately 80% of melanoma patients will eventually succumb to their disease. In an expanded phase I trial of the combination of ipilimumab and nivolumab the 1 and 2 year survival rates were 94% and 88% respectively. Compared to the meta-analysis by Korn et al the 1 and 2 year survival rates were 25.5% and 10 respectively. This combination has been tested in a Phase III trial and initial results show improvements in PFS and overall response rates; however the study remains blinded for overall survival. The use of nivolumab has consistently shown superiority over ipilimumab in PFS and RR and in adverse events, although survival data is pending. Lastly the two trials of PD-1 inhibitors as second line therapy have shown it to be more effective and less toxic than chemotherapy.
In summary the treatment of melanoma has revolutionized in the last 5 years, and it is now recognized as the poster child of personalized therapy. Chemotherapy has largely been abandoned, with good reason.

2.3 Conclusions

Previously Untreated Advanced Melanoma

The Clinical Guidance Panel concluded that there is an overall net clinical benefit to nivolumab monotherapy in the treatment of patients with previously untreated unresectable stage III or IV melanoma compared with chemotherapy. This conclusion is based on one well-conducted randomized controlled trial that demonstrated a clear statistically significant and clinically meaningful benefit in overall survival, progression-free survival, and response rate in favour of nivolumab compared with chemotherapy in patients with BRAF wild-type advanced melanoma.

Furthermore, the Clinical Guidance Panel concluded that there is an overall net clinical benefit to nivolumab monotherapy in the treatment of patients with previously untreated unresectable stage III or IV melanoma, regardless of BRAF mutation status, compared with ipilimumab. This conclusion is based on one well-conducted randomized controlled trial that demonstrated a clear statistically significant and clinically meaningful benefit in progression-free survival in favour of nivolumab monotherapy compared with ipilimumab monotherapy in patients with advanced melanoma.

Advanced Melanoma that was Previously Treated with Ipilimumab

The Clinical Guidance Panel concluded that there is a net overall clinical benefit to nivolumab monotherapy in the treatment of patients with unresectable stage III or IV melanoma that was previously treated with ipilimumab compared with chemotherapy. This conclusion is based on one randomized controlled trial that demonstrated a difference in response rates in favour of nivolumab monotherapy compared with chemotherapy in patients with advanced melanoma that was previously treated with ipilimumab and on the unmet clinical need and significant burden of this illness on patients.

The progression-free survival data and overall survival data from the CheckMate 037 trial are immature; however, due to the high clinical burden that this illness poses to patients and based on the higher response rates observed with nivolumab monotherapy compared with chemotherapy, the Panel concluded that nivolumab has a net clinical benefit in this patient population.

For previously untreated patients and patients who were previously treated with ipilimumab, 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 are generally low on nivolumab with lower rates of diarrhea/colitis than ipilimumab.
- In general, the side profile shows that nivolumab 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 important to patients and clinicians.
- The Clinical Guidance Panel is unaware of any trials directly comparing nivolumab with pembrolizumab. Therefore the Clinical Guidance Panel could not offer an opinion on the relative efficacy of these two agents.
- There is insufficient evidence to recommend the measurement of PD-L1 to guide the use of nivolumab. In addition, there is a lack of consistency in the assays and cut-offs used to assess PD-L1.
- The Clinical Guidance Panel 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 depending on the clinical situation, and prior BRAF drug use should not preclude the use of nivolumab in ipilimumab naïve or refractory patients.

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 including skin, eyes, and gastrointestinal tract. Although primary melanomas can occur in a variety of anatomical sites, the skin is the most common, comprising 95% of cases. In Canada, 6,800 new cases of primary melanoma are expected in 2015 and approximately 1,150 patients will die from melanoma.[17] The incidence of melanoma has been steadily increasing over the past several decades, with recent increases of 2.3% per year in men between 2001 and 2010, and 2.9% per year among women between 2001 and 2010. At present, the lifetime probability of developing a melanoma for women is 1 in 85 and for men is 1 in 67.[18] Risk factors for melanoma include a history of sunburns in childhood, fair skin, and the use of tanning beds. There has been a recent spike in the incidence of melanoma in adolescent females. This is thought to be due to the increased use of tanning beds which is more common in adolescent females as opposed to adolescent males.

Staging of melanoma is based on the current AJCC 7th Edition Classification.[19] The tumour characteristics principally involve the Breslow height, mitotic rate and the presence or absence of ulceration in the primary. The detection of microscopic and macroscopic lymph node involvement, serum lactate dehydrogenase and the sites of metastatic disease are integral components to the staging classification. All of these factors have been shown to be important prognostic variables which influence patient outcomes and which help to guide management decisions.

3.2 Accepted Clinical Practice

In early stage melanoma, cures are commonly achieved with surgery alone. The primary tumour is excised with appropriate margins. Depending upon the Breslow height, mitotic rate, presence of ulceration and location of the primary, a sentinel node biopsy may be performed to assess nodal status. If the sentinel node is positive then a completion node dissection of the surrounding nodal basin is often performed in order to reduce the risk of a regional recurrence.[20] Although only 5% of patients actually present with metastatic disease, the majority of patients who die from melanoma, will have developed recurrent and/or distant disease. Approximately one-third of patients with early stage melanoma will develop metastasis whereas half of patients with nodal disease will recur and likely die from the development of metastatic disease.[21] Brain metastases are relatively common in advanced melanoma and occur in up to 75% of patients with overt metastatic disease.[22] They often prove to be relatively refractory to radiotherapy and systemic treatment and are associated with a particularly dismal prognosis.

Highly selected patients with Stage IV disease may benefit from surgical resection of the metastases and 5 year survival in these patients ranges from 15 to 25%. For those patients who were not candidates for surgical resection systemic treatment with chemotherapy was the most commonly offered treatment outside of a clinical trial. Unfortunately, the prognosis for these patients prior to 2012 remained poor. The median survival was six to nine months and the five-year survival is approximately 6%.[23] In spite of multiple phase II and III trials with systemic therapy, the objective response to systemic chemotherapy agents remains low and has generally been less than 15%. Until recently, the median survival rates with both single and multiple drug combinations had not changed in the past several decades and had remained within the range of six to twelve months.

Over the past 30 years, the standard first line systemic therapy has been dacarbazine.[20,24] There were no randomized studies comparing either versus BSC to show either an improvement in overall survival or improvements in Quality of Life. Although this intravenous alkylating agent is generally well tolerated, complete responses are rare.[25-30] In the 1990's the FDA approved the use of high dose interleukin-2 based on phase II data showing an overall response rate of 16% but also a durable complete response rate of 5%, extending beyond five years.[31,32] Unfortunately, high dose interleukin-2 is accompanied with significant toxicity and requires intense cardiac monitoring and hemodynamic support. Interleukin-2 has been used in a few selective centres but is largely unavailable throughout Canada.

A very wide spectrum of chemotherapeutic and immunological treatments approaches have been explored in metastatic melanoma with, until recently, limited to no success. Patient outcomes have not changed significantly over the past three decades.[25] Nevertheless, what has become apparent is that melanoma represents a heterogeneous group of diseases which appear to have varying genetic abnormalities which drive cellular proliferation and metastases.[33-35] The MAP kinase signalling pathway appears to be a key regulatory mechanism for cell growth, and differentiation in melanoma.[36] Mutations in the BRAF protein in this pathway can alter the activity of BRAF and result in uncontrolled cellular proliferation and increased potential for metastatic spread.[37] Approximately 50% of human melanomas appear to have an activating mutation in BRAF and has consequently become a potential key target for inhibition and potential therapeutic site.[38]

Vemurafenib is a BRAF inhibitor that selectively targets the mutated BRAF V600 and was approved in August 2011 by the FDA as a treatment of late stage or unresectable melanoma in patients harbouring a V600E mutation, and subsequently by health Canada in February 2012.[39-41] Just fewer than 50% of all melanoma patients will harbour a V600 mutation, with the majority being V600E. In the randomized Phase III study (BRIM3) there was a relative reduction of 63% in the risk of death and a 74% relative reduction in the risk of tumor progression. The overall response rate was 48%.[42] This is now a standard first line treatment of advanced, unresectable melanoma in patients harbouring a V600 mutation.

Ipilimumab is a monoclonal antibody that binds to and blocks the cytotoxic T-lymphocyte associated antigen 4 (CTLA4) located on cytotoxic T-lymphocytes. CTLA4 appears to play an important role in the regulation of the immune response.[43,44] In 2012, Ipilimumab received a Health Canada indication for treatment of unresectable or metastatic melanoma in patients who have failed or did not tolerate other systemic therapy for advanced disease. Since that time it has been widely used across Canada as second line therapy given at a dose of 3 mg per kg given every 3 weeks for a total of 4 doses. Provision for re-induction has been provided in patients who progress following a response to ipilimumab treatment.

The initial approval was principally based upon the findings of a multi-center, double blind placebo controlled trial consisting of three treatment arms randomly assigned 3:1:1 to ipilimumab 3 mg/kg + cancer vaccine GP100, ipilimumab alone, GP100 alone.[45] The study demonstrated an improvement on overall survival (HR 0.66) in the two ipilimumab containing arms compared to GP100 alone. Median overall survival for ipilimumab arms was 10 months compared to 6.4 months in GP100 alone arm. Adverse events were primarily immune related which included diarrhea/colitis, and endocrine problems. Fatigue, rash and anorexia were common but were seldom grade 3 or greater. The study represents the first randomized controlled trial which demonstrated an improvement in survival in patients with metastatic disease. In 2011, Robert and colleagues reported on a randomized controlled trial comparing Ipilimumab 10 mg/kg + dacarbazine 850 mg/m^2 versus dacarbazine alone in patients who were previously untreated.[46] Overall survival was improved in the Ipilimumab containing arm (HR 0.72) and appeared to extend out to 3 years. The median survival was 11.2 months in the Ipilimumab arm compared to 9.1 months in the dacarbazine arm. Immune related events were observed in the Ipilimumab arm and grade 3 or 4 adverse events were more common (56.3% vs 27.5%). Rates of elevated liver enzymes

appeared to be higher than observed in other studies in which Ipilimumab was used alone. Although the progression free survival and overall survival were similar in these trials, the relative impact of the 3 and 10 mg doses of ipilimumab which were used cannot be directly assessed. Furthermore the positive or negative effect on outcomes and toxicity which the GP100 or dacarbazine had within the combination arms of each trial also remains uncertain.

Dabrafenib is a BRAF inhibitor that selectively targets the mutated BRAF V600 and has been under clinical trials since 2009.[42,47,48] In 2012, a multicentre non-blinded phase III study of dabrafenib in comparison to dacarbazine in the first line treatment of 250 patients with unresectable or metastatic melanoma with a BRAF V600E mutation was reported. Patients were randomized 3 to 1 to receive either dabrafenib (187) or DTIC (63) respectively. Those patients who received DTIC could cross-over to receive dabrafenib at disease progression. The primary endpoint was Progression Free Survival as determined by the Investigator. The key inclusion criterion was the presence of V600 mutation. The use of dabrafenib is dependent upon the accuracy and availability of BRAF mutation testing of each prospective patient's primary or metastatic tumour (See Section 7.1). The FDA and Health Canada have approved the use of dabrafenib in unresectable Stage III patients or Stage IV patients who harbour a BRAF V600 mutation.

PD-1 inhibitors in phase 1 trials have shown activity in a variety of tumors including melanoma. Response rates are greater than that achieved with ipilimumab, and like ipilimumab responses appear to be very durable. The KEYNOTE-002 trial showed a response rate of 21% for patients treated with 2 mg/kg of pembrolizumab and 25% for patients treated with 10 mg/kg pembrolizumab and the phase 1 trial of nivolumab showed a response rate of 30.8% for all doses of nivolumab.[14,49] A subsequent randomized phase 3 trial in untreated, BRAF wild type metastatic melanoma patients randomized 418 patients in a one-to-one randomization to receive either dacarbazine or nivolumab. The study was stopped by the data safety monitoring committee at the first data analysis as the one year survival for the nivolumab was 73% versus 42% for the dacarbazine arm. The data safety monitoring committee felt it was unethical to continue the study and recommended that patients who had received dacarbazine and had disease progression should be offered nivolumab. Two subsequent randomized studies comparing PD1 inhibitors versus ipilimumab showed clear superiority of PD1 over ipilimumab in both response rates and progression free survival. PD1 inhibitors also had substantially lower toxicity than ipilimumab. Both pembrolizumab and nivolumab were approved by the FDA 2014. Health Canada approved pembrolizumab the treatment of metastatic melanoma patients who have progressed on ipilimumab. The checkmate 067 study randomized patients in a 1:1:1 randomization to either nivolumab versus nivolumab plus ipilimumab versus ipilimumab. Both nivolumab containing arms shown superiority compared to ipilimumab in both response rates in progression free survival. The study remains blinded as patients continue to be followed for overall survival. The prior phase 1 trial of Nivolumab 1 mg/Kg and ipilimumab 3 mg/kg showed one year survival rates of 94% and two year survival rate of 88%. The subsequent checkmate 067 trial was designed to survival in patients treated with the combination of nivolumab plus ipilimumab versus ipilimumab and to compare nivolumab monotherapy with ipilimumab monotherapy. Pembrolizumab is approved by health Canada in patients with metastatic melanoma who have received prior ipilimumab and a BRAF inhibitor in patients with BRAF V600 mutation; however, pembrolizumab is not yet funded in any of the provinces that participate in the pCODR process.

3.3 Evidence-Based Considerations for a Funding Population

There is strong evidence to support the use of PD1 inhibitors as first-line therapy as opposed to ipilimumab or dacarbazine in patients with metastatic melanoma. Randomized studies comparing PD1 inhibitors versus ipilimumab have shown clear superiority in both response rates and progression free survival. The checkmate 066 study showed a 31% improvement in one year

survival rates compared to dacarbazine. Dacarbazine is no longer ethical as a first line therapy. Longer follow-up is required to show if these improvements in response rates and progression free survival translates to an improvement in overall survival. The combination of the PD1 inhibitor plus ipilimumab is very promising but longer follow-up is required to show whether this translates to improvements in overall survival. The combination arm is associated with greater toxicity than ipilimumab or PD1 inhibitors.

There are no current diagnostic tests to predict the benefit of PD1 inhibition. PD1 ligand expression on the tumor predicts higher response rates with PD1 inhibitors are utilized however, patients whose tumors are PD1 ligand negative have still exhibited durable responses. Current research is focusing on genetic signatures to see whether we can predict which patients will respond to PD1 inhibition. At the present time there is no predictive test to assess patient outcomes with PD1 inhibition.

3.4 Other Patient Populations in Whom the Drug May Be Used

PD1 inhibitors are currently being evaluated as an adjuvant therapy in high-risk melanoma patients who have had complete resection of their disease but remain at high risk of recurrence. To date there is no evidence to support their use as adjuvant therapy and longer follow-up of the adjuvant trials is required.

4 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

One patient advocacy group, Melanoma Network of Canada (MNC), provided input on the nivolumab (Opdivo) submission as first line treatment for advanced adult melanoma patients, regardless of BRAF status, and their input is summarized below.

Melanoma Network of Canada conducted a confidential on-line survey of respondents from across Canada, the United States, and Australia. Respondents were recruited through the MNC database as well as a generic email and an on-line link to a survey requesting input from respondents that had been treated with nivolumab as well as those who had been treated with other drugs or who had not been treated but who may have an opinion on the unmet need for this therapy in the future. MNC received a total of 82 respondents from Canada, 18 from the United States, and 2 from Australia. Of the 102 patients that responded, 22 patients (22%) had been treated with nivolumab. The survey had a combination of multiple choice and open ended questions. MNC has provided selected commentary of respondents that are reflective of various perspectives.

From a patient perspective, there are a number of symptoms associated with advanced melanoma, which include pain, scarring, fatigue or disrupted sleep, fear, depression and anxiety. Patients reported about the impact of advanced melanoma on their lives which included an inability to make long term plans and limited normal day to day activities. The most common side effects in these patients included fatigue or weakness (86.4%), headaches (40.9%), and weight loss or loss of appetite (36.6%).

MNC also reported that 71.4% of patients indicated an improvement in quality of life while on nivolumab, 25% have not responded to treatment, 25% reported they are cancer-free, and 50% reported that they had a slowing of their disease. All patients with the exception of two indicated that they are willing to tolerate certain side effects, particularly if these side effects meant a longer or improved quality of life.

Please see below for a summary of specific input received from the patient advocacy groups. Cited responses are not corrected for spelling or grammar.

4.1 Condition and Current Therapy Information

4.1.1 Experiences Patients Have with Advanced Melanoma

MNC asked respondents to identify symptoms and issues associated with melanoma. There were a total of 73 respondents that had responded to this part of the survey below and a number of respondents skipped the question. According to MNC, patients commonly experienced pain, scarring, fatigue, or disrupted sleep, fear, depression and anxiety. Others have expressed the inability to make long term plans and have limited normal day to day activities. Patients also commented on gastrointestinal issues, nausea and vomiting daily and the agonizing pain in their bones due to metastases.

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 your cancer diagnosis? Please select as many responses as appropriate.		
Answer Options	**Response Percent**	**Response Count**
Pain	71.2%	52
Scarring or disfigurement	65.8%	48
Edema or fluid retention	20.6%	15
Lymphedema	30.1%	22
Mobility issues (unable to walk or impaired movement)	19.2%	14
Gastrointestinal issues	24.0%	18
Breathing problems	13.0%	10
Headaches	27.4%	20
Peripheral neuropathy (nerve pain or damage)	20.6%	15
Disrupted sleep	49.3%	36
Appetite loss or weight gain	38.4%	28
Fear or anxiety	74.0%	54
Fatigue	60.3%	44
Depression	52.1%	38
Post-traumatic stress	9.6%	7
Cognitive Impairment	13.0%	10
Nausea or vomiting	20.6%	15
Damage to organs, such a lungs, liver, brain	18.0%	13
Negative Impact to family or social life	6.0%	5
Financial loss or job loss	38.3%	28
None	5.5%	4
Other (please explain)		1

Below are some of the key comments gathered from respondents through the MNC survey:

- Fatigue, anxiety about my family's future. Not being able to work or plan for the future.
- I am scared to have another child, I am constantly worried I have another spot I am unaware of, I avoid situations I will be in the Sun even though I could go and protect myself.
- I have a fear of the sun. When will another bout of cancer show up? I inspect every part of my body for lurking moles and changes. I basically live in fear. My depression increased because of this and I had to go on medication.
- Loss of income due to sick time, sleep deprivation, nausea, lack of interest in life at times, lasting post treatment side effects.
- During treatment with Interferon headaches, fatigue, weight gain were a day to day struggle. Nerve damage and scarring due to surgery still persists.
- Lack of breath. Unable to walk or do normal thinks like wash dress or go to the bathroom. Pain in many forms.
- 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.
- I have lymphedema in my right leg, with pain and swelling. I have had a lobectomy in my right lung to remove a tumour. I have a full body scan every 3 months; these scans are very stressful to my family and myself with the worry of finding new tumours. It would be a comfort to know that the best drugs are available in Canada if new tumours appear.

- Large tumors on legs have led to neuropathic pain, which has made walking and driving difficult.
- A lot of nerve damage and continuing edema from original surgery. Our emotions are on a roller coaster ride; we have created a large prayer team to pray continually for us, for strength and courage through all of this and of course for healing - this is not something I ever would have asked for before cancer. The original surgery to take out 68 lymph nodes in my neck left scaring, nerve damage and some mobility issues.
- I now have hypothyroidism due to the interferon treatment. I have trouble sleeping, have stopped working as I am unable to complete the requirements needed to do my job. I tire easily and have trouble maintaining my home. I used to do Tai Chi and swim but have not been able to do these activities

4.1.2 Patients' Experiences with Current Therapy for Advanced Melanoma

MNC reported that respondents were treated with a variety of therapies for melanoma including interferon, ipilimumab, or a targeted therapy such as vemurafenib, dabrafenib or trametinib.

According to MNC, below were the treatments that respondents reported receiving for the treatment of melanoma.

What other drug therapies have you been treated with for your melanoma?	Response Percent	Response Count
Answer Options		
Interferon	38.9%	28
DTIC	11.1%	8
Zelboraf (vemurafenib)	13.9%	10
Ipilimumab	52.8%	38
Trametinib (Mekinist)	8.3%	6
Dabrafenib (Tafinlar)	16.7%	12
Other (please specify)	41.7%	30
		72

According to MNC, respondents that had 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, and depression. The majority of patients treated with interferon indicated that it wore them down and the length of time they had to be on the drug (generally 1 year) was too much - most did not complete the full year. Respondents indicated that the most common side effects they could not tolerate well were the fatigue, depression, and constantly feeling sick. As such, respondents could not work through this course of treatment, resulting in more negative impacts emotionally (depression and anxiety), financially as well as with family.

MNC also reported that respondents treated with targeted therapies indicated a variety of milder side effects including rash, additional skin cancers, fatigue, sun sensitivity, abdominal pain, diarrhea, headaches and edema. Most of the respondents indicated that these side effects were tolerable, with the exception of two respondents who had dose reductions and were then removed from the treatment due to side effects.

With respect to ipilimumab, MNC indicated that the most common side effects were diarrhea (2 had severe colitis that required steroids), headaches, chills, rashes, stomach cramps, fatigue, nausea, and vomiting. A majority of respondents (87%) indicated that these side effects were

tolerable and short lived, once therapy ceased. One respondent reported symptoms of an extreme reaction to ipilimumab that caused extreme fatigue, severe itching/rash, headaches (meningitis), a need to replace the cortisol that adrenals weren't producing and nausea/vomiting.

According to the survey conducted by MNC, when respondents were asked if they would be willing to tolerate side effects if there was a possibility of a better quality of life or overall survival, all with the exception of two respondents indicated that they were willing to tolerate side effects if it meant a longer or improved quality of life.

From the patient perspective, outcomes and symptoms consistently most important to control for were:

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

Below are some of the key comments gathered from respondents who participated in this part of the survey:

- I would say death - isn't that the worst outcome? I would like to have therapies that work - that stop the massive growths, the disfigurement, the pain, the constant need for new surgery. I can live with some side effects long term, but could we have something to stop the disease progression?
- Pain is the most important one to control followed by fear, anxiety and depression. You can plumb (sic) the depths of depression when things are not going well including increasing thoughts of suicide as means against progressive degeneration of your quality of life and physical being.
- Disfiguration. I have facial paralysis, my ear has been removed, very little feeling in my face, neck and ear. Loss of saliva in my mouth. Loss of muscles in my neck causing shoulder and back pain.

MNC reported that when patients were asked about unmet need, their responses reflected a common theme – that access to this new therapy provides the possibility to stop progression and to provide other treatment options. Below are some of the key comments gathered from respondents:

- A plan 'B' option that doesn't currently exist for B-RAF wild-type melanoma.
- Ipi did not work for me. So the difference means I would be dead without this option that is working!
- Perhaps last hope – more time or a few extra years if lucky.
- EVERYTHING. I was only able to have 2 of the 4 treatments of Ipi when I developed the horrid side effects mentioned earlier…mainly the Aseptic Meningitis which caused so much pain, discomfort and horrible rashes. Once I recovered, the only option left for me was Opdivo (it was just before it was FDA approved but put on a Compassionate Care type of program). My Dr. got Health Canada approval to have it brought to BC the same week we were scheduled to go to the Angeles Clinic in LA where we would have incurred huge financial costs that would have devastated our family. Now I am treated in BC where my Oncologist knows my history,

everything is covered and we can monitor any side effects. I am showing positive results. It has been LIFE SAVING and ALTERING. It has meant everything to me and my family obviously. Timing has been serendipitous.

4.1.3 Impact of Advanced Melanoma and Current Therapy on Caregivers

MNC reported that the impact of advanced stage melanoma on caregivers is significant. MNC did not ask caregivers directly; the question on caregiver impact was a blended one that asked the patient or caregiver to provide their perspective. It was noted that caregivers and families experience a number of challenges, including time lost from work (68%) significant financial impact (over 65%), increased burden of caregiving and responsibilities for the family (71%), anxiety and depression (56%), and the physical challenges of assistance and lifting. A number of caregivers indicated that the frequency of travel and associated costs to attend appointments and receive treatment on an ongoing basis was difficult. Two respondents stated that family members turned to alcohol or drugs to cope.

To help illustrate the experiences of caregivers, below are some of the key responses reported by MNC:

- My pre-teen turned to drugs to cope with my illness and ended up in rehab. He is hyper vigilant of any bump that turns up on his body. My spouse has been left with his own version of PTSD that has held him back professionally. He is so terrified about how much longer I have to live he prefers to spend all the time he can with me.
- My wife could no longer work full time as she had to look after me, take me to appointments, treatments, deal with side effects. She was also active and hasn't been able to do the things lately that she enjoys ie hiking etc. Most of our family members live away from us. Financially, emotionally and in every way, her life has been impacted hugely!
- Big effect on daughter, as she is sole caretaker. Has to take care of house, pets, cook, do transport to various medical appointments. She had to cancel a trip to Europe due to a surgery.
- I was at stage 4 with melanoma and so before Ipilimumab I was given 6 months to live. This takes away any dream for "growing old together". It took away his "happily ever after". He has suffered great stress at work at different times, he lost one job, took a sabbatical from one and quit another to be with me.
- Sadness, stress, exhaustion and disappointment. Loss of work due to caring for me and taking me to appts and surgeries. Hard to stay positive and non-emotional. We have had to cut out family functions and outings due to my pain or fatigue.

4.2 Information about the Drug Being Reviewed

4.2.1 Patient Expectations for and Experiences to Date with Nivolumab (Opdivo)

MNC stated that the unmet need is to find a drug that provides a durable response or that can provide a good quality of life until another treatment is available. According to MNC, respondents indicated that nivolumab provides new options. Many respondents indicated that if and when they stopped responding to ipilimumab, their options were over. MNC reported that patient expectations of nivolumab are for improved overall survival, and a positive impact on quality of life or potential lasting response. MNC stated that from the responses provided, the side effects seem manageable and in many cases were minimal.

According to the survey conducted by MNC, 22 patients responded that had been treated with nivolumab. The most common side effects in these patients included fatigue or weakness (86.4%), headaches (40.9%), and weight loss or loss of appetite (36.6%). However, 100% of patients on this drug indicated the side effects were worth the treatment, although some have not responded to treatment. In addition, the majority indicated that the drug was well tolerated with a few side effects.

Below is the list of responses surveyed:

If you are or have been treated with the intravenous medication Nivolumab (MDX 1106 or Opdivo) to control or eliminate your disease, what side effects (if any) of the treatment did you or are you experiencing?		
Answer Options	**Response Percent**	**Response Count**
Pain	0.0%	0
Skin rash	36.6%	8
Shortness of breath, cough or chest pain (pneumonitis)	13.6%	3
Fatigue or weakness	86.4%	19
Diarrhea or Colitis	9.1%	2
Constipation	27.7%	6
Muscle or Joint pain	18.1%	4
Fever or flu like symptoms	0.0%	0
Headaches	40.9%	9
Hormone or thyroid problems	0.0%	0
Stomach pain	0.0%	0
Liver problems	18.1%	4
Kidney problems	0.0%	0
Bleeding or bruising more easily	0.0%	0
Weight loss or Loss of appetite	36.6%	8
Weight gain	13.6%	3
Cognitive Impairment	0.0%	0
None - no side effects	27.7%	6

MNC also reported that 71.4% of patients indicated an improvement in quality of life while on nivolumab, 25% have not responded to treatment, 25% reported they are cancer-free, and 50% reported that they have had a slowing of the disease.

4.3 Additional Information

MNC stated that they are overwhelmed at the level of commitment patients have to receive this therapy - in light of the requirement to be at the hospital every two weeks for treatment indefinitely. MNC hopes that in the future, all anti-pd1 drugs will provide data to help physicians determine when a patient who has responded to treatment can safely be removed from ongoing 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.pcodr.ca). 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 Nivolumab for metastatic melanoma. Due to the scope expansion, PAG was provided the opportunity to revise input accordingly.

Clinical factors:

- Dacarbazine is no longer the appropriate comparator; Ipilimumab and BRAF inhibitors +/- MEK inhibitors are now the standard of care in first-line setting
- Lack of direct comparison to all other treatments now available for metastatic melanoma
- Use in second-line setting

Economic factors:

- Drug wastage
- Cost-effectiveness compared to other treatments available
- Treatment algorithm and/or sequencing with recently available therapies

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. At the time of the PAG input, pembrolizumab for metastatic melanoma is under review at pCODR.

The current standard of care in the second-line and beyond is ipilimumab, BRAF inhibitors +/- MEK inhibitors or dacarbazine.

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

5.2 Factors Related to Patient Population

Given the many new treatments recently available and possibly more upcoming new treatments, PAG is seeking guidance from tumour groups for a national treatment algorithm and sequencing of therapies for metastatic melanoma. PAG identified that this is a gap in information but recognizes there may be no data to address sequencing of therapies upfront.

PAG also noted that there is the potential the use of nivolumab in combination with ipilimumab.

5.3 Factors Related to Dosing

PAG noted that the every two week administration schedule may be a barrier to implementation.

As treatment with nivolumab can be continued until unacceptable toxicities or disease progression, PAG is seeking information on the range in duration of treatment. The unknown or indefinite treatment duration could be a barrier to implementation and PAG is seeking clarity on treatment discontinuation.

5.4 Factors Related to Implementation Costs

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. Dose is based on weight and there are two vial sizes available to minimize drug wastage. Any unused portion would be discarded as the stability of reconstituted drug is poor.

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

PAG identified that nivolumab appears to have lower incidence of toxicities than ipilimumab as well as lower incidence of secondary malignancies compared to BRAF inhibitors. These are enablers to implementation.

PAG noted that recent data indicates that ipilimumab could safely be infused over 30minutes instead of 90 minutes (Momtaz et al. Safety of Infusing Ipilimumab Over 30 Minutes. J Clin Oncol 2015 June 29. http://jco.ascopubs.org/content/early/2015/06/24/JCO.2015.61.0030.abstract). Nivolumab is infused over 60 minutes, which could be a shorter or longer infusion time than ipilimumab, depending on the infusion time being used for ipilimumab.

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

5.5 Factors Related to Health System

Nivolumab, 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 nivolumab 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 nivolumab or treat serious adverse events. This is a barrier for those patients who will need to travel to larger cancer centres that have the resources and expertise to administer nivolumab.

5.6 Factors Related to Manufacturer

The high cost of nivolumab would be a barrier to implementation.

PAG noted that nivolumab is undergoing trials for numerous other tumour sites and is seeking information from the manufacturer on drug access for these other indications.

6 SYSTEMATIC REVIEW

Initially, the review for nivolumab was in the previous untreated population. However, input was received from the pCODR Provincial Advisory Group (PAG) expressing an interest in understanding the evidence for nivolumab in the previously treated population given the availability of evidence and possible pressure from clinicians and patients in light of its approval in the United States. As a result, the pCODR Secretariat conducted an assessment in consultation with a three-person panel of pERC (consisting of the pCODR Expert Review Committee (pERC) Chair, the pERC Vice-Chair, and one additional pERC member), the PAG and the submitter to determine the clinical need, jurisdictional need and feasibility of expanding the review into the previously treated population. This assessment resulted in the scope of the review being expanded to include the previously treated population.

6.1 Objectives

i. To evaluate the effectiveness and safety of nivolumab (OPDIVO™) for the treatment of advanced (unresectable or metastatic) melanoma in previously untreated adult patients, regardless of BRAF status.
ii. To evaluate the effectiveness and safety of nivolumab (OPDIVO™) for the treatment of advanced (unresectable or metastatic) melanoma in previously treated adult patients, regardless of BRAF status.

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 Table 6.1. Outcomes considered most relevant to patients, based on input from patient advocacy groups are those in bold.

Table 6.1 Selection Criteria

First-line therapy

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Published or unpublished randomized controlled trials	Previously untreated patients with unresectable or metastatic melanoma (stage III or IV), regardless of BRAF status	Nivolumab monotherapy 3 mg/kg administered intravenously over 60 minutes every 2 weeks	• Best supportive care • Dacarbazine • Carboplatin • Paclitaxel • Temozolomide • Placebo • Ipilimumab • Vemurafenib • Trametinib • Dabrafenib • Dabrafenib+Trametinib • Pembrolizumab**	• **Overall survival** • Progression-free survival • **Quality of life** • Response rate • Duration of response • Adverse Events • Withdrawal due to adverse events

Second-line or later therapy				
Clinical Trial Design	**Patient Population**	**Intervention**	**Appropriate Comparators***	**Outcomes**
Published or unpublished randomized controlled trials	Previously treated patients with unresectable or metastatic melanoma (stage III or IV), regardless of BRAF status	Nivolumab monotherapy 3 mg/kg administered intravenously over 60 minutes every 2 weeks	• Best supportive care • Dacarbazine • Carboplatin • Paclitaxel • Temozolomide • Placebo • Ipilimumab • Vemurafenib • Trametinib • Dabrafenib+Trametinib • Pembrolizumab** • Interferon-alfa 2b • Interleukin-2	• **Overall survival** • Progression-free survival • **Quality of life** • Response rate • Duration of response • Adverse Events • Withdrawal due to adverse events
* *Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions)* ** *Identified as agent of interest although not currently available in Canada*				

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 to Present) with in-process records & daily updates via Ovid; Embase (1974-2015 August 25) via Ovid; The Cochrane Central Register of Controlled Trials (July 2015) via Ovid; 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 Opdivo, nivolumab and melanoma.

Methodological filters were applied to limit retrieval to randomized controlled trials and controlled clinical trials. Where possible, retrieval was limited to the human population. The search was also limited to English language documents, but was not limited by publication year. The search is considered up to date as of January 7, 2016.

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 - clinicaltrials.gov and Canadian Partnership Against Cancer Corporation - Canadian Cancer Trials) and relevant conference abstracts. Searches of conference abstracts of the American Society of Clinical Oncology (ASCO) was 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 additional 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. One member of the pCODR Methods Team made the final selection of studies to be included in the review.

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. A data audit was conducted by another member of 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:

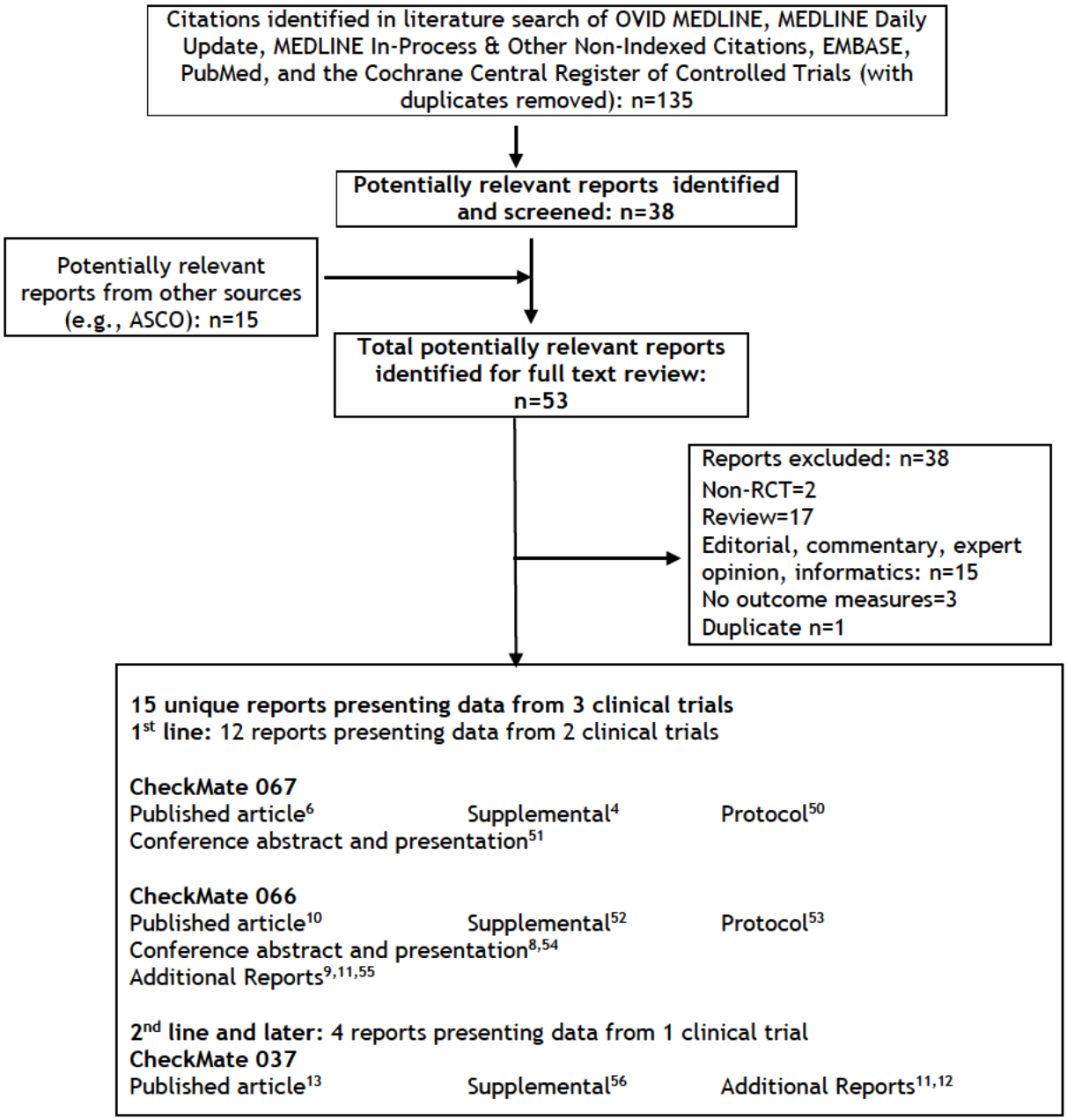
- The Methods Team wrote a systematic review of the evidence and summaries of evidence for supplemental issues (if any).
- The pCODR Clinical Guidance Panel wrote a summary of background clinical information, the interpretation of the systematic review and wrote guidance and conclusions for the report.
- The pCODR Secretariat wrote summaries of the input provided by patient advocacy groups and by PAG.

6.3 Results

6.3.1 Literature Search Results

Of the 135 citations identified in the literature search, three studies (CheckMate 067, CheckMate 066, and CheckMate 037) were included in the systematic review.

Figure 6.1 QUOROM Flow Diagram for Inclusion and Exclusion of Studies



Note: Additional data related to CheckMate 067, CheckMate 066, and CheckMate 037 were also obtained through requests to the Submitter by pCODR.[57]

Table 6.2 Summary of Trial Characteristics of the Included Studies[6,10,11,50,53,58,59]			
Trial Design	**Key Inclusion Criteria**	**Intervention and Comparator**	**Outcomes**
CheckMate 067 (NCT01844505) Multicenter international double-blind phase III randomized control trial Enrolment: Jul 2013 - Mar 2014 n enrolled=1296 Data cut-off date: Feb 17, 2015 with a median progression-free survival follow-up: 12.2-12.5 months Estimated study completion date: Oct 2017 Randomized 1:1:1 ratio, stratified by: • PD-L1 status (positive vs. negative) • BRAF status (positive vs. wildtype) • Metastasis stage (M0/M1a/M1b vs. M1c) n randomized = 945 Funded by: Bristol-Meyers Squibb	• Histologically confirmed, stage III (unresectable) or IV melanoma • Treatment naïve for unresectable or metastatic melanoma • Age 18+ • ECOG PS 0-1 • Measurable disease as assessed by CT or MRI per RECIST 1.1 criteria • Availability of tumour tissue for PD-L1 assessment • Known $BRAF^{v600}$ status or consent to testing **Key Exclusion Criteria:** • ECOG performance status 2+ • Active brain or leptomeningal metastases • Ocular melanoma • Active, known or suspected autoimmune disease • Condition requiring systemic treatment with corticosteroids or other immunosuppressive medication within 14 days of study drug administration • Prior treatment with anti-PD-1, anti-PD-L1, anti-PD-L2, or anti-CTLA-4 antibody or other antibody or drug specific targeting T-cell or immune checkpoint pathways	Nivolumab 3mg/kg every 2 weeks, plus ipilimumab-matched placebo Nivolumab 1mg/kg every 3 weeks, plus ipilimumab 3mg/kg every 3 weeks for 4 doses, followed by nivolumab 3mg/kg every 2 weeks for cycle 3 and beyond Comparator: Ipilimumab 3mg/kg every 3 weeks for 4 doses, plus nivolumab-matched placebo By means of intravenous infusion	Primary outcomes: • Progression-free survival • Overall survival Secondary outcomes: • Objective response rate • PD-L1 expression as a predictive biomarker for progression-free survival and overall survival • Health-related quality of life

CheckMate 066 (NCT01721772) Multicenter international double-blind phase III randomized control trial Enrolment: Jan 2013 – Feb 2014 n enrolled = 518 Data cut-off date: Jun 24, 2014 Estimated study completion date: Nov 2016 Randomization ratio 1:1 stratified by: • PD-L1 status • Metastasis stage n randomized = 418 Funded by: Bristol-Myers Squibb	• Histologically confirmed, stage III (unresectable) or IV melanoma • Treatment naïve for unresectable or metastatic melanoma • Age 18+ • ECOG performance status 0-1 • Measurable disease as assessed by CT or MRI per RECIST 1.1 criteria • Availability of tumour tissue for PD-L1 assessment • Known BRAF wild-type status as per regionally acceptable V600 mutational status testing **Key Exclusion Criteria:** • Active brain metastases or leptomeningeal metastases • Ocular melanoma • Active, known or suspected autoimmune disease • Prior malignancy active within the previous 3 years (exception: locally curable cancers that have been apparently cured) • Require systemic treatment with either corticosteroids or other immunosuppressive medications within 14 days of study drug administration • Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 • Antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways Patients who had previous adjuvant therapy were not excluded.	• Nivolumab 3mg/kg every 2 weeks, plus dacarbazine-matched placebo every 3 weeks Comparator: • Dacarbazine 1000mg/m^2 every 3 weeks, plus nivolumab-matched placebo every 2 weeks By means of intravenous infusion	Primary outcome: • Overall survival Secondary outcomes: • Progression-free survival • Objective response rate • PD-L1 expression as a predictive biomarker for overall survival • Health-related quality of life
CT = computed tomography; ECOG PS = Eastern Cooperative Oncology Group performance status; MRI = magnetic resonance imaging; RECIST = Response Evaluation Criteria in Solid Tumours; PD-1 = programmed cell death protein 1; PD-L= programmed death-ligand; vs. = versus.			

a) Trials

Trial details are found in Table 6.2.

CheckMate 067

CheckMate 067 was a three arm double-blind phase 3 randomized controlled trial conducted to evaluate the safety and efficacy of nivolumab alone or nivolumab combined with ipilimumab in comparison with ipilimumab alone in patients with previously untreated metastatic melanoma.[6]

The study was sponsored by Bristol-Meyers Squibb. CheckMate 067 enrolled 1296 patients with histologically confirmed, stage III (unresectable) or IV melanoma in 137 sites in Australia, Europe, Israel, New Zealand, and North America (including Canada).[6,50] A total of 945 patients were randomly assigned in a 1:1:1 ratio to receive, (1) 3mg/kg nivolumab every 2 weeks plus ipilimumab-matched placebo (n=316); (2) 1mg/kg nivolumab every 3 weeks plus 3mg/kg ipilimumab every 3 weeks for 4 doses, followed by 3mg/kg nivolumab every 2 weeks for cycle 3 and beyond (n=314); or (3) 3mg/kg ipilimumab every 3 weeks for 4 doses, plus nivolumab-matched placebo (n=315) by means of intravenous infusion.[6] Randomization was stratified by PD-L1 status (positive or negative), BRAF status (positive or wild-type), and metastatic stage (M0/M1a/M1b or M1c).[6] Crossover was not permitted.[3]

OS and PFS were the co-primary endpoints. Secondary endpoints included objective response rate, PD-L1 expression in tumour as a predictive biomarker for PFS and OS, and health-related quality of life. Analyses for OS and PFS were planned at different time points, with no planned interim analysis. The study was designed with an overall alpha of 0.05, which allocated 0.01 for PFS (using the Bonferroni adjustment) and 0.04 for OS (using Hochberg's procedure).[50] For PFS, the study design required a minimum of 266 events in the ipilimumab arm and 223 events in each experimental arm to ensure 83% power to detect a hazard ratio of 0.71 at a type I error of 0.005 (two-sided).[50] This meant that for each comparison, in order to accept a statistically significant difference, the p value of the hazard ratio for death or disease progression needed to be ≤ 0.005. For OS, the study designed required a minimum of 240 events in the ipilimumab arm and 202 events in each experimental arm to ensure 99% power to detect a hazard ratio of 0.65 at a type I error of 0.02 (two-sided).[50] This meant that for each comparison, in order to accept a statistically significant difference, the p value of the hazard ratio for death needed to be ≤ 0.02.[50]

The study consisted of three phases: screening, treatment, and follow-up (after patient discontinued therapy).[6] After the first two follow-up visits, survival was assessed every 3 months after the discontinuation of treatment.[6] Safety was assessed regularly during treatment phase and document at minimum 100 days after the last dose of the treatment.[50] Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.[6] Tumour response was assessed at week 12 following randomization, then every 6 weeks up for 49 weeks, and then every 12 weeks until progression or treatment discontinuation (whichever occurred later).[6,50]

CheckMate 067 was not designed for a formal statistical comparison between nivolumab monotherapy and nivolumab plus ipilimumab. For CheckMate 067, the information reported in this review came from the PFS analysis with a data cut-off of February 17, 2015. CheckMate 067 is still ongoing and remains blinded with respect to OS.[6] Estimated study completion date is October 2017.[58]

CheckMate 066

CheckMate 066 was a double-blind phase 3 randomized controlled trial conducted to determine whether nivolumab, as compared with dacarbazine, improves overall survival (OS) among previously untreated patients who have advanced melanoma without a BRAF mutation.[10]

A total of 518 patients with histologically confirmed, stage III (unresectable) or IV melanoma were enrolled in 80 sites in Europe, Australia, Canada and South America.[10] A total of 418 patients were randomly assigned in a 1:1 ratio to receive (1) 3 mg/kg nivolumab every 2 weeks plus dacarbazine-matched every 3 weeks (n=210) or (2) 1000 mg/m^2 dacarbazine every 3 weeks plus nivolumab-matched placebo every 2 weeks by means of intravenous infusion. Randomization was stratified by PD-L1 status (positive or negative/intermediate) and metastasis stage (M0/M1a/M1b or M1c).[10] Prior to the amendment, crossover was not permitted.[3]

OS was the primary endpoint. Secondary endpoints included PFS, objective response rate, PD-L1 expression in tumour as a predictive biomarker for OS, and health-related quality of life. The study design required a minimum of 312 deaths, with an interim analysis after 218 deaths (70% of total deaths needed for final analysis) to ensure 90% power to detect a hazard ratio of 0.69 at a type I error of 0.05 (two-sided).[53]

The study consisted of three phases: screening, treatment, and follow-up (after patient discontinued therapy).[12,53] After the first two follow-up visits, survival was assessed every 3 months after the discontinuation of treatment.[10] Safety was assessed regularly during treatment phase and document at minimum 100 days after the last dose of the treatment.[53] Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.[10] Tumour response was assessed at week 9 following randomization, then every 6 weeks up for the first year, and then every 12 weeks until progression or treatment discontinuation (whichever occurred later).[10,53]

CheckMate 066 was stopped by the data safety monitoring committee for superior efficacy reasons (data showed a significant difference in OS in favour of nivolumab) during an earlier safety review (before the interim analysis). The data safety monitoring committee felt it was unethical to continue the study and recommended that the study be unblinded and amended to allow patients who had initially received dacarbazine and had disease progression to receive nivolumab. The information reported in this review is before the (open-label) amendment with a data cut-off of June 24, 2014, unless otherwise specified.[10] At the time of the data cut-off date, a total of 146 deaths were observed.[10]

b) Populations

Baseline patient characteristics for both studies can be found in Table 6.3.

CheckMate 067

In CheckMate 067, a total of 945 patients were randomized to receive nivolumab (n=316), nivolumab plus ipilimumab (n=314), or ipilimumab (n=315). The average age was 60 years and male patients constituted about 65% of the population.[6] Less than a quarter of the population tested positive for PD-L1 expression and almost all patients had no history of brain metastases.[6] Patients were well-balanced between the three treatment arms. In all three arms, most patients had an ECOG performance status of 0 (75.3% versus 73.2% versus 71.1%) and over 30% had a BRAF V600 mutation (31.6% versus 32.2% versus 30.8%).[6]

CheckMate066

In CheckMate 066, the patients were balanced between the two treatment arms, with the exception of ECOG performance status. More patients in the nivolumab arm had an ECOG performance status of 0 compared to patients in the dacarbazine arm (70.5% versus 58.2%).[10] A total of 418 patients were randomized to receive nivolumab (n=210) or dacarbazine (n=208).[10] The median age was 65 and males constituted more than half of the population.[10] About 35% of the population tested positive for PD-L1 expression and almost all patients had no history of brain metastases.[10]

Table 6.3 Baseline Characteristics					
	CheckMate 067[6]			CheckMate 066[10]	
	Nivolumab (n=316)	Nivolumab plus ipilimumab (n=314)	Ipilimumab (n=315)	Nivolumab (n=210)	Dacarbazine (n=208)
Age					
Mean (range)	59(25-90)	59(18-88)	61(18-89)	NR	NR
Median (range)	NR	NR	NR	64(18-86)	66(26-87)
Gender, male	202(63.9%)	206(65.6%)	202(64.1%)	121(57.6%)	125(60.1%)
Geographic region					
Europe or Canada	NR	NR	NR	145(69.0%)	145(69.7%)
Other	NR	NR	NR	65(31%)†	63(30.3%)†
ECOG PS					
0	238(75.3%)	230(73.2%)	224(71.1%)	148(70.5%)	121(58.2%)
1	77(24.4%)	83(26.4%)	91(28.9%)	60(28.6%)	84(40.4%)
2‡	1(0.3%)	0	0	1(0.5%)	3(1.4%)
NR	0	1(0.3%)	0	1(0.5%)	0
BRAF mutation	100(31.6%)	101(32.2%)	97(30.8%)	NA	NA
LDH					
≤ ULN	196(62.0%)	199(63.4%)	194(61.6%)	120(57.1%)	125(60.1%)
> ULN	112(35.4%)	114(36.3%)	115(36.5%)	79(37.6%)	74(35.6%)
NR/Unknown	8(2.5%)	1(0.3%)	6(1.9%)	11(5.2%)	9(4.3%)
PD-L1 positive status	80(25.3%)	68(21.7%)	75(23.8)	74(35.2%)	74(35.6%)
Metastatic stage					
M0, M1a, M1b	132(41.8%)	133(42.4%)	132(41.9%)	82(39.0%)	81(38.9%)
M1c	184(58.2%)	181(57.6%)	183(58.1%)	128(61.0%)	127(61.1%)
No history brain metastases	308(97.5%)	303(96.5%)	300(95.2%)	203(96.7%)	96.2(96.2%)
Prior systemic therapy					
Adjuvant therapy	NR	NR	NR	32(15.2%)	36(17.3%)
Neoadjuvant therapy	NR	NR	NR	1(0.5%)	1(0.5%)

ECOG PS = Eastern Cooperative Oncology Group performance status; LDH = lactate dehydrogenase; NA = not applicable; NR = not reported; PD-L1 = programmed death-ligand 1; ULN = upper limit of the normal range.
†Israel, Australia, or South America;
‡patient inadvertently enrolled in the study, despite having an ECOG PS of 2

c) Interventions

CheckMate 067

Patients were randomized to receive: (1) 3 mg/kg nivolumab every 2 weeks plus ipilimumab-matched placebo; (2) 1 mg/kg nivolumab every 3 weeks plus 3 mg/kg ipilimumab every 3 weeks for 4 doses followed by 3 mg/kg nivolumab every 2 weeks for cycle 3 and beyond; or (3) 3 mg/kg ipilimumab every 3 weeks for 4 doses plus nivolumab-matched placebo.[6]

Nivolumab was administered in accordance with the product monograph. Treatment in all three arms was continued until disease progression, unacceptable toxicity effects or withdrawal of consent.[6] Treatment with nivolumab monotherapy, nivolumab plus ipilimumab and ipilimumab monotherapy beyond disease progression (beyond initial RECIST 1.1 defined progressive disease) was permitted, for patients who had a clinical benefit (assessed by investigator) and did not have substantial adverse events.[6,50]

According to the submitter, the assessment of clinical benefit by the investigator took into account whether the patient was clinically deteriorating and unlikely to receive further benefit from continued treatment.[57] The submitter sought the opinion of a clinical expert to summarize clinical benefit. According to the clinical expert, there is no strict definition of clinical benefit, however, indicators (i.e., clinical, radiological, and biochemical signs) are used in assessing the role for continuing immunotherapy. The clinical expert stated that clinical, radiological, and biochemical signs include, but were not limited to: a mixed response, progression in the face of improving performance status or improving tumor markers, and early progression.[57]

Dose delay or discontinuation in all three arms was permitted; however, dose escalation or reduction in all three arms was not permitted.[50]

CheckMate 066

Patients were randomized to receive: (1) receive 3 mg/kg nivolumab every 2 weeks plus dacarbazine-matched every 3 weeks (n=210) or (2) 1000 mg/m^2 dacarbazine every 3 weeks plus nivolumab-matched placebo every 2 weeks.[10]

Nivolumab was administered in accordance with the product monograph. Treatment was continued until disease progression, unacceptable toxicity effects or withdrawal of consent. Treatment beyond disease progression (beyond initial RECIST 1.1 defined progressive disease) was permitted, for patients who had a clinical benefit and did not have substantial adverse events with both arms.[10]

According to the submitter, the assessment of clinical benefit by the investigator took into account whether the patient was clinically deteriorating and unlikely to receive further benefit from continued treatment.[57] The submitter sought the opinion of a clinical expert to summarize clinical benefit. According to the clinical expert, there is no strict definition of clinical benefit, however, indicators (i.e., clinical, radiological, and biochemical signs) are used in assessing the role for continuing immunotherapy. The clinical expert stated that clinical, radiological, and biochemical signs include, but were not limited to: a mixed response, progression in the face of improving performance status or improving tumor markers, and early progression.[57]

Dose delay or discontinuation was permitted for nivolumab and dacarbazine.[53] Dose escalation or reduction was not permitted for nivolumab, however, dose reduction was permitted for dacarbazine or dacarbazine-matched placebo.[53]

Subsequent therapy with anti-PD-1 agents was received by 1 (0.5%) patients in the nivolumab arm and 3 (1.4%) patients in the dacarbazine arm.[57]

Treatment beyond progression

Results of a retrospective analysis of CheckMate 067 and 066 indicate that of all randomized patients who received nivolumab (N=526; where n=313 in CheckMate 067 and n=206 in CheckMate 066), 58.2% (306 of 526) experienced RECIST-defined progression. Of the 306 of patients who experienced RECIST-defined progression, 27.8% (85 of 306) were patients who continued nivolumab after progression or were treated beyond progression.[60]

Patient Disposition

Details of the disposition of patients in both studies can be found in Table 6.4. In CheckMate 067, a total of 1296 patients were enrolled, 945 of whom were randomized. A total of 937 patients received at least one dose of treatment. Of those that received treatment, a total of 196 out of 313 patients discontinued treatment with nivolumab, 220 out of 313 patients discontinued treatment with nivolumab plus ipilimumab, and 261 out of 311 discontinued

treatment with ipilimumab. The main reason for discontinuing treatment was disease progression for patients treated with nivolumab alone and ipilimumab alone. For patients treated with nivolumab plus ipilimumab, the main reason for discontinuing treatment was study drug toxicity.[4]

In CheckMate 066, a total of 518 patients were enrolled, 418 of which were randomized. A total of 411 patients received at least one dose of treatment. Of those that received treatment, a total of 111 out of 206 patients discontinued treatment with nivolumab compared to 192 out of 205 patients treated with dacarbazine. The main reason for discontinuing treatment was disease progression.[52]

Table 6.4 Patient Disposition

	CheckMate 067[4]			CheckMate 066[52]	
	Nivolumab	Nivolumab plus ipilimumab	Ipilimumab	Nivolumab	Dacarbazine
Enrolled	1296			518	
Randomized	316	314	315	210	208
Received treatment	313	313	311	206	205
Patients remain on treatment	117	93	50	95	13
Discontinued treatment†	196	220	261	111	192
Reasons for discontinuing treatment:					
disease progression	154	69	202	96	175
study drug toxicity	27	120	47	5	7
death	5	5	4	0	0
adverse event unrelated to study drug	5	12	4	2	3
requested to discontinue	5	5	4	5	2
withdrew consent	0	3		2	3
maximum clinical benefit	2	2	0	1	1
poor compliance	1	1	1	NR	NR
lost to follow-up	1	0	0	NR	NR
no longer meets study criteria	0	1	0	NR	NR
other	0	3	2	0	1
Analysis population:					
ITT analysis for efficacy	316	314	315	210	208
ITT analysis for safety‡	313	313	311	206	205

ITT = intent-to-treat.
†Some patients may have had >1 reason for withdrawal
‡all the patients who received at least 1 dose of study drug

d) Limitations/Sources of Bias

CheckMate 067 is still not yet completed; estimated study completion date is October 2017.[58] Critical appraisal of the trial was based on information from the progression free survival analysis (data cut-off February 17, 2015). At the time of the PFS analysis, overall survival data were immature and therefore, no OS analysis has been conducted yet.

Checkmate 066 was stopped by the data safety monitoring committee for superior efficacy reasons (data showed a significant difference in OS in favour of nivolumab) during an earlier safety review (in an unplanned interim analysis). The information reported in this review is from before the (open-label) amendment (data cut-off of June 24, 2014), unless otherwise specified.

Overall, the risk of bias in both studies appears low. Details are provided below.

1. Randomization and allocation concealment

In CheckMate 067, patients were randomized via permuted blocks within each stratum (PD-L1 status, M Stage, and BRAF status) and allocated in a 1:1:1 fashion. Similarly, in CheckMate 066, patients were randomized via permuted blocks within each stratum (PD-L1 status, and M Stage) and allocated in a 1:1 fashion.

In both studies, baseline characteristics were well balanced, with the exception of ECOG performance status in CheckMate 066. Patients in the nivolumab arm appeared slightly healthier than patients in the dacarbazine arm (70.5% versus 58.2% with an ECOG performance status of 0); this may have a potential to affect the internal validity of the study and therefore, potentially bias the treatment effect to favour nivolumab. Overall, a statistically significant improvement in OS at 1 year, was found in favour of nivolumab [hazard ratio for death (N=418): 0.42(99.79% CI, 0.25 to 0.73). Results from a pre-specified subgroup analysis of ECOG performance status suggest a statistically significant improvement in OS in favour of nivolumab among patients with an ECOG performance status of 0 [hazard ratio for death (N=269): 0.32 (95% CI, 0.20 to 0.53)].

Overall, the risk of selection bias was low.

2. Blinding

In both CheckMate 067 and Checkmate 066, the study sponsor, patients, investigator, and site staff (with the exception of pharmacist/designee and site monitor for each investigative site) were blinded. CheckMate 067 is still ongoing and remains blinded with respect to overall survival. Checkmate 066 is now unblinded and amended to allow patients who had initially received dacarbazine and had disease progression to receive nivolumab.

In both studies, within each arm, placebo and active treatment were in identical forms and the dosing schedule was identical. In CheckMate 067, to protect the blind, patients in the nivolumab plus placebo arm received 1 mg/kg of nivolumab diluted in the same volume as the 3 mg/kg nivolumab placebo. In CheckMate 066, to protect the blind, dose reduction was permitted for both dacarbazine and dacarbazine-matched placebo. The side effect profile for PD-1 inhibitors may differ from ipilimumab; with PD-1 inhibitors, greater rates of pneumonitis are expected, however, in Checkmate 067, the rates of grade 3-4 pneumonitis were similar in all three arms.

Overall, the risk of performance bias and detection bias was low.

3. Attrition

The primary reason for withdrawal in CheckMate 067 was due to disease progression (for the nivolumab arm and ipilimumab arm) and study drug toxicity (for the nivolumab plus ipilimumab arm). In Checkmate 066, the primary reason for withdrawal was due to disease progression.

In both studies, the efficacy outcomes were analysed according to the intent-to-treat principle and drop outs were included in the analysis. As well, safety outcomes were analysed according to the intent-to-treat principle, using all the patients who received at least 1 dose of study drug. In both studies, only a small proportion of patients did not receive at least 1 dose of study drug.

Overall, the risk of attrition bias was low.

4. Reporting of outcomes

In CheckMate 067, progression-free survival and overall survival were co-primary endpoints. Overall survival data were immature and therefore, no OS analysis has been conducted yet. Estimated study completion date is October 2017.[58] No interim overall survival analysis was planned. As a result, only progression-free survival data were reported. It is important to note that progression-free survival was originally a secondary outcome and the protocol was later amended (Amendment 06) to include progression-free survival as a co-primary outcome.[50] It is also important to highlight that it is unknown whether progression-free survival data are a reliable surrogate for overall survival in trials with immunotherapies such as ipilimumab.[61]

It is worth noting that not reporting data when data are immature is appropriate and therefore, and not considered selective reporting or reporting bias.

5. Protocol deviation

Inclusion criteria within both protocols included patients with an ECOG performance status of ≤1; however, 1 patient in CheckMate 067 and 4 patients in CheckMate 066 were enrolled and randomized, despite having in ECOG performance status of 2. These patients were included in the intent-to-treat analysis. Despite this protocol deviation, the risk of affecting the true treatment effect is low given the small proportion of included patients with an ECOG performance status of 2.

6.3.1.2A Detailed Outcome Data and Summary of Outcomes (Previously untreated population)

In both trials, subgroup analyses were specified a priori and performed. However, the CGP did not identify relevant subgroups, and therefore the results presented encompass the entire study population. Subgroup analysis (BRAF status) pertinent to the indication: treatment of unresectable or metastatic BRAF V600 wild-type melanoma in previously untreated adults; is briefly highlighted for CheckMate 067.

In CheckMate 067, the efficacy outcomes were analyzed according to the intent-to-treat principle (n=316, 314, 315 respectively). Safety population included only patients who have received at least one treatment after randomization (n=313, 313, 311 respectively).

Similarly, in Checkmate 066, the efficacy outcomes were analyzed according to the intent-to-treat principle (n=210, 208 respectively). Safety population included only patients who have received at least one treatment after randomization (n=206, 205 respectively).

Details of efficacy outcome data are listed in Tables 6.5 - 6.8, and found in Figures 6.2 and 6.3. Details of harms outcome data are listed in Table 6.9.

a) Efficacy Outcomes

Overall Survival

Details of OS data are listed in Table 6.5, Table 6.6 and Figure 6.2. In CheckMate 067, overall survival data were immature (the pre-specified number of deaths was not reached) and therefore, no OS analysis has been conducted yet. Estimated study completion date is October 2017.[58]

In CheckMate 066, the survival rate at 1 year was 72.9% for the nivolumab arm compared to 42.1% for the dacarbazine arm (Table 6.5 and Figure 6.2). A statistically significant improvement in overall survival at 1 year was found in favour of nivolumab [hazard ratio for death: 0.42(99.79%CI, 0.25 to 0.73); *P*<0.001]. The median overall survival was not reached for patients in the nivolumab arm, whereas the median overall survival for patients in the dacarbazine arm was 10.8 months. The median follow-up for overall survival was 6.8 months for the dacarbazine group and 8.9 months for the nivolumab group.[55]

Refer to Table 6.6 for updated overall survival data (database lock of July 15, 2015). Updated overall survival data suggest the overall survival rate at 12 months and 24 months was 70.7% and 57.7% in the nivolumab group.[7]

Progression-Free Survival

Details of PFS data are listed in Table 6.5 and Figure 6.3. In CheckMate 067, the estimates of median progression-free survival were 6.9 months for patients in the nivolumab monotherapy group, 11.5 months for patients in the nivolumab plus ipilimumab group, and 2.9 months for patients in the ipilimumab monotherapy group. A statistically significant improvement in progression-free survival was found in favour of nivolumab compared to ipilimumab and in favor of nivolumab plus ipilimumab compared to ipilimumab alone. Estimates of the rate of progression-free survival at 1 year were 44% for patients in the nivolumab arm (with 50 patients at risk), 51% for patients in the nivolumab plus ipilimumab arm (with 64 patients at risk), and 20% for patients in the ipilimumab monotherapy arm (with 24 patients at risk) (estimated from published Kaplan-Meier plot of progression-free survival). A PFS benefit was observed in nivolumab compared to ipilimumab for BRAF wild type patients [hazard ratio for death or disease progression in BRAF wildtype patients: 0.50 (95% CI, 0.39 to 0.63; *P* not reported)]; however, PFS was not statistically significant for patients with BRAF V600 [hazard ratio for death or disease progression in BRAF V600 patients: 0.77 (95% CI, 0.54 to 1.09; *P* not reported)].[4] For BRAF wildtype patients, the median PFS was 7.89 for the nivolumab monotherapy group and 2.83 for the ipilimumab monotherapy group.[4] Of note, while patients were stratified by BRAF mutation status at randomization, the required sample size for the trial was based on determining the treatment effect for the entire study population. Therefore, the subgroup analysis of patients with BRAF mutation-positive disease may not have been adequately powered to detect a difference in effect.

In CheckMate 066, the estimates of median progression-free survival were 5.1 months in the nivolumab group and 2.2 months in the dacarbazine group. A statistically significant improvement in progression-free survival was found in favour of nivolumab compared to dacarbazine. Estimates of the rate of progression-free survival at 1 year were 43% for patients in the nivolumab arm (with 12 patients at risk) and 0% for patients in the dacarbazine arm (with 0 patients at risk) (estimated from published Kaplan-Meier plot of progression-free survival).

Table 6.5 Efficacy Outcomes

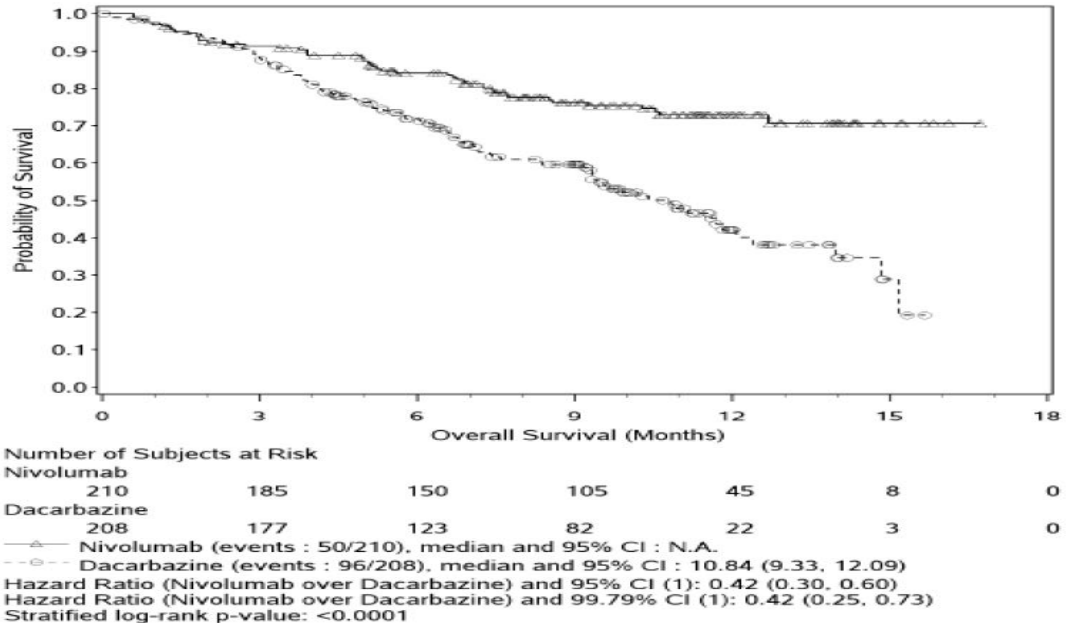
	CheckMate 067[6] Data cut-off: Feb 17, 2015			CheckMate 066[10] Data cut-off: June 24, 2014	
Outcome	**Nivolumab (n=316)**	**Nivolumab plus ipilimumab (n=314)**	**Ipilimumab (n=315)**	**Nivolumab (n=210)**	**Dacarbazine (n=208)**
Median OS months (95%CI)	NA	NA	NA	Not reached	10.8(9.3-12.1)
Hazard ratio† (99.79%CI)	NA	NA	-	0.42(0.25-0.73)	
1 year OS rate	NA	NA	NA	72.9%	42.1%

Table 6.5 Efficacy Outcomes					
	CheckMate 067[6] Data cut-off: Feb 17, 2015			CheckMate 066[10] Data cut-off: June 24, 2014	
no. at risk				45	22
Median PFS months (95%CI)	6.9(4.3-9.5)	11.5(8.9-16.7)	2.9(2.8-3.4)	5.1(3.5-10.8)	2.2(2.1-2.4)
Hazard ratio[†] (95%CI) (99.5%CI)	- 0.57(0.43-0.76)	- 0.42(0.31-0.57)	- -	0.43(0.34-0.56) -	
1 year PFS rate[‡] no. at risk	44% 50	51% 65	20% 24	43% 12	0% 0
Objective response n (%)	138(43.7%) CR:28(8.9%) PR:110(34.8%)	181(57.6%) CR:36(11.5%) PR:145(46.2%)	60(19.0%) CR:7(2.2%) PR:53(16.8%)	84(40.0%) CR:16(7.6%) PR:68(32.4%)	29(13.9%) CR:2(1.0%) PR:27(13.0%)
Odds Ratio[†] (95%CI)	3.40(2.02-5.72)	6.11(3.59-10.38)	-	4.06(2.52-6.54)	

CI = confidence interval; CR = complete response; NA = not available; OS = overall survival; PFS = progression-free survival; PR = partial response.
[†]p value <0.001
[‡]estimated from published Kaplan-Meier plot of progression-free survival

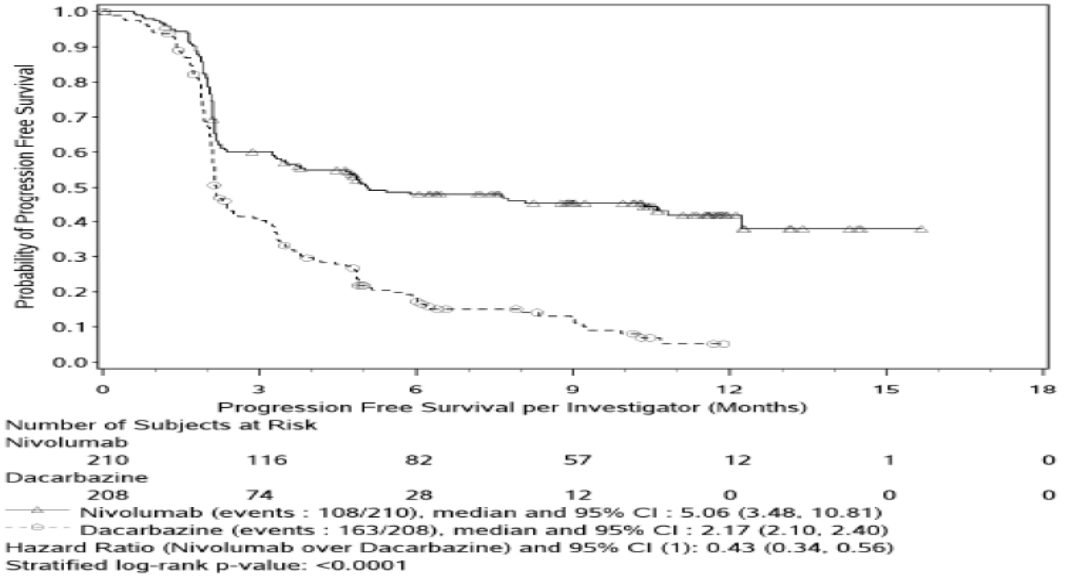
Table 6.6 CheckMate 066 Updated Overall Survival Data (After Amendment)[7]		
Data cut-off: July 15, 2015	**Nivolumab (n=210)**	**Dacarbazine (n=208)**
OS rate		
12 months	70.7%	46.3%
24 months	57.7%	26.7%
Hazard ratio, (95%CI),p<0.0001	0.43(0.33-0.57)	

Figure 6.2 CheckMate 066 – Kaplan-Meier plot of overall survival[11]



Source: Opdivo assessment report. European Medicines Agency; 2015 Apr 23. p.64[11] (Database locked on May 27, 2014)

Figure 6.3 CheckMate 066 – Kaplan-Meier plot of progression-free survival[11]



Source: Opdivo assessment report. European Medicines Agency; 2015 Apr 23. p.65[11] (Database locked on May 27, 2014)

Quality of life

The assessment of health-related quality of life using the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 was a secondary objective, while the assessment of the general health status using the EQ-5D utility index and VAS were exploratory objectives. A presentation from the 2015 Society for Melanoma Research International Congress summarized the health-related quality of life data assessed in CheckMate 067. Results are presented below.[5]

The minimum important difference (MID) used for assessing health-related quality of life using the EORTC QLQ-C30 was greater than or equal to 10 points. At baseline, EORTC QLQ-C30 completion

rates were 89.9% (n=284 out of 316) in the nivolumab arm, 92.4% (n= 290 out of 314) in the nivolumab plus ipilimumab arm, and 88.6% (n=279 out of 315) in the ipilimumab arm. The EORTC QLQ-C30 completion rates at baseline and one or more post-baseline visits were 85.1% (n=269 out of 316) in the nivolumab arm, 87.3% (n=274 out of 314) in the nivolumab plus ipilimumab arm, and 82.2% (n=259 out of 315) in the ipilimumab arm. It appears that quality of life was maintained over time (from baseline to week 67) for the nivolumab and nivolumab plus ipilimumab arms since the EORTC QLQ-C30 Global Health mean change scores appeared stable over time (never equivalent or exceeding the MID from baseline to week 67). In the ipilimumab arm, it appears that quality of life was maintained from baseline to week 61 (at week 61, 5.4%, n=17 out of 315) since the EORTC QLQ-C30 Global Health mean change scores appeared stable, after which it appears that quality of life may have worsened, where EORTC QLQ-C30 Global Health mean change scores appears to be equivalent to the MID (at week 67, 2.9%, n=9 out of 315). Similar results were noted for most EORTC QLQ-C30 scales over time.[5]

In the exploratory analysis, the MID used for assessing the general health status using the EQ-5D utility index was greater than or equal to 0.08 points. At baseline, EQ-5D completion rates were 89.2% (n=282 out of 316) in the nivolumab arm, 92.4% (n= 290 out of 314) in the nivolumab plus ipilimumab arm, and 88.3% (n=278 out of 315) in the ipilimumab arm. The EQ-5D completion rates at baseline and one or more post-baseline visits were 84.5% (n=267 out of 316) in the nivolumab arm, 87.3% (n=274 out of 314) in the nivolumab plus ipilimumab arm, and 81.9% (n=258 out of 315) in the ipilimumab arm. Using the EQ-5D utility index, it appears that quality of life may be trending to clinical improvement at week 67 (4.1%, n=13 out of 316) for the nivolumab arm (exceeding the MID at week 67). The minimum important difference used for assessing the general health status using the EQ-5D VAS was greater than or equal to 7 points. Using the EQ-5D VAS, it appears that quality of life was maintained over time for the nivolumab, nivolumab plus ipilimumab, and ipilimumab arms (never equivalent or exceeding the MID from baseline to week 67).[5]

CheckMate 066

In CheckMate 066, the assessment of health-related quality of life using the EORTC QLQ-C30 was a secondary objective, while the assessment of the general health status using the EQ-5D utility index and VAS were exploratory objectives.

Details of the health-related quality of life assessment in CheckMate 066 are listed in Table 6.7. An American Society of Clinical Oncology (ASCO) poster summarized the health-related quality of life data assessed in CheckMate 066.[8] Completion rates at baseline or baseline and at least one post-baseline visit were not reported. The author indicated that although baseline completion rates were high in both arms, a higher proportion of patients were available for assessment in the nivolumab arm compared to the ipilimumab arm as a results of high attrition in the dacarbazine arm. For EORTC QLQ-C30, the minimal important difference was ≥ 10 points, while for EQ-5D utility index and EQ-5D VAS, the minimal important difference were ≥ 0.08 points, and ≥ 7 points respectively. The authors noted that baseline scores for EORTC QLQ-C30, EQ-5D utility index and EQ-5D VAS were comparable among both groups. In a cross-sectional analysis, the authors stated that EORTC QLQ-C30 subscale scores did not change over time for either arm, however, some clinically meaningful changes were observed in patients treated with nivolumab for EORTC QLQ-C30 emotional and social functioning scales at certain time points (data not shown in poster) and for EQ-5D utility index score, some clinically meaningful improvement was observed in patients treated with nivolumab at week 37 (25.7%, n=53 out of 210), 61 (6.7%, n=14 out of 210) and 67 (2.9%, n=6 out of 210). The authors concluded that health-related quality of life in patients treated with nivolumab generally showed no deterioration over the course of treatment.[8]

A longitudinal mixed-effects model was used to assess the longitudinal changes from baseline scores while controlling for certain baseline covariates (Patient reported outcome score, ECOG

performance status, region, PD-L1 status, lactate dehydrogenase, gender, age, BRAF mutation test, and blinding status). The authors stated that no significant changes for EQ-5D utility index or EQ-5D VAS were observed between- and within-treatment arms. Although across 61 weeks, significant improvements versus baseline were found in some EORTC QLQ-C30 scales (nausea and vomiting, insomnia, and emotional functioning) for patients treated with nivolumab, none of the changes were clinically meaningful.[8]

At a patient level, a cox proportional hazard regression model was used to determine the time from randomization to first deterioration and the time from randomization to first improvement. Only patients with ≥1 follow-up assessment were included in the analysis. According to the authors, results from the cox proportional hazard regression model showed that patients who received nivolumab were significantly more likely to experience a longer time to first decline in EORTC QLQ-C30 global health status score (where the rate of deterioration reached 50% at 276 days for nivolumab arm compared to 179 days for the dacarbazine arm) or EQ-5D utility index score compared with patients who received dacarbazine. The authors stated that nivolumab was significantly more likely to lead to a shorter time to improvement in EORTC QLQ-C30 global health status score and EQ-5D utility index score compared with dacarbazine.[8]

Table 6.7 CheckMate 066 - Health-related quality of life assessment[8]

	Hazard Ratio (95%CI)[a]	P value[b]
Time to First Decline[c]		
EORTC QLQ-C30 Global health status	0.66(0.47-0.94)	0.021
EQ-5D utility index	0.55(0.38-0.80)	0.002
EQ-5D VAS	0.82(0.59-1.14)	Not significant
Time to First Improvement[d]		
EORTC QLQ-C30 Global health status	1.52(NR)	0.043
EQ-5D utility index	1.86(NR)	0.002
EQ-5D VAS	NR	NR

CI = confidence interval; EORTC = European Organisation for Research and Treatment of Cancer; NR = not reported; VAS = visual analog scale.
[a] Only patients with ≥1 follow-up assessment were included in the analysis; baseline score included in model as covariate
[b] p value from Chi-Square test
[c] hazard ratio <1 favor nivolumab
[d] hazard ratio >1 favor nivolumab

Utility data from Long et al were calculated using UK weights.[8] An abstract from Harrison and Kim highlighted utility data calculated using Australian weights.[9] Harrison et al. described that utility data were collected during the CheckMate 066 study every 6 weeks via the EQ-5D-3L instrument and questionnaires scored using Australian specific weights within Microsoft Excel. Details of mean utility scores at baseline, prior to the development of progressive disease, and following the development of progressive disease are listed in Table 6.8.[9]

According to Harrison and Kim, for patients randomised to nivolumab, the development of progressive disease per RECIST v1.1 criteria did not significantly impact utility (mean change = 0.01, P=0.4618); however, for patients randomise to dacarbazine, the development of progressive disease per RECIST v1.1 criteria did significantly impact utility (mean change = 0.08, P=0.0005).[9]

Table 6.8 CheckMate 066 - Mean utility scores using Australian weights[9]		
HRQoL Assessment using EQ-5D-3L	Nivolumab Mean Utility(95%CI)	Dacarbazine Mean Utility(95%CI)
At Baseline	0.78(0.75-0.81)	0.71(0.67-0.75)
Prior to the development of progressive disease	0.84(0.83-0.85)	0.78(0.76-0.81)
Following the development of progressive disease	0.83(0.80-0.86)	0.70(0.66-0.74)
CI = confidence interval; HRQoL = health related quality of life.		

Overall response rate

Details of objective response rate data are listed in Table 6.5. In CheckMate 067, the objective response rates were 43.7% for patients in the nivolumab monotherapy group, 57.6% for patients in the nivolumab plus ipilimumab group, and 19.0% for patients in the ipilimumab monotherapy group. A statistically significant improvement in objective response was found in favour of nivolumab compared to ipilimumab and in favor of nivolumab plus ipilimumab compared to ipilimumab alone. The ORR results from the BRAF status subgroup analysis were not reported.

In CheckMate 066, the objective response rates were 40.0% for patients in the nivolumab group compared to 13.9% for patients in the dacarbazine group. A statistically significant improvement in objective response was found in favour of nivolumab compared to dacarbazine.

Duration of Response

For those who achieved a response, the duration of response was not yet reached in any arm in CheckMate 067.[6] For those who achieved a response in CheckMate 066, the duration of response was not yet reached (range: 0.0-12.5 months; n=84) in the nivolumab arm and was 6.0 months (range: 1.1 -10.0 months, n=29) in the dacarbazine arm (data were censored for the range values since observations were ongoing. Data cut-off for clinical date was August 5, 2014).[10,11]

b) Harms Outcomes

Grade 3 and 4 treatment related adverse events

Details of harms outcome are listed in Table 6.9. In CheckMate 067, less frequent grade 3 or 4 TRAEs were reported for nivolumab treated patients (16.3%) compared to nivolumab-plus-ipilimumab treated patients (55.0%) and ipilimumab treated patients (27.3%). Diarrhea was the most common grade 3 or 4 TRAE for patients treated with nivolumab alone and nivolumab-plus-ipilimumab (2.2%, 9.3%) and colitis was the most common grade 3 or 4 TRAE for patients treated with ipilimumab alone (8.7%). Other grade 3 or 4 TRAEs included fatigue, increased alanine-transferase level, increased aspartate amino-transferase level, rash, colitis, vomiting, and dyspnea were experienced in less than 2% of patients who received nivolumab.

Similarly, in CheckMate 066, less frequent grade 3 or 4 TRAEs were reported for nivolumab treated patients (11.7%) compared to dacarbazine treated patients (17.6%). Diarrhea was the most commonly reported grade 3 or 4 TRAE among nivolumab treated patients (1.0%). Thrombocytopenia and neutropenia were the most commonly reported grade 3 or 4 TRAEs among dacarbazine treated patients (4.9%, 4.4%). Other grade 3 or 4 TRAEs included pruritus, rash, and vomiting were experienced in less than 1% of patients who received nivolumab.

Adverse events of special interest

In CheckMate 067, one case of grade 3 or 4 hypothyroidism was found in patients treated with nivolumab plus ipilimumab combination therapy and no cases of grade 3 or 4 hypothyroidism were found in patients treated with nivolumab monotherapy or ipilimumab monotherapy. Rates of grade 3 or 4 pneumonitis were low in all three arms. No cases of grade 3 or 4 neutropenia were reported. Two cases of grade 3 or 4 colitis were reported in patients treated with nivolumab compared to 24 cases reported in patients treated with nivolumab plus ipilimumab and 27 cases reported in patients treated with ipilimumab.

In CheckMate 066, no cases of grade 3 or 4 hyperthyroidism or pneumonitis were found in either group. No cases of grade 3 or 4 neutropenia were reported in patients treated with nivolumab, while nine cases of grade 3 or 4 neutropenia were reported in patients treated with dacarbazine.

Withdrawal due to adverse events

Among the 937 patients in the safety population in CheckMate 067, the rate of withdrawal due to grade 3 or 4 TRAEs was 5.1% (16 out of 313) for patients treated with nivolumab monotherapy, 29.4% (92 out of 313) for patients treated with nivolumab plus ipilimumab combination therapy, and 13.2% (41 out of 311) for patients treated with ipilimumab monotherapy. Two deaths were attributed to study-drug toxicity in CheckMate 067: one death in patients treated with nivolumab (neutropenia) and one other death in patients treated with ipilimumab (cardiac arrest).

Among the 411 patients in the safety population in CheckMate 066, the rate of withdrawal due to grade 3 or 4 adverse events was 5.8% (12 out of 206) for patients treated with nivolumab, and 9.3% (19 out of 205) for patients treated with dacarbazine. Withdrawal due to TRAEs was not reported. No deaths were attributed to study-drug toxicity in CheckMate 066.

Table 6.9 Harms Outcomes

	CheckMate 067[4,6] Reported in at least 5% of the patients in any of the three study groups, unless otherwise specified			CheckMate 066[10,52] Reported greater than 2% of population	
	Nivolumab (n=313)	Nivolumab plus ipilimumab (n=313)	Ipilimumab (n=311)	Nivolumab (n=206)	Dacarbazine (n=205)
	Grade 3 or 4	Grade 3 or 4	Grade 3 or 4	Grade 3 or 4	Grade 3 or 4
Any AE	136(43.5%)[a]	215(68.7%)[a]	173(55.6%)[a]	70(34.0%)	78(38.0%)
TRAEs	51(16.3%)[a]	172(55.0%)[a]	85(27.3%)[a]	24(11.7%)	36(17.6%)
Skin					
Pruritus	0	6(1.9%)	1(0.3%)	1(0.5%)	0
Rash	1(0.3%)	9(2.9%)	5(1.6%)	1(0.5%)	0
Gastrointestinal					
Diarrhea	7(2.2%)	29(9.3%)	19(6.1%)	2(1.0%)	1(0.5%)
Colitis	2(0.6%)	24(7.7%)	27(8.7%)	1(0.5%)	0
Constipation	NR	NR	NR	0	0
Nausea	0[a]	7(2.2%)[a]	2(0.6%)[a]	0	0
Vomiting	1(0.3%)[a]	8(2.6%)[a]	1(0.3%)[a]	1(0.5%)	1(0.5%)
Hepatic					
Increase in ALT	4(1.3%)	26(8.3%)	5(1.6%)	2(1.0%)	1(0.5%)
Increase in AST	3(1.0%)	19(6.1%)	2(0.6%)	1 (0.5%)	1 (0.5%)
Endocrine					
Hypothyroidism	0	1(0.3%)	0	0	0

Table 6.9 Harms Outcomes					
	CheckMate 067[4,6] Reported in at least 5% of the patients in any of the three study groups, unless otherwise specified			CheckMate 066[10,52] Reported greater than 2% of population	
Hyperthyroidism	0	3(1.0%)	0	1(0.5%)	0
Pulmonary					
Pneumonitis	1(0.3%)	3(1.0%)	1(0.3%)	0	0
General					
Fatigue	4(1.3%)	13(4.2%)	3(1.0%)	0	2(1.0%)
Neutropenia	NR	NR	NR	0	9(4.4%)
AE leading to discontinuation	NR	NR	NR	12(5.8%)	19(9.3)
TRAEs leading to discontinuation	16(5.1%)[a]	92(29.4%)[a]	41(13.2%)[a]	NR	NR
Death due to toxic effect of study drug	1(0.3%)[b]	0	1(0.3%)[c]	0	0

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; NR = not reported; TRAE = treatment-related adverse event.
[a]Reported in at least 10% of patients in any of three study groups;
[b]neutropenia
[c]cardiac arrest

6.3.1.1B Detailed Trial Characteristics (Previously Treated Population)

Table 6.10 Summary of Trial Characteristics of the Included Studies[11-13,56,62]			
Trial Design	**Key Inclusion Criteria**	**Intervention &Comparator**	**Outcomes**
CheckMate 037 (NCT01721746) Multicenter international phase III open label randomized control trial Enrolment: Dec 21, 2012 - Jan 10, 2014 n enrolled=631 Clinical database lock: April 30, 2014 ORR analysis database lock: May 30, 2014 OS interim analysis database lock: Nov 12, 2014	• Histologically confirmed, stage III (unresectable) or IV melanoma • Age 18+ • ECOG performance status 0-1 • Classified as PD-L1 positive, negative, or intermediate by pre-treatment recent core, excision or punch biopsy from unresectable or metastatic site; with no intervening systemic therapy administered between time of biopsy and randomization. • Measurable disease as assessed by CT or MRI per RECIST 1.1 criteria. • Objective evidence of disease progression (e.g.: clinical or radiological) during or after at least 1 (wildtype) or at least 2 (V600 positive) prior treatment regimens for advanced melanoma: o Patient with BRAF wild-type: evidence of disease progression during or following anti-CTLA-4 treatment for advanced melanoma and those who received another treatment must have objective evidence of disease progression during or following at least	Nivolumab 3mg/kg every 2 weeks <u>Comparator:</u> Investigator's choice (dacarbazine 1000mg/m^2 or paclitaxel 175mg/m^2 combine with carboplatin area under the curve 6) every 3 weeks By means of intravenous infusion	Primary outcomes: • Objective response rate • Overall survival Secondary outcomes: • Progression-free survival • PD-L1 expression as a predictive biomarker for objective response rate and overall survival

Table 6.10 Summary of Trial Characteristics of the Included Studies[11-13,56,62]			
Trial Design	**Key Inclusion Criteria**	**Intervention &Comparator**	**Outcomes**
Estimated study completion date: Sept 2016 Randomized 2:1 ratio, stratified by: • PD-L1 status (positive vs. negative) • BRAF status (positive vs. wildtype) • Prior anti-CTLA-4 best response (CR, PR or SD vs. PD) n randomized = 405 Funded by: Bristol-Meyers Squibb	1 cycle of treatment for advanced melanoma. ○ Patients with BRAFv600 positive mutation: evidence of disease progression with anti-CTLA-4 treatment and a BRAF inhibitor, in any sequence or combination. • Prior chemotherapy or immunotherapy completed ≥4 weeks before study drug administration, and all adverse events have returned to baseline or stabilized. • Prior anti-CTLA-4 therapy completed ≥6 weeks before study drug administration. <u>Exclusion Criteria:</u> • Active brain or leptomeningal metastases • Ocular melanoma • Unknown BRAF status • Active, known or suspected autoimmune disease • Condition requiring systemic treatment with corticosteroids or other immunosuppressive medication within 14 days of study drug administration • Prior systemic melanoma therapy with both dacarbazine and carboplatin and paclitaxel • Had grade 4 toxic effects or used infliximab to manage adverse events from previous ipilimumab treatment • Previous treatment with anti-PD-1, anti-PD-L1, or anti-PD-L2 antibodies;		• Health-related quality of life
CR = complete response; CT = computed tomography; CTLA-4 = cytotoxic T-lymphocyte-associated protein 4; ECOG PS = Eastern Cooperative Oncology Group; MRI = magnetic resonance imaging; ORR = objective response rate; OS = overall survival; PD = progressive disease; PD-L1 = programmed death-ligand 1; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumours; SD = stable disease; vs. = versus.			

a) Trial

Trial characteristics are found in Table 6.10.

In Checkmate 037, an open label phase 3 randomized controlled trial was conducted to assess the efficacy and safety of nivolumab compared with investigator's choice of chemotherapy (ICC) in patients who progressed on or after anti-CTLA-4 treatment, and for patients with BRAF V600 mutation, who had progressed on or after anti-CTLA-4 treatment and a BRAF inhibitor.[11,13]

CheckMate 037 was sponsored by Bristol-Meyers Squibb. CheckMate 037 enrolled 631 patients with histological confirmed, stage III (unresectable) or IV melanoma who have had progression after anti-CTLA-4 treatment (i.e.: ipilimumab), or anti-CTLA-4 treatment and a BRAF inhibitor if they were BRAF V600 mutation positive. The study recruited patients at 90 sites within 14 countries, a total 4 Canadian sites recruited 44 patients.[13,56] A total of 405 patients were randomly assigned in

a 2:1 ratio to receive nivolumab 3 mg/kg every 2 weeks (n=272) or ICC (dacarbazine 1000 mg/m² or paclitaxel 175 mg/m² combine with carboplatin area under the curve 6) every 3 weeks (n=133) by means of intravenous infusion.[13] Crossover was not permitted.[12] Randomization was stratified by PD-L1 status (positive versus negative), BRAF status (positive versus wildtype), and prior anti-cTLA-4 best response (complete response, partial response or stable disease versus progressive disease).[13]

The primary outcomes of CheckMate 037 were to obtain (1) an estimation of the proportion of patients who achieved an objective response, which was planned after 120 patients had received nivolumab were followed up for at least 24 weeks, and (2) a comparison of overall survival between the two arms.[13] Secondary outcomes included progression-free survival, PD-L1 expression as a predictive biomarker for objective response rate and overall survival, and health-related quality of life.[13]

The study consisted of three phases: screening, treatment, and follow-up (after patient discontinued therapy).[12] Survival was assessed every 3 months after the discontinuation of treatment.[12] Tumour response was assessed at week 9 following randomization, then every 6 weeks up for the first year, and then every 12 weeks until progression or treatment discontinuation (whichever occurred later).[11] Safety was assessed at screening, on-study (at each cycle), and follow-up (at 30 days after the last dose of the study drug, followed by 84 days from the first follow-up).[12] Data on adverse events were collected continuously during the treatment period and for a minimum of 100 days following the last dose of study treatment.

The analyses for objective response rate and OS were planned at different time points.[12] The planned analysis of ORR was originally designed to compare nivolumab to ICC; then, the study was modified to allow non-comparative estimation of ORR in the nivolumab arm.[12] According to the author, they arbitrarily spent an administrative alpha of 0.001 to acknowledge the single-arm estimation but did not define a significance level.[13] Hence, there was no formal hypothesis test of ORR.[12] The study design required a minimum of 260 deaths, with an interim analysis after 169 deaths (65% of total deaths needed for final analysis) to ensure 90% power to detect a hazard ratio of 0.65 at a type I error of 0.049 (two-sided).[11] Final PFS analysis was planned when the minimum number of deaths was achieved.[13]

The formal analysis for objective response rate is completed and occurred when the first 120 patients treated with nivolumab had a minimum follow-up of 24 weeks. The OS data presented in this review are from the pre-specified interim analysis of OS (database locked on November 12, 2014).[11] Estimated study completion date is September 2016.[62]

b) Population

Details of baseline characteristics are listed in Table 6.11.Patients with BRAF wild-type must have had progression after anti-CTLA-4 treatment (i.e.: ipilimumab), while patients with BRAFv600 positive mutation must have had progression with anti-CTLA-4 treatment and a BRAF inhibitor.

The average age was 59 years and male patients contributed to 64% of the population. About half of the population tested positive for PD-L1 expression and most patients had no history of brain metastases. Overall, patients were balanced with the exception of high lactate dehydrogenase and history of brain metastases. Almost all patients previously received ipilimumab, and over half of patients previously received chemotherapy in metastatic disease setting. One patient received ipilimumab in adjuvant disease setting. About half of patients received two previous systemic therapies for metastatic disease, less than a quarter received more than two previous systemic treatments for metastatic disease.

Table 6.11 CheckMate 037 - Baseline Characteristics[a] [11,13]			
	Nivolumab (n=272)	ICC (n=133)	Total (N=405)
Mean age(range)	58.7(23-88)	60.3(29-85)	59.2(23-88)
Gender, male	176(64.7%)	85(63.9%)	261(64.4%)
Race			
White	269(98.9%)	29(97.0%)	398(98.3%)
Black or African America	1(0.4%)	2(1.5%)	3(0.7%)
Asian	2(0.7%)	0	2(0.5%)
Other	0	2(1.5%)	2(0.5%)
ECOG performance status			
0	162(59.6%)	84(63.2%)	246(60.7%)
1	110(40.4%)	48(36.1%)	158(39.0%)
2[b]	0	1(0.8%)	1(0.2%)
BRAF mutation	60(22.1%)	29(21.8%)	89(22.0%)
LDH			
≤ ULN	129(47.4%)	77(57.9%)	206(50.9%)
> ULN	139(51.1%)	46(34.6%)	185(45.7%)
NR	4(1.5%)	10(7.5%)	14(3.5%)
PD-L1 positive status	134(49.3%)	67(50.4%)	201(49.6%)
Metastatic stage			
M0, M1a, M1b	69(25.4%)	31 (23.3%)	100(24.7%)
M1c	203(74.6%)	102(76.7%)	305(75.3%)
No history brain metastases	219(80.5%)	115(86.5%)	334(82.5%)
Type of previous therapies in metastatic disease setting[c]			
Ipilimumab	271(99.6%)	133(100%)	404(99.8%)
Vemurafenib	49(18.0%)	23(17.3%)	72(17.8%)
Chemotherapy	145(53.3%)	72(54.1%)	217(53.6%)
Other immunotherapy[d]	37(13.6%)	35(26.3%)	72(17.8%)

ECOG PS = Eastern Cooperative Oncology Group; LDH = lactate dehydrogenase; NR = not reported; PD-L1 = programmed death-ligand 1; ULN = upper limit of the normal range.
[a] % may add up to >100% due to rounding
[b] patient inadvertently enrolled in the study, despite having in ECOG PS of 2
[c] 1 patient in the nivolumab arm was treated with ipilimumab in the adjuvant disease setting
[d] excludes ipilimumab, includes interferon α2a and b, interleukin 2 and 21, and T-cell infusion immunotherapies

c) Intervention

Patients were randomized to receive either nivolumab 3mg/kg every 2 weeks (n=272) or ICC (dacarbazine 1000 mg/m^2 or paclitaxel 175 mg/m^2 combine with carboplatin area under the curve 6) every 3 weeks (n=133) by means of intravenous infusion.[13]

Treatment was continued until disease progression or unacceptable toxicity effects. Patients treated with nivolumab were permitted to continue beyond progression (beyond initial RECIST 1.1 progressive disease) as long as they experienced clinical benefit (assessed by investigator) and tolerated the drug. According to the submitter, the assessment of clinical benefit by the investigator took into account whether the patient was clinically deteriorating (and unlikely to receive further benefit from continued treatment. The submitter sought the opinion of a clinical expert to summarize clinical benefit. According to the clinical expert, there is no strict definition of clinical benefit, however, indicators (i.e., clinical, radiological, and biochemical signs) are used in assessing the role for continuing immunotherapy. The clinical expert stated that clinical,

radiological, and biochemical signs include, but were not limited to: a mixed response, progression in the face of improving performance status or improving tumor markers, and early progression.[57]

Treatment beyond progression with ICC was not permitted.

Dose escalation or reduction with nivolumab was not permitted; however, dose delay was permitted. Dose escalation with ICC was not permitted; however, dose reduction and dose delay with ICC were permitted.[11,13]

Nivolumab has yet to be approved by Health Canada for the treatment of advanced (unresectable or metastatic) melanoma in previously treated patients.

Treatment Beyond Progression

Of the first 120 patients in the nivolumab arm with a minimum of 6 months follow-up, 31% (n=37) of patients continued nivolumab beyond progression by RECIST v1.1 criteria.[11]

d) Patient Disposition

Details of patient disposition are listed in Table 6.12. A total of 631 patients were enrolled, 405 of whom were randomized. A total of 370 patients received at least one dose of treatment. Of those that received treatment, a total of 139 out of 268 patients discontinued treatment with nivolumab compared to 84 out of 102 patients treated with ICC. The main reason for discontinuing treatment was disease progression. Of the randomized patients, a small proportion of patients in the nivolumab arm (1.5%; 4 out of 272) did not receive treatment (at least 1 dose of study drug), whereas a large proportion of patients in the ICC arm (23.3%; 31 out of 133) did not receive treatment.[13]

Table 6.12 CheckMate 037 - Patient Disposition[11]

	Nivolumab	ICC (dacarbazine/ paclitaxel plus carboplatin)
Enrolled	631	
Randomized	272	133
Received treatment	268	102(45/57)
Patients remain on treatment	129	18(7/11)
Discontinued treatment	139	84(38/46)
Reasons for discontinuing treatment:		
disease progression	116	62(35/27)
Death	6	0
study drug toxicity	7	7(2/5)
adverse events unrelated to study drug	4	2(0/2)
patient requested to discontinue	3	6(0/6)
withdrew consent	2	3(0/3)
maximum clinical benefit	0	3(0/3)
poor compliance	1	0
Other	1	1(1/0)
Analysis Population:		
All randomized population: all subjects randomized to any group	272	133
All Treated Population: All subjects treated with ≥ 1 dose of study drug	268	102

Table 6.12 CheckMate 037 - Patient Disposition[11]		
	Nivolumab	ICC (dacarbazine/ paclitaxel plus carboplatin)
ORR Population: All randomized subjects to either treatment groups with ≥ 6 months of follow-up at the time of the ORR analysis	122	60
Treated Subjects among ORR Population: All subjects who received ≥ 1 dose of treatment and had ≥ 6 months of follow-up at the time of the ORR analysis	120	47
ICC = investigator's choice of chemotherapy; ORR=objective response rate.		

e) Limitations/Sources of Bias

Overall, the risk of bias was moderate. Details are provided below.

1. Randomization and allocation concealment

Patients were randomized via permuted blocks within each stratum (PD-L1 status, BRAF status, and prior anti-cTLA-4 best response) and allocated in a 2:1 fashion.

A rationale for disproportionate randomization (2:1) was not identified. The CGP felt that 2:1 allocation was used for pragmatic reasons.

Baseline characteristics were balanced, with the exception of high lactate dehydrogenase and history of brain metastases. There were a higher proportion of patients in the nivolumab arm with an elevated lactate dehydrogenase (51.1% versus 34.6%) and a history of brain metastases (19.5% versus 13.5%).[11] This may have a potential to affect the internal validity of the study, as a results of confounding since history of brain metastases and elevated lactate dehydrogenase are risk factors known to negatively affect the outcome of melanoma patients.[11] The intent-to-treat ORR analysis (provided by EMA), which included all randomized patients, suggested that the ORR (N=405) was 25.4% for patients in the nivolumab group and 8.3% for patients in the ICC group. A subgroup analysis of patients with elevated lactate dehydrogenase (n=177), which included all randomized, treated patients suggest that the ORR was 20.4% for patients in the nivolumab group and 10.0% for patients in the ICC group.[11] A subgroup analysis of patients with history of brain metastases (n=70), which included all randomized, treated patients suggest that the ORR was 16.7% for patients in the nivolumab group and 18.8% for patients in the ICC group.[11]

2. Blinding

CheckMate 037 was an open label study. Thus, treating physicians and patients were not blinded to the treatment received.[11] Treatment was given open-label because of the investigator's choice of chemotherapy for the comparator group.[13] As a result, this may have introduced a moderate-high risk of bias in the assessment of subjective measures such as health-related quality of life and the reporting of adverse events. However, an independent radiology review committee assessed the objective response rate and progression-free survival as per RECIST v1.1 criteria. The risk of performance bias and detection bias were low. Overall survival was unlikely to be influenced by subjective bias results.

3. Attrition

The primary reason for drop out in CheckMate 037 was due to disease progression. Efficacy data for the intent-to-treat population were available and drop outs were included. The risk of attrition bias with respect to efficacy outcomes was low. Safety outcomes were analysed according to the intent-to-treat principle, using all the patients who received at least 1 dose of study drug. Of the randomized patients, a large proportion of patients in the ICC arm (23.3%; 31 out of 133) did not receive treatment; 22 patients from the ICC arm withdrew consent prior to receiving treatment, 5 patients did not want to receive treatment but were willing to continue with the follow-up survival period, 2 patients no longer met the study criteria, and 2 additional patients had other reasons (not specified) for not receiving treatment.[13] The risk of attrition bias with respect to harms outcome was moderate-high.

4. Reporting of outcomes

Estimated study completion date is September 2016.[62] OS interim analysis and PFS descriptive analysis were reported by EMA.[11] Health-related quality of life data are not yet available; an analysis will be performed at the time of the final OS analysis.[3]

Although PFS descriptive analysis was reported by EMA, PFS data were immature and therefore, results should be interpreted with caution. It is worth noting that not reporting data when data are immature is appropriate and is not considered selective reporting or reporting bias.

5. Protocol deviation

Inclusion criteria within the study protocol included patients with an ECOG performance status of ≤1; however, one patient was enrolled and randomized, despite having in ECOG performance status of 2. As well, inclusion criteria included objective evidence of disease progression during or after at least one (wildtype) or at least two (BRAF v600) prior regimens for advanced melanoma; however one patient was enrolled and randomized, despite having been previously treated with ipilimumab in the adjuvant disease setting, rather than in the metastatic disease setting. These patients were included in the intent-to-treat analysis. Despite this protocol deviation, the risk of affecting the true treatment effect is low given the small proportion of included patients with an ECOG performance status of 2 and previously treated with ipilimumab in the adjuvant disease setting, rather than in the metastatic disease.

6.3.1.1B Detailed Outcome Data and Summary of Outcomes (Second-Line and Later Setting)

In CheckMate 037, subgroup analyses were specified a priori and performed. However, the CGP did not identify relevant subgroups, and therefore the results presented encompass the entire study population. Subgroup analysis (BRAF status) pertinent to the indication: treatment of unresectable or metastatic BRAF V600 wild-type melanoma in previously treated adults; is briefly highlighted for CheckMate 037.

Details of efficacy outcome data are listed in Table 6.13 and found in Figure 6.4. Details of harms outcome data are listed in Table 6.14.

a) Efficacy Outcomes

Overall survival

Details of OS data are listed in Table 6.13 and Figure 6.4. At the time of the pre-specified interim analysis for overall survival (database locked on November 12, 2014), the survival rate at 6 months was 76.7% for patients for patients in the nivolumab arm and 78.6% for patients treated in the ICC

arm.[11] The median overall survival was 15.5 months for patients in the nivolumab group compared to 13.7 months for patients in the ICC group.[11] The OS results from the BRAF status subgroup analysis were not reported.

Progression-free survival

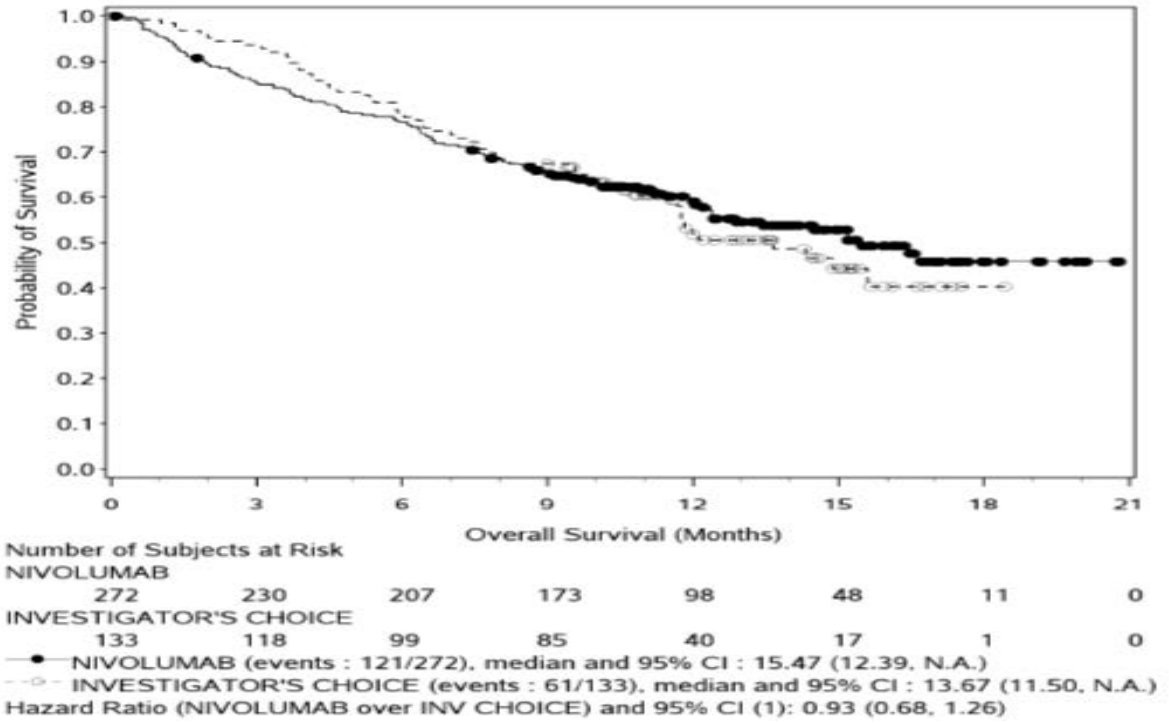
Details of PFS data are listed in Table 6.13. At the time of the objective response rate analysis, the progression-free survival data were not mature. In a descriptive analysis (provided by EMA and FDA), estimates of the median progression-free survival were 4.7 months for patients in the nivolumab group and 4.2 months for patients in the ICC group.[11,12] No statistically significant PFS benefit was found; the unadjusted PFS hazard ratio was 0.74 (95% CI, 0.47 to 1.16).[12]

Table 6.13 CheckMate 037 - Efficacy Outcomes[11,13]

All randomized patients (N=405)	**Nivolumab (n=272)**	**ICC (n=133)**
Median OS[a] (interim analysis) months (95% CI)	15.5 (12.39-NA)	13.7 (11.5-NA)
6 months OS rate (%) no. at risk	76.7% 207	78.6% 99
Hazard ratio (95% CI),p=NR	0.93 (0.68-1.26)	
1 year OS rate[†] (%) no. at risk	58.9% 98	52.1% 40
Objective response[b] (intent-to-treat formal analysis) n (%)	69(25.4%) CR:10(3.7%) PR:59(21.7%)	11(8.3%) CR:0 PR:11(8.3%)
Odds Ratio (95% CI),p=NA	NA	
ORR Population[‡] **(N=182)**	**Nivolumab (n=122)**	**ICC (n=60)**
Median PFS[c] (descriptive analysis) months (95% CI)	4.7 (2.3-6.5)	4.2 (2.1-6.3)
Hazard ratio (95%CI), p=NR	0.74 (0.47-1.16)	
Treated patients among ORR population[‡] **(N=167)**	**Nivolumab (n=120)**	**ICC (n=47)**
Objective response (per-protocol formal analysis) n (%)	38(31.7%) CR:4(3.3%) PR:34(28.3%)	5(10.6%) CR:0 PR:5(10.6%)
Odds Ratio (95% CI), p=NA	NA	

CI = confidence interval; CR = complete response; ICC = investigator's choice of chemotherapy; NA = not applicable; NR = not reported; OS = overall survival; PR = partial response.
[a] interim analysis - database locked November 14, 2014
[b] formal analysis - database locked May 30, 2014
[c] descriptive analysis - database locked May 30, 2014
[†]estimated from published Kaplan-Meier plot of overall survival
[‡]all randomized subjects to either treatment group with at least 6 months of follow-up at the time of the objective response rate analysis

Figure 6.4 CheckMate 037 – Kaplan-Meier plot of overall survival (Interim analysis)[11]



Source: Opdivo assessment report. European Medicines Agency; 2015 Apr 23. p.88[11] (Database locked on Nov 12, 2014)

Quality of Life

In CheckMate 037, health-related quality of life data are not yet available; analysis will be performed at the time of the final OS analysis.[62] EORTC QLQ-C30 will be used to assess quality of life and EQ-5D will be used to assess general health status

Overall response rate

Details of objective response rate data are listed in Table 6.13. Within the publication, the objective response rate analysis was conducted on the first 120 patients treated with nivolumab had a minimum follow-up of 24 weeks.[13] The publication reported that objective response rates were 31.7% for patients in the nivolumab arm and 10.6% for patients in the ICC arm.[13]

An intent-to-treat objective response rate analysis (provided by EMA), which included all randomized patients to any treatment group, suggested that objective response rates were 25.4% for patients in the nivolumab group and 8.3% for patients in the ICC group.[11] Among the patients that received at least one dose of treatment, objective responses were observed in nivolumab regardless of BRAF status [ORR:34.0%(95% CI, 24.6 to 44.5) in BRAF wild-type patients and ORR:23.1%(95% CI, 9.0 to 43.6) in patients with BRAF mutation].[11]

Duration of response

Among those who achieved a response, the median duration of response was not yet reached (range: 1.4+ to 10.0+ months, n=38) in the nivolumab arm and was 3.5 months (range: 1.3+ to 3.5 months, n=5) in the ICC arm.[11,13]

b) Harms Outcomes

Grade 3 and 4 treatment related adverse events

Details of harms outcomes are listed in Table 6.14. Less frequent grade 3 or 4 TRAEs were reported within 30 days of the last dose of study therapy for nivolumab treated patients (9.0%) compared to ICC treated patients (31.4%).[13] Increased lipase, increased alanine aminotransferase, fatigue, and anemia were the most commonly reported grade 3 or 4 TRAEs among nivolumab treated patients (1.1%,1.1%, 0.7%, 0.7%).[13] Neutropenia, thrombocytopenia and anemia were the most commonly reported grade 3 or 4 TRAEs among ICC treated patients (13.7%, 5.9%, 4.9%).[13]

Adverse events of special interest

No cases of grade 3 or 4 of hypothyroidism or pneumonitis were reported in either group.[11] No cases of neutropenia were reported in patients treated with nivolumab, while 14 cases were reported in patients treated with ICC.[11] No cases of colitis were reported in either arm.

Withdrawal due to adverse events

Among the 370 patients in the safety population, the rates of withdrawal due to study drug toxicity were 2.6% for patients treated with nivolumab and 6.9% for patients treated with ICC.[11] No deaths were attributed to study-drug toxicity were reported.[11,13]

Table 6.14 CheckMate 037 - Harms Outcomes[11,13]

Reported in ≥5 patient in either treatment group, unless otherwise specified	Nivolumab (n=268)	ICC (n=102)
	Grade 3 or 4	Grade 3 or 4
Any AE	NR	NR
TRAE	24(9.0%)[a]	32(31.4%)[a]
Skin		
Pruritus	0	0
Rash	1(0.4%)	0
Gastrointestinal		
Diarrhea	1(0.4%)	2(2.0%)
Colitis	NR	NR
Constipation	0[a]	1(1.0%)[a]
Nausea	0[a]	2(2.0%)[a]
Vomiting	1(0.4%)[a]	2(2.0%)[a]
Hepatic		
Increase in ATL	3(1.1%)	0
Increase in AST	2(0.7%)	0
Endocrine		
Hypothyroidism	0	0
Hyperthyroidism	0	0
Pulmonary		
Pneumonitis	0	0
General		
Fatigue	2(0.7%)[a]	4(3.9%)[a]
Neutropenia	0[a]	14(13.7%)[a]
TRAE leading to discontinuation	0[b]	NR
Death due to toxic effect of study drug	0	0[a]

AE = adverse event; ICC = investigator's choice of chemotherapy; NR = not reported; TRAE = treatment-related adverse event.
[a] Reported in ≥ 10% of patients[13]
[b] Reported in > 2% of patients[11]

6.4 Ongoing Trials

No ongoing trial that met our inclusion criteria was identified by our search.

7 SUPPLEMENTAL QUESTIONS

No supplemental questions were addressed in this review.

8 ABOUT THIS DOCUMENT

This Clinical Guidance Report was prepared by the pCODR Melanoma 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 [drug name and indication]. 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 CADTH 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. There was no non-disclosable information in the Clinical Guidance Report provided to pERC for their deliberations.

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 clinicians. The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package, which is available on the CADTH 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

Database(s): **EBM Reviews - Cochrane Central Register of Controlled Trials** July 2015, **Embase** 1974 to 2015 August 25, **Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)** 1946 to Present
Search Strategy:

#	Searches	Results
1	(Opdivo* or nivolumab* or 946414-94-4 or MDX 1106 or MDX1106 or BMS936558 or BMS 936558 or ONO4538 or ONO 4538 or UNII-31YO63LBSN).ti,ot,ab,sh,rn,hw,nm,kw.	1270
2	1 use pmez	254
3	1 use cctr	15
4	*nivolumab/ or (Opdivo* or nivolumab* or MDX 1106 or MDX1106 or BMS936558 or BMS 936558 or ONO4538 or ONO 4538 or UNII-31YO63LBSN).ti,ab.	505
5	4 use oemezd	323
6	2 or 3 or 5	592
7	limit 6 to english language	568
8	remove duplicates from 7	403
9	(Randomized Controlled Trial or Controlled Clinical Trial).pt.	929385
10	Randomized Controlled Trial/	792277
11	Randomized Controlled Trials as Topic/	188433
12	"Randomized Controlled Trial (topic)"/	80932
13	Controlled Clinical Trial/	483677
14	Controlled Clinical Trials as Topic/	10128
15	"Controlled Clinical Trial (topic)"/	4893
16	Randomization/	173777
17	Random Allocation/	173777
18	Double-Blind Method/	365855
19	Double Blind Procedure/	125354

20	Double-Blind Studies/	220773
21	Single-Blind Method/	54797
22	Single Blind Procedure/	20834
23	Single-Blind Studies/	54797
24	Placebos/	329781
25	Placebo/	274098
26	Control Groups/	80227
27	Control Group/	80139
28	(random* or sham or placebo*).ti,ab,hw.	3021118
29	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw.	618517
30	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw.	1578
31	(control* adj3 (study or studies or trial*)).ti,ab.	986254
32	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw.	71728
33	allocated.ti,ab,hw.	126831
34	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw.	72507
35	or/9-34	3807694
36	exp Melanoma/ or (melanoma* or melanocarcinoma* or melanomalignoma* or naevocarcinoma* or nevocarcinoma* or pigmentary cancer*).ti,ab.	247808
37	7 and 36	339
38	7 and 36 and 35	93
39	remove duplicates from 38	66

2. Literature search via PubMed

Search	Query	Items found
#7	Search **#5 OR #6**	13
#6	Search **#1 AND #3** Filters: **Publication date from 2015/08/21**	1
#4	Search **#1 AND #3**	129

Search	Query	Items found
#5	Search **#4 AND publisher[sb]**	12
#3	Search **Melanoma[mh] OR melanoma*[tiab] OR melanocarcinoma*[tiab] OR melanomalignoma*[tiab] OR naevocarcinoma*[tiab] OR nevocarcinoma*[tiab] OR pigmentary cancer*[tiab]**	102863
#1	Search **nivolumab[Supplementary Concept] OR nivolumab*[tiab] OR Opdivo*[tiab] OR Opdivo*[ot] OR nivolumab*[ot] OR 946414-94-4[tiab] OR MDX 1106[tiab] OR MDX1106[tiab] OR BMS936558[tiab] OR BMS 936558[tiab] OR ONO4538[tiab] OR ONO 4538[tiab]**	225

3. **Cochrane Central Register of Controlled Trials (Central)**
   Searched via Ovid (see above)

4. **Northern Light database**
   Searched via Ovid separately

5. **Grey Literature search via:**

   Clinical trial registries:

   U.S. NIH ClinicalTrials.gov
   http://www.clinicaltrials.gov/

   Canadian Partnership Against Cancer Corporation. Canadian Cancer Trials
   http://www.canadiancancertrials.ca/

   Search terms: Opdivo/nivolumab

   Select international agencies including:

   Food and Drug Administration (FDA):
   http://www.fda.gov/

   European Medicines Agency (EMA):
   http://www.ema.europa.eu/

   Search terms: Opdivo/nivolumab

   Conference abstracts:

   American Society of Clinical Oncology (ASCO)
   http://www.asco.org/
   Search terms: Opdivo/nivolumab / last 5 years

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