CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Nivolumab (Opdivo) for Adjuvant Melanoma

March 7, 2019

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1 GUIDANCE IN BRIEF

This Clinical Guidance Report was prepared to assist the pCODR Expert Review Committee (pERC) in making recommendations to guide funding decisions made by the provincial and territorial Ministries of Health and provincial cancer agencies regarding nivolumab (Opdivo) for adjuvant 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 is based on: a systematic review of the literature regarding nivolumab (Opdivo) for adjuvant melanoma conducted by the Melanoma Clinical Guidance Panel (CGP) and the pCODR Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group; input from Registered Clinicians; and supplemental issues relevant to the implementation of a funding decision.

The systematic review and supplemental issues are fully reported in Sections 6 and 7. A background Clinical Information provided by the CGP, a summary of submitted Patient Advocacy Group Input on nivolumab (Opdivo) for adjuvant melanoma, a summary of submitted Provincial Advisory Group Input on nivolumab (Opdivo) for adjuvant melanoma, and a summary of submitted Registered Clinician Input on nivolumab (Opdivo) for adjuvant melanoma, and are provided in Sections 2, 3, 4, and 5 respectively.

1.1 Introduction

The objective of this review is to evaluate the safety and efficacy of nivolumab (Opdivo) for the adjuvant treatment of patients with completely resected Stage III and IV melanoma. The Health Canada regulatory approval is for melanoma with regional lymph node involvement, in transit metastases/satellites without metastatic nodes, or distant metastases, as adjuvant therapy after complete resection. This is similar to the reimbursement request. The recommended dose of nivolumab is 3 mg/kg administered intravenously over 60 minutes every 2 weeks until progression or unacceptable toxicity.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

The pCODR systematic review included one randomised controlled trial (RCT).

CheckMate 238 was a double-blind, multicentre phase III RCT that assessed the effect of nivolumab and ipilimumab on recurrence free survival (RFS) in 906 patients with resected stage III or IV melanoma.[1] The trial included patients aged 15 years and older with histologically confirmed but resected stage IIIB, IIIC or IV melanoma. Eligible patients were randomized (1:1) to receive nivolumab (N = 453) or ipilimumab (N = 453) for up to one year. Patients continued to be treated with their assigned therapies until they had documented disease progression, developed unacceptable toxic events or withdrew consent.

The primary outcome assessed in CheckMate 238 was RFS. The secondary efficacy endpoints included overall survival (OS), health-related quality of life (HRQoL) and safety. A key exploratory outcome was distant metastasis-free survival (DMFS).

The study was designed to have 85% power to detect a hazard ratio (HR) of 0.75 for disease recurrence or death, using a two-sided significance level of α=0.05 for a minimum of 36 months follow-up period. An interim analysis was planned at 18 months of follow-up for all patients.

As of the data cutoff in May 2017, the minimum follow-up was 18 months (median 19.5 months) for all the study participants, and all 905 treated patients were no longer receiving the study drug. The 18 month interim analysis of RFS was conducted. A post hoc 24 month analysis was also conducted and presented in this report.

Efficacy

At the time of the interim analysis for RFS (data cutoff on May 15, 2017), the median RFS had not been reached in either treatment group, and the OS data were not mature.

At 18 months, the rates of RFS were 66.4% (95% confidence interval [CI] 61.8% to 70.6%) for nivolumab and 52.7% (95% CI 47.8% to 57.4%) for ipilimumab. Adjuvant therapy with nivolumab was associated with a prolonged RFS as compared to ipilimumab in patients with resected stage III or IV melanoma (HR: 0.65; 97.56% CI 0.51 to 0.83; P < 0.001).[1] Results of RFS at 24 months were reported in an update of CheckMate 238.[2] The median (95% CI) RFS was 30.8 (30.8, not reached) months for nivolumab and 24.1 (16.6, not reached) months for ipilimumab (HR: 0.66; 95% CI 0.54 to 0.81; P < 0.0001). Study findings of subgroup analyses of RFS based on disease stage were consistent with the primary analyses, treatment with nivolumab was associated with a prolonged RFS as compared to ipilimumab in patients with resected advanced melanoma, at 18 months and 24 months. However, multiple comparisons were not adjusted for in the subgroup analyses. Subgroup analysis may not have sufficient power to detect a statistically significant between-group difference.

Longer DMFS was observed in the nivolumab group compared to the ipilimumab group. The HRQoL scores (EORTC QLQ-C30 and EQ-5D) remained close to baseline values in the two treatment groups, and there were no clinically meaningful changes with respect to the scores observed on any of the HRQoL instruments.

Harms

Safety analysis was performed in 905 patients who received at least one dose of the study drug, 452 in the nivolumab arm and 453 in the ipilimumab arm. At the database cut-off of May 15, 2017, two deaths were reported for the ipilimumab group, and both cases were considered to be treatment-related. In general, the proportion of patients reporting at least one AE of any cause was similar between the two treatment arms, 96.9% for nivolumab and 98.5% for ipilimumab. The commonly reported (>10%) AEs which were considered treatment-related included fatigue, diarrhea, pruritus, rash, nausea, arthralgia, asthenia, hypothyroidism, headache, abdominal pain, increased ALT level, increased AST level, maculopapular rash, hypophysitis, and pyrexia. In addition, patients in the nivolumab group were less likely to report a Grade 3 or 4 AE (25.4%) when compared to those in the ipilimumab group (55.2%). The risk of serious adverse events (SAEs) was lower in the nivolumab group (17.5%) compared with the ipilimumab group (40.4%). Furthermore, patients in the nivolumab (9.7%) were less likely to report an AE which led to treatment discontinuation compared to those in the ipilimumab group (42.6%). In general, incidence of selected AEs involving the skin, gastrointestinal tract, liver, and lungs that were deemed to be related to the study drug was lower in the nivolumab group compared with the ipilimumab group.

Table 1: Highlights of key outcomes in CheckMate 238

	Nivolumab	Ipilimumab
ITT population		
	N=453	**N=453**
Recurrence-free survival		
12 months, % (95% CI)	70.5 (66.1-74.5)	60.8 (56.0-65.2)
18 months, % (95% CI)	66.4 (61.8-70.6)	52.7 (47.8-57.4)
24 months, % (95% CI)	63 (NR)	50 (NR)
Median RFS, months (95% CI)	30.8 [a] (30.8, not reached)	24.1 (16.6, not reached)
HR (95% CI)	0.66 (0.54-0.81), p < 0.0001	
Overall survival		
24 months (95% CI)	Not reached	
Distant metastasis-free survival		
18 months, % (95% CI)	75 (NR)	67 (NR)
24 months, % (95% CI)	71 (NR)	64 (NR)
HR (95% CI)	0.76 (0.59-0.98), p = 0.034	
Safety Population		
	N = 452	**N = 453**
Any AEs, n (%)	438 (96.9)	446 (98.5)
SAE, n (%)	79 (17.5)	183 (40.4)
AEs leading to discontinuation, n (%)	44 (9.7)	193 (42.6)
Deaths, n (%)	0	2 (1 marrow aplasia, 1 colitis)

AE = adverse event; CI = confidence interval; HR = Hazard ratio; ITT = intention-to-treat; NR = Not reported; SAE = serious adverse event.
[a] The median RFS of 30.8 months in the nivolumab group was considered not reliable or stable by the investigators due to few patients at risk.
Data sources: Weber et al. main report (2017),[1] Weber et al. supplemental appendix (2017),[3] and Weber et al. 2018 updates[2]

1.2.2 Additional Evidence

See Section 3, Section 4, and Section 5 for a complete summary of patient advocacy group input, Provincial Advisory Group (PAG) Input, and Registered Clinician Input, respectively.

Patient Advocacy Group Input

From a patient's perspective, mental health challenges including anxiety, depression and fear are common issues faced during the course of their disease. Patients responding to both the Save Your Skin Foundation (SYSF)'s and the Melanoma Network of Canada (MNC)'s surveys indicated their condition as having a negative impact on their mental health. Physical symptoms such as, scarring, fatigue and lymphedema were reported by patients. The impact of patient's condition on their family and social life was also noted; family members also face anxiety regarding the lack of treatment options for their loved ones, in addition to facing financial stress due to costs of treatments.

Therapies patients reported having previous experience with included surgery, interferon, ipilimumab, dabrafenib and trametinib, and watch and wait. Common side effects included flu-like symptoms, weight loss, depression, hair loss, and nausea and vomiting. Of patients responding to MNC's survey, 14% received nivolumab in the adjuvant setting, while 9% received it in the metastatic setting. Fifteen percent of patients responding to SYSF's survey reported receiving nivolumab, however it is not clear in what setting it was received. Compared to previous treatments, patients seemed to prefer nivolumab for its

better tolerance and improved effectiveness. Issues related to nivolumab included the large number of hospital visits required for infusions, and the financial impact of having to take time off work for the drug, or having to pay for it out of pocket. Both MNC and SYSF highlighted the lack of accessibility of nivolumab, and treatments in general for patients with melanoma.

Please see Section 3 below for a summary of specific patient input received.

Provincial Advisory Group (PAG) Input

Input was obtained from all nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation:

Clinical factors:

- Sequencing with current therapies
- Re-initiation following treatment interruption

Economic factors:

- Appropriate dosing and infusion times
- Resources required to administer intravenous infusion, monitor and treat infusion related reactions and monitor and treat adverse events

Please see Section 4 below for a summary of PAG input.

Registered Clinician Input

Two clinician inputs were provided: one from an individual oncologist and one from a group of five oncologists associated with Cancer Care Ontario (CCO).

In summary, there is a significant unmet need for treatment of melanoma, as the currently available treatment options for adjuvant treatment of melanoma is limited to high-dose interferon (IFN), which provides a small benefit alongside significant toxicity. The authors of the clinician submissions believe that the patient population eligible for funding is appropriate and meets the needs of clinical practice; however, it was noted that the clinical trial under review did not address all of the patients that the manufacturer is requesting funding for. It was also noted that this treatment is very important for patients who are stage III or higher, having undergone resection, to avoid a palliative situation. It is believed that nivolumab would replace the currently available treatment of IFN and not have an impact on treatment options for metastatic disease.

Summary of Supplemental Questions

In addition, one supplemental question was identified during the review as relevant to the pCODR review of nivolumab and is discussed as supporting information:

- Critical appraisal of manufacturer-submitted network meta-analysis (NMA) of the relative efficacy and safety of nivolumab as adjuvant therapy versus other therapies in adult patients with resected advanced stage melanoma.

The results of an NMA suggested that adjuvant treatment with nivolumab was associated with a significant reduction in the risk of cancer recurrence or death as compared to interferon or watchful observation/placebo; however there were no statistically significant differences in recurrence-free survival observed between nivolumab and other active treatment in the study population. In addition, nivolumab had a similar safety profile

compared with placebo, but treatment with nivolumab was associated with statistically significantly lower risks of Grade 3 or 4 adverse events and discontinuation due to adverse events, as compared with interferon. Effect of nivolumab on health-related quality of life relative to placebo was examined in an indirect treatment comparison analysis, and the between-group differences were not statistically significant, suggesting comparable quality of life for patients received nivolumab and placebo. Overall survival was not assessed in the comparisons between nivolumab and other active treatments due to the unavailability of data. Subgroup analysis based on disease stage was performed to examine the impact of this treatment effect modifier; other treatment effect modifiers were not evaluated, thus the results of the network meta-analysis and indirect comparison analysis should be interpreted with caution.

See section 7.1 for more information.

Comparison with Other Literature

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

1.2.3 Factors Related to Generalizability of the Evidence

Table 2 addresses the generalizability of the evidence and an assessment of the limitations and sources of bias can be found in Sections 6.3.2.1 (regarding internal validity).

Table 2: Assessment of generalizability of evidence for nivolumab for resected stage III/IV melanoma

<table>
<tr><th>Domain</th><th>Factor</th><th>Evidence</th><th>Generalizability Question</th><th>Clinical Guidance Panel Assessment of Generalizability</th></tr>
<tr><td rowspan="3">Population</td><td>Age</td><td>Patient's ≥ 15 years of age, with historically confirmed, resected, stage III or IV melanoma were eligible for the CheckMate 238 trial.
<table><tr><th></th><th>Nivolumab (N = 453)</th><th>Ipilimumab (N=453)</th></tr><tr><td>Age, years, median (range)</td><td>56 (19-83)</td><td>54 (18-86)</td></tr></table></td><td>Although patients older than 15 years of age were eligible, study participants in CheckMate 238 were all older than 18 years old. Are the results of the trial applicable to younger patients, e.g. adolescents?</td><td>The CGP agreed treatment of patients <18 years of age who otherwise met the CheckMate 238 inclusion criteria could be considered on an individual patient basis; but felt it inappropriate to specify a minimum treatment age, given the absence of supporting data.</td></tr>
<tr><td>Performance Status</td><td>Only patients with an ECOG performance status of 0 to 1 were enrolled. Those with an ECOG ≥ 2 were excluded.
<table><tr><th>ECOG, n (%)</th><th>Nivolumab (N = 453)</th><th>Ipilimumab (N=453)</th></tr><tr><td>0</td><td>413 (91.2)</td><td>405 (89.4)</td></tr><tr><td>1</td><td>40 (8.8)</td><td>48 (10.6)</td></tr></table></td><td>Does performance status limit the interpretation of the trial results (efficacy or toxicity) with respect to the target population (e.g., Canadian clinical practice, patients without the factor, etc.)?</td><td>The CGP felt agreed treatment of patients with ECOG performance status >1 who otherwise met the CheckMate 238 inclusion criteria could be considered on an individual patient basis; but felt it inappropriate to specify a maximum performance status, given the absence of supporting data;</td></tr>
<tr><td>Type of lymph node involvement</td><td>In CheckMate 238, "all the patients with stage III nodal disease underwent completion lymphadenectomy; 28% of the patients with stage III disease in the nivolumab group and 30% of those in the ipilimumab group had microscopic disease."
Type of lymph-node involvement in stage III
<table><tr><th></th><th>Nivolumab (N=453)</th><th>Ipilimumab (N=453)</th></tr><tr><td>Microscopic</td><td>125/369 (33.9)</td><td>134 (366 (36.6)</td></tr><tr><td>Macroscopic</td><td>219/369 (59.3)</td><td>214/366 (58.5)</td></tr><tr><td>Not reported</td><td>25/369 (6.8)</td><td>18/366 (4.9)</td></tr></table></td><td>In practice, completion lymphadenectomy may not be considered the standard of care for all the melanoma patients.

Does the type of surgery impact the interpretation of the trial results (efficacy or toxicity) with respect to the target population (e.g., Canadian clinical practice, patients undergoing other surgeries)?</td><td>The CGP felt completion lymph node dissection for patients with micrometastatic lymph node involvement detected on sentinel lymph node biopsy should not be a requirement for consideration of treatment with nivolumab as adjuvant therapy to surgery.
This is based on recent clinical trials which have established observation within this patient population as a viable treatment strategy, as melanoma-specific survival was not improved with reflexive completion lymph node dissection. Notably, more recent clinical trials investigating systemic therapy as adjuvant to surgical treatment have not mandated reflexive completion lymph node dissection in the case of patients with micrometastatic disease detected on sentinel lymph node biopsy.;</td></tr>
</table>

<table>
<tr><th>Domain</th><th>Factor</th><th>Evidence</th><th>Generalizability Question</th><th>Clinical Guidance Panel Assessment of Generalizability</th></tr>
<tr><td></td><td>Autoimmune Disorders</td><td>Checkmate 238 excluded patients if they had a previous history of autoimmune disorders.</td><td>Does the exclusion of patients with autoimmune disorders limit the interpretation of the trial results with respect to the target population?</td><td>Despite their exclusion from the CheckMate 238 clinical trial the CGP agreed patients with pre-existing immune-mediated illnesses who otherwise met the CheckMate 238 inclusion criteria could be considered for treatment with nivolumab as adjuvant therapy to surgery on an individual patient basis. The CGP noted the risk of toxicity may be higher within this subset of patients, and recommends individual clinicians weigh this risk against potential benefit when considering adjuvant treatment with nivolumab. The CGP was of the opinion that patients with completely resected melanoma who also had a requirement for treatment with therapeutic immunosuppression could be considered on an individual patient basis for treatment with nivolumab as adjuvant treatment to surgery;</td></tr>
<tr><td></td><td>Biomarkers</td><td>CheckMate 238 looked into the effect of PD-L1. Randomization was stratified based on disease stage, as well as PD-L1 expression.<table><tr><th>PD-L1 expression, n (%)</th><th>Nivolumab (N = 453)</th><th>Ipilimumab (N=453)</th></tr><tr><td>< 5%</td><td>275 (60.7)</td><td>286 (63.1)</td></tr><tr><td>≥ 5%</td><td>152 (33.6)</td><td>154 (34.0)</td></tr><tr><td>Undetermined or not reported</td><td>26 (5.7)</td><td>13 (2.9)</td></tr></table></td><td>Is the biomarker an effect modifier (i.e., differences in effect based on biomarker status)? Are the results of the trial applicable to all subgroups equally? Is there a substantial group of patients excluded from the trial to whom the results could be generalized?</td><td>The CGP agreed there was insufficient data to support this practice, and recommended consideration of treatment with nivolumab as adjuvant therapy to surgery for patients who otherwise met the CheckMate 238 inclusion criteria, regardless of PD-L1 testing.</td></tr>
<tr><td></td><td>Disease staging system</td><td>Trial was conducted based on AJCC 7th edition staging system.[4] Currently 8th edition is being used.</td><td>What is the generalizability of trial results to patient's staged using 8th edition?</td><td>Although the new AJCC 8th edition staging system would exclude some patients that were included in the CheckMate 238 trial (patients with micrometastatic nodal disease and ulcerated T1 and T2 primary melanoma lesions have been reclassified from stage IIIb to stage IIIa) while including</td></tr>
</table>

Domain	Factor	Evidence	Generalizability Question	Clinical Guidance Panel Assessment of Generalizability
				other (patients with micrometastatic nodal disease and non-ulcerated primary melanoma lesions), the CGP agree that the overall trial results are generalizable to patients with completely resected stage IIIb through IV disease using the AJCC 8th edition staging system.

1.2.4 Interpretation

Melanoma is the most commonly diagnosed cancer in individuals between the ages of 20 and 29 years, impacting otherwise healthy individuals with active family, career and social lives, thus adding to the stress of a diagnosis. Despite recent advancements in treatment, a diagnosis with malignant melanoma still indicates a guarded prognosis, leading to the introduction of effective palliative therapies to the adjuvant treatment setting. Immune checkpoint inhibitors targeting the PD-1 molecule have been demonstrated to confer a durable treatment response to a subset of patients with metastatic melanoma, and have more recently demonstrated efficacy when utilized as adjuvant therapy following surgical resection of disease.

Within the CheckMate 238 randomized clinical trial a recurrence-free survival benefit and a reduction in treatment-related toxicities was observed in patients treated with nivolumab versus ipilimumab. With a minimum follow-up of 18 months, the 12-month rate of recurrence-free survival was 70.5% in the nivolumab group and 60.8% in the ipilimumab group.[1] Furthermore, the incidence of grade 3 or 4 adverse events (the majority of which were immune-related) resulting from treatment with nivolumab was less than half that seen in patients treated with ipilimumab (25.4 and 55.2% in patients treated with nivolumab and ipilimumab, respectively). Focusing on diarrhea alone further underscores the favorable toxicity profile attributable to nivolumab versus ipilimumab. Arguably the most problematic immune-related adverse event and one to which treatment-related deaths, while uncommon, are most commonly attributed, the rate of grade 3-4 diarrhea in patients treated with nivolumab was just 1.5%, in comparison with 9.5% of ipilimumab-treated patients. Lastly, the proportion of patients treated with nivolumab who discontinued treatment due to toxicity was just 8%, compared against the more than 30% of patients who received treatment with ipilimumab.

The primary outcome under study in the CheckMate 238 clinical trial was recurrence-free survival. Important secondary endpoints included overall survival, safety and side-effect profiles, recurrence-free survival according to tumor PD-L1 expression, and health-related quality of life. The choice of recurrence-free survival as primary endpoint was a pragmatic one, as access to treatment for relapsed patients has improved the survival of a patient with metastatic melanoma from months to years; upon relapse patients have access to immune checkpoint inhibitors and in the case of patients with BRAF-mutated melanoma, highly efficacious targeted therapy. For the population of patients with metastatic disease treated with immunotherapy, in some cases, deep and durable tumour responses following treatment with immune checkpoint inhibitors may last years. For this reason the choice of recurrence-free survival as a primary outcome seems reasonable and as witness to this fact, while a sufficient number of recurrences have occurred to detect a benefit to treatment with nivolumab versus ipilimumab, a comparatively small number of patient deaths have been reported.[2] Ideally, when recommending a systemic therapy as adjuvant treatment to surgery an improvement in overall survival would be demonstrated, but the reality (fortunate for patients living with metastatic melanoma) is that effective treatments in the metastatic setting creates a scenario where sample size would have to be unacceptably large or follow-up unacceptably long to detect this difference. As it stands, CheckMate 238 demonstrates an improvement in recurrence-free survival with a significantly improved toxicity profile versus ipilimumab. Although cross-trial comparisons should be avoided, when the improvement in overall survival associated with ipilimumab versus placebo as adjuvant treatment to surgery[5] is considered the observed differences in recurrence free survival in the CheckMate 238 clinical trial, statistically significant, also become clinically meaningful.

In the Canadian landscape the only Health Canada approved systemic therapy for use as adjuvant therapy to surgery is interferon alpha. This agent is indicated in patients 18 years of age or older with malignant melanoma who are free of disease but at high risk for systemic recurrence. For this reason, the decision to compare nivolumab against ipilimumab has raised question as to whether this was the appropriate or optimal comparator. Again, scrutiny of this decision suggests the choice was a pragmatic one. Despite meta-analyses which support a modest improvement in patient survival with the use of interferon as adjuvant treatment to surgery[6] the regimen is uncommonly prescribed in practice. Chief among the reasons for non-utilization is the toxicity associated with the regimen and the resulting negative impact on patient preference. Further, the clinical trials which previously demonstrated the benefit to treatment with interferon following surgery were primarily conducted in the era predating both targeted and immune checkpoint inhibitor therapy, calling in to question the relevance of the data in the current treatment landscape. Likewise, the use of high-dose interferon-alpha as the comparator to nivolumab would have precluded a blinded study design, significantly increasing the risk of bias within the study, as interferon is dosed on a daily schedule through the first four weeks, followed by subcutaneous injections three times per week. In practice most patients decline high-dose interferon-alpha treatment, instead choosing observation alone.

In the absence of direct comparison between nivolumab with observation or high dose interferon, an indirect treatment comparison and network meta-analysis were presented by the submitter. Notwithstanding limitations of indirect comparisons, the conclusions of the NMA suggested that adjuvant treatment with nivolumab was associated with a reduction in the risk of cancer recurrence, distant metastasis or death as compared to interferon or watchful observation/placebo. Nivolumab had a similar safety profile as placebo, but treatment with nivolumab was associated with statistically significantly lower risks of Grade 3 or 4 adverse events and discontinuation due to adverse events, as compared with interferon. The effect of nivolumab on health-related quality of life relative to placebo was examined in the indirect treatment comparison analysis, and the between-group differences were not statistically significant, suggesting comparable quality of life for patients who received nivolumab and placebo. Overall survival was not assessed in the comparisons between nivolumab and other active treatments due to the unavailability of data.

The introduction to the Canadian treatment landscape of nivolumab as adjuvant treatment to surgery for patients with completely resected melanoma thus offers a clinically meaningful benefit in recurrence-free survival, and fills a need that at present is unmet. This unmet need is clearly represented within the commentary of Patient Advocacy Groups submitting input for review. A theme common among patient voices is the anxiety that surrounds a diagnosis with malignant melanoma. Patients spoke on the stress and strain the diagnosis and treatments placed on their work, social and family lives. The uncertainty following a diagnosis with melanoma, particularly in those for whom only post-surgical observation was appropriate, represents a significant negative impact on well-being, and it is expected that access to a tolerable and efficacious adjuvant therapy such as nivolumab may in part alleviate this burden.

The Provincial Advisory Group (PAG) raises a number of salient points which were considered within this review, most of which center on themes of generalizability of the supporting data. Where applicable, data supporting the interpretation and guidance recommendations are cited in section 2.4.

- Sequencing of currently available adjuvant therapies: patients previously treated with interferon-alpha as adjuvant to surgery were permitted enrolment to the CheckMate

238 clinical trial if therapy with interferon had concluded at least 6 months prior. Patients who relapse more than 6 months following completion of interferon who are treated with radical surgery should therefore be eligible for treatment with nivolumab as adjuvant to surgery. Interferon-alpha is the only Health Canada approved systemic therapy available to patients as adjuvant treatment to surgery.

  - Following the posting of the pERC initial recommendation, the CGP provided additional context to respond to feedback received from stakeholders on the appropriate time frame of switching patients currently on interferon to nivolumab. The CGP noted that questions related to switching from interferon are of minimal importance as interferon is rarely prescribed by clinicians. For patients who may be on interferon, the CGP agreed that a switch can be made at any time to nivolumab as long as adjuvant treatment started within 12 weeks of surgery. Furthermore, the CGP agreed that clinicians are likely to treat patients for the full one year course upon switching.

- Re-initiation of nivolumab as adjuvant treatment to surgery after interruption for toxicity: in practice, a subset of the adverse events associated with the use of immune checkpoint inhibitors are biochemical in nature, and are without significant clinical sequelae. Treatment-related hypothyroidism, for instance, occurs with relative frequency but is considered by clinicians to be a manageable toxicity and is generally easily managed with replacement pharmacologic therapy. The decision to re-initiate treatment with nivolumab as adjuvant therapy to surgery should be based on clinical judgment, but may be considered in certain circumstances. High quality, evidence-based guidelines are available as an aid to practice.[7]
- Impact of utilization of nivolumab as adjuvant treatment to surgery on subsequent treatment decision-making in the metastatic (relapsed) setting: no data to guide treatment decision-making in this context is currently available. A review of post-protocol treatments reveals that patients treated with nivolumab as adjuvant treatment to surgery received BRAF-targeted agents (in the case of patients with BRAF-mutated melanoma), anti-CTLA-4 immune checkpoint inhibitor therapy, anti-PD-1 immune checkpoint inhibitor therapy, chemotherapy or experimental agents upon relapse. Clinicians will likely wish to consider all of these options for the relapsed patient following treatment with adjuvant nivolumab, taking in to account factors such as time-to-relapse and patient performance status.
  - Following the posting of the pERC initial recommendation, the CGP provided additional context to respond to feedback received from stakeholders on the appropriateness of re-challenging patients with an anti-PD1 therapy after having received nivolumab as adjuvant therapy. The CGP agreed that there is evidence available on the use of an anti-PD1 therapy in the metastatic setting in patients who had already received an anti-PD1 agent. These were however patients that had been responsive to prior anti-PD1 treatment in the metastatic setting. The CGP do however agree that the option to reuse an anti-PD1 agent following its use in the adjuvant setting should be made available.
  - The CGP also responded to feedback on the optimal sequencing of agents in the metastatic setting following adjuvant treatment with nivolumab. The CGP stressed that there is no clear path forward to guide sequencing. The CGP's clinical opinion is that most clinicians will base their decision on how to treat their relapsed

patient on multiple factors: time-to-relapse, BRAF status, extent of disease relapse, patient clinical status and perhaps most importantly, available treatment options at the time of relapse (for instance, the presence or absence of a clinical trial which offers a PD1 therapy in combination with an additional agent). As an example, for a BRAF wild-type patient (i.e., one who is not eligible for targeted therapy) metastatic treatment options will be more limited – hence the inclination to use the adjuvant agent in the metastatic setting will be greater, and clinicians may try challenging a patient irrespective of the time that has lapsed between ending adjuvant therapy and metastatic recurrence.

- Time between surgery and initiation of nivolumab as adjuvant treatment to surgery: to have been considered for enrolment within CheckMate 238 patients must have been surgically rendered free of macroscopic disease within 12 weeks of randomization. This is an acceptable benchmark for consideration for the use of nivolumab as adjuvant treatment to surgery in practice, and aligns with general principles of oncologic management.
- Degree of metastatic lymph node involvement: the CheckMate 238 clinical trial enrolled patients with a relatively higher risk of relapse than do most clinical trials investigating adjuvant therapies; patients with completely resected stage IIIb through IV[4] were eligible for screening. In the time since the trial was designed and conducted, an updated melanoma staging classification system has been adopted.[8] Under the previous staging classification system, to be considered for trial enrolment patients with micrometastatic nodal involvement must have presented with ulcerated primary melanoma lesions (stage IIIb, AJCC 7th edition); utilizing the current classification system (AJCC 8th edition) stage IIIb includes patients with micrometastatic nodal disease and non-ulcerated primary melanoma lesions (T3a and T4a) who would have been ineligible for study enrolment. Likewise, patients who would have been eligible for study enrolment under the former classification criteria would now be deemed ineligible if stage grouping alone were considered (patients with micrometastatic nodal disease and ulcerated T1 and T2 primary melanoma lesions have been reclassified from stage IIIb to stage IIIa). In pragmatic fashion, Health Canada has granted approval for the use of nivolumab as adjuvant treatment to surgery for patients with completely resected melanoma with regional lymph node involvement, a basis that simplifies the scenario in the clinic and honors the oncologic principle of systemic therapy as adjuvant to surgery. Patients with resected stage IV disease represent a distinct classification of patients, but were eligible for enrolment to the CheckMate 238 clinical trial, and in an intent-to-treat analysis (that was supported by a subgroup analysis of patients with resected stage IV disease) a benefit to treatment with nivolumab as adjuvant to surgery was supported.
    - Following the posting of the pERC initial recommendation, the CGP provided additional context to respond to feedback received from stakeholders on the eligible patient population. The CGP acknowledged the complexity of the evidence presented given the revision to the AJCC staging system where patients who were AJCC 7th edition stage IIIb are now AJCC 8th edition stage IIIa (and vice versa). Despite this, the CGP is of the opinion that all patients with nodal disease (following resection, but not requiring completion lymphadenectomy for patients

with microscopic nodal disease detected on sentinel lymph node biopsy) would benefit from adjuvant treatment with nivolumab.

- Selection of optimal systemic therapy as adjuvant treatment to surgery for patients with BRAF-mutated melanoma: patients with BRAF-mutated melanoma were permitted enrolment to the CheckMate 238 clinical trial. At the present time, there are no data to guide treatment decision-making for the patient with completely resected, BRAF-mutated melanoma.
- The utility of PD-L1 testing: at the present time the role for testing of tumoral PD-L1 expression in patients with melanoma remains unclear. A benefit from treatment with nivolumab (versus ipilimumab) as adjuvant treatment to surgical resection of disease was seen in both patients with PD-L1 expression levels greater than and less than 5% (hazard ratio for relapse/death 0.50 and 0.71, respectively). Interestingly, PD-L1 expression greater than 5% may be more prognostic than predictive, as patients within this subset had outcomes superior to their low-expressing counterparts whether treated with nivolumab or ipilimumab.

  Clinic resource utilization: PAG raises a number of appropriate questions regarding clinic resource utilization, pertaining to infusion time, schedule of infusions, and weight-based versus fixed or capped dosing. The CheckMate 238 clinical trial mandated a 60 minute infusion of nivolumab every 14 days administered at a dose of 3 mg/kg. No evidence is presently available to support altering this schedule or dose

1.3 Conclusions

The Clinical Guidance Panel (CGP) was unanimous in their opinion that adoption of nivolumab as adjuvant treatment to surgery following complete resection of melanoma represents a net clinical benefit to the patient population. The CGP felt treatment with nivolumab could be considered for the group of patients included within the CheckMate 238 randomized clinical trial, including patients with completely resected regional lymph node metastases as well as patients with completely resected stage IV disease. Patients with both BRAF-wildtype and BRAF-mutated melanoma were permitted enrolment to study, and therefore both patient populations should be considered for treatment. Patients with both cutaneous and mucosal melanoma were permitted enrolment to study, however patients with ocular melanoma were not; on this basis the CGP felt treatment of both cutaneous and mucosal melanoma patients should be considered, whereas the evidence for extrapolating the data to include treatment of patients with resected ocular melanoma was lacking, suggesting assumption of benefit within this subset of patients cannot be inferred.

The CheckMate 238 randomized clinical trial represents a high quality of evidence with which to guide treatment decision-making. Although not approved for the indication by Health Canada, the CGP felt the utilization of ipilimumab as the comparator to nivolumab was acceptable. A minority of clinicians in Canada may feel that interferon-alpha should have been utilized as the comparator, but in practice this regimen is infrequently prescribed, and would have hampered the design of the clinical trial (specifically, blinding would have been difficult, if not impossible). At the current time in Canada, surveillance is the most commonly adopted practice after complete resection of locally advanced melanoma (outside of clinical trials investigating adjuvant systemic therapy) and by including ipilimumab - a treatment with known efficacy in the adjuvant setting - as the treatment to which nivolumab was compared the data within the clinical trial is of the highest possible quality.

The fact that nivolumab represents an improvement in recurrence-free survival over ipilimumab while presenting a highly favorable treatment option with respect to toxicity cannot be understated. When considering the adoption of a systemic therapy such as nivolumab as adjuvant treatment to surgical resection, one would ideally like to see an improvement in the overall survival of patients, but the CGP recognizes the challenges this would present in terms of clinical trial design. Post-relapse, patients with metastatic melanoma have access to highly efficacious treatment options, some of which offer the prospect of a durable tumor response; for this reason, the CGP was unanimous in considering recurrence-free survival as an acceptable outcome from which to infer a net clinical benefit. The CGP also noted the comparator within the CheckMate 238 clinical trial (ipilimumab) offers an improvement in overall patient survival when compared against placebo (arguably the appropriate treatment comparator in the current Canadian treatment landscape). Given the recurrence-free survival superiority of nivolumab over ipilimumab, it is anticipated that with time an overall survival benefit from treatment with nivolumab as adjuvant therapy to surgery may emerge.

A number of additional key clinical factors impacting the adoption of nivolumab as adjuvant therapy to surgery following complete resection of melanoma will emerge with time. These factors will each require further study, but in the interest of providing guidance for the adoption of nivolumab as adjuvant therapy, and in addition to the statements above the CGP offered the following opinions:

- Treatment of pediatric patients: the CGP agreed treatment of patients <18 years of age who otherwise met the CheckMate 238 inclusion criteria could be considered on an individual patient basis; but felt it inappropriate to specify a minimum treatment age, given the absence of supporting data;
- Treatment of patients with marginal/poor performance status: the CGP agreed that treatment of patients with ECOG performance status >1 who otherwise met the CheckMate 238 inclusion criteria could be considered on an individual patient basis; but felt it inappropriate to specify a maximum performance status, given the absence of supporting data;
- Optimal treatment of patients with BRAF-mutated melanoma: the CGP agreed that patients with completely resected BRAF-mutated melanoma who otherwise met the CheckMate 238 inclusion criteria should be offered treatment with nivolumab as adjuvant therapy to surgery. Notably, the CGP acknowledged that there is evidence evaluating the efficacy and safety of dabrafenib plus trametinib and pembrolizumab in the adjuvant setting but the data are yet to be evaluated and approved for reimbursement;
- Patients with pre-existing immune-mediated illnesses: despite their exclusion from the CheckMate 238 clinical trial the CGP agreed that patients with pre-existing immune-mediated illnesses who otherwise met the CheckMate 238 inclusion criteria could be considered for treatment with nivolumab as adjuvant therapy to surgery on an individual patient basis. The CGP noted the risk of toxicity may be higher within this subset of patients, and recommends individual clinicians weigh this risk against potential benefit when considering adjuvant treatment with nivolumab. The CGP was of the opinion that patients with completely resected melanoma who also had a requirement for treatment with therapeutic immunosuppression could be considered on an individual patient basis for treatment with nivolumab as adjuvant treatment to surgery;
- Deferral of completion lymph node dissection: the CGP agreed that completion lymph node dissection for patients with micrometastatic lymph node involvement detected on sentinel lymph node biopsy should not be a requirement for consideration of treatment with nivolumab as adjuvant therapy to surgery. This is based on recent clinical trials which have established

observation within this patient population as a viable treatment strategy, as melanoma-specific survival was not improved with reflexive completion lymph node dissection. Notably, more recent clinical trials investigating systemic therapy as adjuvant to surgical treatment have not mandated reflexive completion lymph node dissection in the case of patients with micrometastatic disease detected on sentinel lymph node biopsy;

- Utility of PD-L1 testing as a predictive biomarker: the CGP agreed that there were insufficient data to support this practice, and recommended consideration of treatment with nivolumab as adjuvant therapy to surgery for patients who otherwise met the CheckMate 238 inclusion criteria, regardless of PD-L1 testing;
- Sequential use of systemic therapies as adjuvant treatment to surgical resection of disease: the CGP agreed that the use of nivolumab as adjuvant therapy to surgery could be considered in the subset of patients who had received prior adjuvant systemic therapy, provided disease was amenable to radical resection following recurrence, and provided patients otherwise met the CheckMate 238 inclusion criteria;
- Impact of utilization of nivolumab as adjuvant treatment to surgery on therapy selection in the metastatic (relapsed) setting: the CGP agreed that there was insufficient data to allow for recommending treatment(s) for the relapsed patient, but noted patients who participated within the CheckMate 238 clinical trial received a variety of post-study treatments, including anti-PD-1 directed immune checkpoint inhibitors. Until such time as data are available to guide treatment decision-making in this context, the CGP felt that treatment decisions in this context were best left to the individual treating clinician;
- Clinic resource utilization: at the present time, no data exist that would support altering the treatment schedule or dose utilized for patients treated under the CheckMate 238 clinical trial. Nonetheless, this strategy has been adopted for patients with metastatic melanoma, despite a similar lack of evidence. The CGP felt that optimal treatment would mirror the schedule and dosage supported by the CheckMate 238 trial, but also recognized that clinicians may wish to adopt the use of a "capped dose," or adopt a 28-day treatment schedule, on an individual basis.
- Following the posting of the pERC initial recommendation, the CGP provided additional context to respond to feedback received from stakeholders on the dosing of nivolumab. The CGP noted that there is no evidence for dose-capping in the adjuvant patient population. Further, it is unlikely that toxicity will be increased with doses >240 mg (for those patients >80 kg). Until such time that evidence is available for capped dosing, most clinicians will likely wish to adhere to the CheckMate 238 study design. Furthermore, the CGP noted agreed it is reasonable to consider 4 week dosing on occasion for extraordinary patients (i.e. those required to travel excessively long distances for treatment), but otherwise the practice should be to adhere to the best available evidence. Thus far the evidence for per 4 week dosing is only through pharmacokinetic modeling and there is no clinical evidence to support the practice.

2 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.

2.1 Description of the Condition

Malignant melanoma is a relatively uncommon but aggressive skin cancer with an estimated incidence in Canada of 7 200 cases per year.[9] Approximately 1 in 50 Canadians will be diagnosed with a malignant melanoma in their lifetime. While the disease may be uncommon melanoma is the most commonly diagnosed cancer in individuals between the ages of 20 and 29, creating a disproportionate societal impact. Unfortunately, the incidence of melanoma in Canada continues to rise, despite efforts of patient advocacy groups and public awareness campaigns to educate the public regarding risk factor modification, specifically avoidance of ultraviolet radiation. Most diagnoses of melanoma represent early stage disease and are cured with surgery alone, however a proportion of patients will present with locally advanced cancers which, while also amenable to surgery, portend a high risk of relapse and death. Prognosis varies within the subset of patients presenting with nodal involvement, but for those at highest risk for relapse (stage IIID, American Joint Committee on Cancer 8th edition)[8] the five and ten year disease specific survival rate is 32 and 24 percent, respectively.

For patients with metastatic melanoma, effective systemic treatment strategies prior to the era of targeted and immunotherapies did not exist. More recently, targeted inhibition of the mitogen-activated protein kinase (MAPK) signalling pathway has emerged as an extremely effective palliative therapy that has also improved the survival of patients with melanoma that harbors a mutation in the BRAF gene. Occurring in approximately 40 percent of the total patient population, mutations at the BRAF V600 codon results in constitutive activation of the signalling cascade, leading to dysregulated cellular proliferation and metastatic spread of disease. For those patients with BRAF-mutant melanoma, agents such as dabrafenib and vemurafenib (now commonly prescribed in combination with the MEK inhibitors trametinib and cobimetinib, respectively) represent highly effective palliative therapy[10,11].

As an alternative to targeted therapy (or for the majority of melanoma patients with non-mutated or wild-type BRAF disease) immune checkpoint inhibitors have similarly impacted patient survival. Ipilimumab, an inhibitor of cytotoxic T-Lymphocyte antigen-4 (CTLA-4) was the first immunotherapy to improve the survival of patients with metastatic melanoma [12], followed by similar successes with agents such as nivolumab [13] and pembrolizumab [14]. The latter study demonstrated targeting the Programmed Death-1 (PD-1) checkpoint molecule was superior to CTLA-4 inhibition, however more recent data suggests there may be further gain from dual blockade of CTLA-4 and PD-1, extending the three year survival for patients with metastatic melanoma to nearly 60%.[15]

With these improvements in patient survival, it should not be surprising that attempts have been made to reduce the risk of relapse and death in patients with locally advanced, non-metastatic melanoma. Both targeted and immunotherapies have been tested in the adjuvant setting, and both strategies have yielded improved patient outcomes. In the COMBI-AD study, combined dabrafenib and trametinib improved relapse-free survival at three years when compared against matched placebos (hazard ratio for relapse or death 0.47) and a trend towards improved overall survival was also observed.[16] Similarly, when compared against placebo ipilimumab improved patient survival for patients with resected stage III melanoma (5-year survival is increased 11% from 54.4% to 65.4%, hazard ratio for

death 0.72).[17] And most recently, when compared against ipilimumab treatment with nivolumab following complete resection of stage III or IV melanoma improved recurrence-free survival at one year (70.5% versus 60.8%, hazard ratio for relapse or death 0.65).[1] An adjuvant clinical trial comparing dual blockade of CTLA-4 and PD-1 against nivolumab is ongoing (NCT03068455).

2.2 Accepted Clinical Practice

For patients presenting with resected stage III or IV melanoma current adjuvant treatment options are limited, particularly with respect to systemic therapy. In Canada, high-dose interferon-alpha is indicated as adjuvant to surgical treatment in patients 18 years of age or older with malignant melanoma who are free of disease but at high risk for systemic recurrence, within 56 days of surgery (product monograph). In practice however, interferon is infrequently prescribed. The approval for the use of adjuvant high-dose interferon came at a time when no efficacious treatments were available for patients with recurrent disease, a clinical scenario which fortunately has changed for the better with the introduction of targeted and immunotherapies. Furthermore, interferon as adjuvant to surgical treatment for patients with melanoma has been well studied, and meta-analyses support the use of the treatment in a relatively small proportion of patients. As an example, a recent Cochrane meta-analysis examining 10 499 patients across 18 randomized clinical trials identified a benefit from the use of adjuvant interferon with respect to disease-free and overall survival, reporting a hazard ratio for the latter of 0.91.[6] The same meta-analysis reported a number needed to treat (NNT) of 35 to prevent one death from melanoma recurrence, and when the significant toxicity of the treatment regimen is considered the actual benefit to the patient population is further diminished, particularly when one recognizes the data utilized within the meta-analysis predates the use of checkpoint inhibitor therapy; although unproven, it seems plausible that the durable immunotherapy responses observed in patients with metastatic disease could further diminish the small gains seen with the use of interferon. Attempts have been made to identify a subset of patients for whom the use of adjuvant interferon may confer a greater benefit; although not supported by the previously referenced Cochrane meta-analysis, more recent studies suggest patients with ulcerated primary melanomas may derive greater benefit versus the unselected patient population.[18] If confirmed, the use of ulceration as a predictive biomarker could in theory reduce the NNT to confer a benefit from interferon, although it is worth noting the aforementioned clinical trial utilized pegylated interferon-alpha, a treatment not currently approved in Canada as an adjuvant to surgery.

Given the relatively modest benefit observed after treatment with adjuvant interferon, in practice most patients decline this treatment option, instead choosing observation alone. Although not rooted in evidence, the option of active surveillance is routinely offered to patients with resected melanoma. This is a relevant point, as active surveillance is not without an associated cost. Practice will differ between Canadian cancer centres, but most will offer a variant of a schedule of assessments that includes clinical assessments performed on a 3-6 month basis as well as periodic re-staging imaging studies, although the benefit from diagnostic imaging has not yet been conclusively proven. In a subset of patients with resected nodal disease (or in patients with resected in-transit metastatic disease) radiation therapy may be considered as an adjuvant to surgical resection, although neither relapse-free nor overall survival is improved with this strategy.[19]

2.3 Evidence-Based Considerations for a Funding Population

High quality randomized clinical trials support the use of targeted or immunotherapy as adjuvant treatment following surgical resection of stage III malignant melanoma. In the COMBI-AD trial, patients were randomized to receive the combination of dabrafenib with trametinib versus treatment with matched placebos, with relapse-free survival as the primary endpoint and overall survival and safety included as secondary endpoints. To be eligible for this international, multi-centre clinical trial, adult patients (≥18 years of age) must have undergone complete resection of histologically confirmed stage IIIA (limited to lymph-node metastasis of >1 mm), IIIB, or IIIC cutaneous melanoma (according to the criteria of the American Joint Committee on Cancer, seventh edition[4]) with BRAF V600E or V600K mutations. None of the patients had undergone previous systemic anticancer treatment or radiotherapy for melanoma. All the patients had undergone completion lymphadenectomy with no clinical or radiographic evidence of residual regional node disease within 12 weeks before randomization, had recovered from definitive surgery, and had an Eastern Cooperative Oncology Group performance status of 0 or 1. As reported in 2017, with a median follow-up of 2.8 years, the estimated 3-year rate of relapse-free survival was 58% in the combination-therapy group and 39% in the placebo group (hazard ratio for relapse or death, 0.47; 95% confidence interval [CI], 0.39 to 0.58; P<0.001). The 3-year overall survival rate was 86% in the combination-therapy group and 77% in the placebo group (hazard ratio for death, 0.57; 95% CI, 0.42 to 0.79; P=0.0006). While the overall survival data was not statistically significant according to a prespecified interim analysis threshold, a strong trend towards improvement with treatment with dabrafenib/trametinib was demonstrated.[16] A benefit with respect to relapse or death across all subgroups studied was seen with the exception of the 10% of patients included with V600K BRAF mutations, although a strong trend favoring the active treatment arm was observed even in this small subset of patients. Importantly, the hazard ratio for relapse or death was 0.50 or less in each of stage IIIA, IIIB and IIIC disease. In addition to demonstrating improvement in relapse-free survival, the tolerability of treatment in this patient population was similar to that seen in the metastatic setting, with 41% of patients experiencing a grade 3 or 4 toxicity (versus 14% of placebo-treated patients), and 26% of patients experiencing an adverse event leading to treatment discontinuation. The most commonly reported toxicities stemmed from the so-called pyrexic syndrome, including fever, chills, headache, fatigue and nausea.

The use of checkpoint inhibitor therapy has also yielded success as adjuvant treatment to surgery for patients with resected stage III melanoma. The Keynote-054 randomized clinical trial enrolled patients who were 18 years of age or older and had histologically confirmed cutaneous melanoma with metastasis to regional lymph nodes.[20] The patients had to have either stage IIIA melanoma (patients with stage N1a melanoma had to have at least one micrometastasis measuring >1 mm in greatest diameter) or stage IIIB or IIIC disease with no in-transit metastases as defined by the American Joint Committee on Cancer 2009 classification, 7th edition.[4]14 A complete regional lymphadenectomy was required to have been performed within 13 weeks before the start of treatment. Exclusion criteria included an Eastern Cooperative Oncology Group (ECOG) performance status score of more than 1 (scores range from 0 to 5, with higher numbers indicating greater disability), autoimmune disease, uncontrolled infections, use of systemic glucocorticoids, and previous systemic therapy for melanoma. Patients were randomly assigned in a 1:1 ratio to receive either an intravenous infusion of 200 mg of pembrolizumab or placebo every 3 weeks for a total of 18 doses, or until disease recurrence, unacceptable toxic effects, a major protocol violation, or withdrawal of consent occurred. With a primary endpoint of relapse-free survival and with a median follow-up of 15 months, the 1-year rate of recurrence-free survival in patients who received pembrolizumab was 75.4%, versus

61% in the placebo-treated group (hazard ratio for recurrence or death, 0.54). The benefit in recurrence-free survival was seen patients with both BRAF-mutated and -wildtype disease, and while all subgroup analyses indicated a trend that favored treatment with pembrolizumab, a clear benefit from treatment was observed in patients with stage IIIB and C disease, patients with PD-L1 positive tumors and patients with ulcerated primary lesions. The rate of grade 3 or greater toxicities was roughly doubled in pembrolizumab-treated patients (31.6% versus 18.5%), with an overall toxicity profile in the adjuvant setting similar to that seen in patients with metastatic disease. A cooperative group study is currently underway which will compare pembrolizumab against interferon-alpha as adjuvant treatment to surgery.[21]

CTLA-4 directed therapy has been compared against placebo in patients with resected stage III melanoma.[17] After patients had undergone complete resection of stage III cutaneous melanoma, they were randomly assigned to receive ipilimumab at a dose of 10 mg per kilogram (475 patients) or placebo (476) every 3 weeks for four doses, then every 3 months for up to 3 years or until disease recurrence or an unacceptable level of toxic effects occurred. Recurrence-free survival was the primary end point. Secondary end points included overall survival, distant metastasis–free survival, and safety. At a median follow-up of 5.3 years, the 5-year rate of recurrence-free survival was 40.8% in the ipilimumab group, as compared with 30.3% in the placebo group (hazard ratio for recurrence or death 0.76). The rate of overall survival at 5 years was 65.4% in the ipilimumab group, as compared with 54.4% in the placebo group (hazard ratio for death 0.72). Despite the fact that more patients in the placebo arm received post-protocol treatment with both CTLA-4, PD-1 and BRAF-directed therapies at the time of relapse, the survival advantage to adjuvant ipilimumab was preserved, suggesting this treatment strategy is unlikely to be negated by a potential salvage effect of reserving the use of immune checkpoint inhibitors for the time of relapse. Subgroup analyses demonstrated the benefit to treatment with ipilimumab as adjuvant to surgery was greatest in those patients at highest risk for disease relapse (stage IIIC patients, specifically those with four or more lymph nodes positive for metastatic melanoma) and again, patients with ulcerated primary melanomas seemed to derive proportionally greater benefit (hazard ratio for death 0.64). Treatment with ipilimumab at a dose of 10 mg/kg resulted in nearly half of patients experiencing a grade 3-5 immune-related adverse event (42.7% versus 2.7% in the placebo arm). In the ipilimumab group of treated patients, five patients died from a drug-related cause: three patients died of intestinal perforation (colitis), while one patient each died from myocarditis and multi-organ failure secondary to Guillain Barré syndrome. An approval from Health Canada for the use of ipilimumab as adjuvant therapy to surgery was not sought.

Most recently, the CheckMate 238 randomized clinical trial compared adjuvant CTLA-4 - directed therapy against inhibition of PD-1.[1] In this randomized, double-blind, phase 3 trial 906 patients (≥15 years of age) who had undergone complete resection of stage IIIB, IIIC, or IV melanoma received an intravenous infusion of either nivolumab at a dose of 3 mg per kilogram of body weight every 2 weeks (453 patients) or ipilimumab at a dose of 10 mg per kilogram every 3 weeks for four doses and then every 12 weeks (453 patients). The patients were treated for a period of up to 1 year or until disease recurrence, a report of unacceptable toxic effects, or withdrawal of consent. The primary end point was recurrence-free survival in the intention-to-treat population. This was a positive study; with a minimum follow-up of 18 months, the 12-month rate of recurrence-free survival was 70.5% in the nivolumab group and 60.8% in the ipilimumab group (hazard ratio for disease recurrence or death 0.65). Importantly, treatment with nivolumab as adjuvant to surgery was significantly safer versus treatment with ipilimumab. Treatment-related grade 3 or 4 adverse events were reported in 14.4% of the patients in the nivolumab group and in 45.9% of those in the ipilimumab group; treatment was discontinued because of any adverse

event in 9.7% and 42.6% of the patients, respectively. Two deaths (0.4%) related to toxic effects were reported in the ipilimumab group more than 100 days after treatment. The utility of tumoral PD-L1 staining as a predictive biomarker was studied but failed to identify a subset of patients with preferential benefit from the use of adjuvant nivolumab. Nivolumab was superior to ipilimumab in both patients with PD-L1 expression greater than and less than 5%. The 12-month rate of recurrence-free survival was greater in patients with PD-L1 expression greater than 5%, however the gain was consistent whether treatment was with nivolumab or ipilimumab, suggesting PD-L1 expression may offer better prognostic versus predictive insight. For the most part, subgroup analyses tended to favor treatment with nivolumab as opposed to ipilimumab; of particular importance, both patients with BRAF-mutant and wild-type melanoma derived preferential benefit from treatment with nivolumab. Of the adjuvant randomized clinical trials include in this review, the CheckMate 238 study was unique in that patients with completely resected stage IV disease (including patients with resected CNS metastases) were eligible for enrolment, and also allowed for treatment of non-cutaneous melanoma (mucosal and acral-lentiginous melanoma patients were permitted to enroll, however patients with ocular melanoma were excluded). The hazard ratio for relapse or death was statistically non-significant within each of these subgroups, however this may be due to the fact small numbers of patients from these subgroups were enrolled.

The evidence seems clear that for cutaneous melanoma patients surgically rendered free of macroscopic disease clinical benefit may be derived from the use of either targeted or immune checkpoint therapy as adjuvant treatment to surgery. In most studies, the available evidence reveals a benefit with respect to recurrence-free survival, although one study comparing ipilimumab against a matched placebo as adjuvant treatment to surgery also supports an advantage in terms of overall patient survival. Not coincidentally, that clinical trial also offers the longest duration of follow-up study. The strongest evidence for treatment exists within the stage III patient population, with just one randomized clinical trial (the CheckMate-238 randomized clinical trial comparing nivolumab against ipilimumab) allowing for treatment of patients with completely resected stage IV disease. There exists inter-trial heterogeneity between the populations of patients with stage III disease, with some but not all studies allowing for the treatment of patients with stage IIIA melanoma, and in two of the cited studies patients with stage IIIA disease must have had a minimum focus of nodal disease of 1 mm. None of the included studies were powered for subgroup analyses which might otherwise have indicated a preferential benefit within the unselected stage III patient population. Likewise, with the exception of the COMBI-AD study which only allowed for treatment of patients with BRAF-mutated melanoma, none of the included immunotherapy studies identified a preferential benefit to treatment in either BRAF-mutated or -wildtype melanoma.

2.4 Other Patient Populations in Whom the Drug May Be Used

The use of systemic therapy, targeted or immune checkpoint inhibiting, as adjuvant treatment to surgery demonstrates a clinical benefit to patients with completely resected malignant melanoma with lymph node involvement. The populations included within these clinical trials were mostly comprised of adult patients with cutaneous melanoma. However, clinicians and patients alike may to consider the use of systemic therapy as adjuvant to surgery for patients not necessarily included within these studies. Examples include:

- Children (patients <18 years of age): only one of the clinical trials reviewed (CheckMate 238) allowed for the inclusion of pediatric patients. Patients 15 years or older were permitted for screening, however no patients younger than age 18 were actually enrolled to study. Melanoma is a disease typified by extremes of age, and is

the most commonly diagnosed cancer in patients aged 20-29, however, pediatric diagnoses are uncommon. Nonetheless, while level one evidence for the use of either targeted or immunotherapy in patients younger than 18 years of age is lacking, abstract data indicates treatment to be safe.[22,23] It therefore seems reasonable to consider the use of systemic therapy as adjuvant to surgery for the treatment of pediatric patients with completely resected malignant melanoma.

- Patients with performance status > ECOG 1: patients enrolled to the CheckMate 238 clinical trial had performance status ECOG 0-1. It is anticipated clinicians and patients alike may wish to consider utilizing nivolumab as adjuvant treatment to surgery for patients with a performance status of ECOG 2 or greater. In general, cytotoxic chemotherapy (particularly later lines of therapy) is associated with substantial toxicities, impaired quality of life, and a short lifespan in patients with an ECOG performance status ≥ 2.[24] By contrast, immune checkpoint inhibitors, particularly anti-PD-1 monotherapy, may have favorable toxicity profiles, even in patients with a poor performance status. This issue will need further study, particularly because of the high costs of therapy, but at the present time data does not exist to refute the possibility patients with performance status ≥ 2 may benefit from adjuvant nivolumab as treatment to surgery.
- Patients with non-cutaneous melanoma: the large majority of patients with melanoma present with cutaneous disease, however non-cutaneous variants of disease are well recognized. Included within this heterogenous population are patients with mucosal and ocular melanoma. The former group of patients were permitted enrolment to the CheckMate 238 trial, while all other referenced studies were restricted to patients with cutaneous melanoma. In the subset of CheckMate 238 patients with mucosal melanoma the hazard ratio for death or relapse following treatment with nivolumab was statistically non-significant, although this likely relates to the very small number of enrolled patients (<5% of the total cohort) versus a true absence of benefit. The treatment of patients with non-cutaneous melanoma may be challenging, in both the adjuvant and metastatic settings, as there is a lack of high-quality data to inform treatment decision making. In practice, patients with mucosal melanoma are generally offered treatment with the same systemic therapy as would be offered to patients with cutaneous disease. This is largely due to the absence of data which would refute the expectation of a clinical benefit but also relates to the fact that the natural history of disease seen with mucosal melanoma is at least similar to that seen in cutaneous melanoma. Conversely, the molecular biology of disease varies significantly between cutaneous and non-cutaneous melanoma. For instance, while activating BRAF mutations occur in approximately 50% of patients with cutaneous melanoma, this oncogenic pathway is mutated in fewer than 10% of patients with mucosal disease.[25] Furthermore, tumor mutational burden (theorized to be important in predicting response to immunotherapy) is significantly lower in patients with mucosal versus cutaneous melanoma.[26] Notwithstanding these considerations, extrapolation of cutaneous treatment outcomes have been made to patients with mucosal melanoma in the metastatic setting. A pooled analysis from 2015 demonstrates activity of immune checkpoint inhibitors for the treatment of mucosal melanoma[27], lending credence to this approach, and providing a rationale for extending the benefit of immunotherapy as adjuvant treatment to surgery to patients with mucosal melanoma. Unfortunately, these same arguments cannot be made for patients with ocular melanoma, where immunotherapy has shown little impact to patients with metastatic disease. Here the data is limited mostly to individual case reports or small patient series, although prospective clinical trials evaluating the efficacy of immune checkpoint inhibitors within this patient population are in development.[28]

- Patients with resected stage IV disease: following the complete resection of stage IV metastatic melanoma, patients meeting all other eligibility criteria for the CheckMate 238 clinical trial were permitted enrolment. Of the clinical trials included within this review, the CheckMate 238 study was the only study to permit enrolment of patients with resected stage IV disease. This subpopulation of patients represented approximately 20% of the entire study cohort, and in the intent-to-treat analysis a recurrence-free survival advantage to patients treated with nivolumab was evident. In subgroup analyses the hazard ratio for recurrence or death was statistically non-significant, although a trend which favored treatment with nivolumab over ipilimumab was reported in stage M1a and M1b patients (patients without visceral or central nervous system metastases). As with all subgroup analyses within this clinical trial results should be considered exploratory but the poor prognosis associated with resected stage IV melanoma should also be factored in to consideration, and clinicians and patients may wish to consider treatment with nivolumab as adjuvant to surgery.
- Re-treatment with nivolumab as adjuvant treatment to surgery after treatment with alternative adjuvant systemic therapy: despite treatment with systemic therapy as adjuvant treatment to surgery, a subset of patients will recur in a manner amenable to surgical resection rendering them free of macroscopic disease. In this situation, patients and clinicians alike may wish to consider repeating treatment with systemic therapy as adjuvant treatment to metastatectomy. In the current Canadian landscape, specific examples include patients previously treated with interferon-alpha as well as patients who may have participated in clinical trials offering adjuvant treatment with either BRAF-targeted therapy or immune checkpoint inhibitors (including anti-CTLA-4 and anti-PD-1 therapy). The CheckMate 238 study stipulated that subjects who received prior therapy with anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody (including ipilimumab or any other antibody or drug specifically targeting T cell co-stimulation or checkpoint pathways) were not eligible for enrolment; however, prior adjuvant treatment with interferon-alpha was permitted, provided a period of 6 months or more had lapsed between the end of treatment with interferon and treatment randomization.
- Patients who defer completion lymph node dissection following positive sentinel lymph node biopsy: The second multicenter selective lymphadenectomy trial (MSLT-II) compared observation against completion lymph node dissection for patients with melanoma and positive sentinel lymph node biopsy.[29] The results of this clinical trial established observation within this patient population as a viable treatment strategy, as melanoma-specific survival was not improved with reflexive completion lymph node dissection. Consequently, patients and clinicians alike may wish to defer completion lymph node dissection following positive sentinel lymph node biopsy. The CheckMate 238 clinical trial allowed for enrolment and treatment of patients who had been surgically rendered free of disease with negative margins on resected specimens, and all patients received completion lymphadenectomy. However, subsequent to publication of the MSLT-II trial results, more recent clinical trials investigating systemic therapy as adjuvant to surgical treatment have not mandated reflexive completion lymph node dissection in the case of patients with micrometastatic disease detected on sentinel lymph node biopsy. In the face of a change in surgical management of melanoma, patients and clinicians alike may wish to consider treatment with nivolumab following surgical resection of disease with deferral of completion lymph node dissection for patients with micrometastatic disease detected on sentinel lymph node biopsy.
- Patients treated with radiation as adjuvant therapy to surgery: as discussed above, radiation as adjuvant therapy to surgical resection of melanoma confers an advantage

in terms of locoregional control, however this benefit does not translate to improvement in patient survival.[19] Nonetheless, the situation may arise where clinicians may wish to consider radiation and systemic therapy as adjuvant treatment to surgery. In the CheckMate 238 clinical trial patients were not permitted to receive radiation as adjuvant therapy prior to enrolment.

Patients with pre-existing autoimmune disease: active immune mediated illnesses (ie. inflammatory bowel disease, rheumatoid arthritis or multiple sclerosis) are exclusionary criteria for most immunotherapy clinical trials, including the CheckMate 238 study. The CheckMate 238 clinical trial excluded from enrolment patients with active, known, or suspected autoimmune disease, as well as patients with a condition requiring systemic treatment with either corticosteroids (≥ 10 mg daily prednisone or equivalent) or other immunosuppressive medications. In practice, with increasing clinician confidence in the management of immune-related adverse events select patients with metastatic disease and pre-existing immune-mediated illnesses have been offered treatment with immune checkpoint inhibitors, and the toxicity profile within this group of patients is comparable to that seen in the unselected patients population, as is treatment efficacy.{Johnson, 2016 #653} Patients with pre-existing immune-mediated illness, as well as there caregivers may therefore wish to consider utilizing nivolumab as adjuvant to surgical treatment following complete resection of disease.

3 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

Two patient advocacy groups, the Melanoma Network of Canada (MNC) and the Save Your Skin Foundation (SYSF), provided input on the nivolumab (Opdivo) submission for the adjuvant treatment of patients with melanoma.

MNC conducted an online survey which was emailed to their database of patients and caregivers, and made available for respondents to complete between August 1, 2018 and September 8, 2018. MNC also mailed postcards to each major treatment centre for oncologists to hand out. The online survey was promoted through MNC's social media, including Facebook and Twitter. Patient and caregiver responses were obtained from 205 and 113 respondents, respectively. All respondents were Canadian patients; 66% were from Ontario, 12% were from Alberta, 7% were from BC, 6% were from Quebec, and the remaining 9% of patients were from the other provinces. The greatest proportion of patients were between 51 and 60 years of age (29%) (Table 1). Of the 205 patients, 63% (n=130) were female. MNC's survey was made available to respondents regardless of stage of disease; the majority of patients (60%) were between stage 0 and stage □□□ (Table 1). Forty-seven respondents of MNC's survey had experience with nivolumab for melanoma, of whom 28 were receiving it for adjuvant therapy, while 19 patients were on treatment for metastatic disease (stage IIIC unresectable or stage IV unresectable).

Table 1: Patient Characteristics of MNC's Survey (n=205)

Age (years)	**n (%)**
18 to 30	8 (3.90)
31 to 40	19 (9.27)
41 to 50	40 (19.51)
51 to 60	60 (29.27)
61 to 70	51 (24.88)
>70	27 (13.17)
Sex	**n (%)**
Male	75 (37)
Female	130 (63)
Stage of Disease	**n (%)**
0-□□□	123 (60)
□V	54 (26)
Unknown	28* (14)
* MNC indicated that these patients did not know their stage of disease	

SYSF gathered information through surveys, personal experience, and through one-on-one conversations; a total of 48 respondents were captured via the survey and 15 patients underwent one-on-one interviews. SYSF recruited patients both with and without experience with nivolumab. Over 80% of respondents were female, and ages of respondents ranged from 18 to over 60 years of age. SYSF reported that over 50% of respondents were employed, and over 18% were retired. The majority of interviewed respondents (80%) were from Canada; the remaining interviewed respondents were from Australia and the US. Nine patients reported having experience with nivolumab.

In total, 381 responses from patients and caregivers were obtained from both MNC and SYSF, with 37 patients receiving nivolumab in the adjuvant setting for the treatment of melanoma. From a

patient's perspective, mental health challenges including anxiety, depression and fear are common issues faced during the course of their disease. Patients responding to both SYSF's and MNC's surveys indicated their condition as having a negative impact on their mental health. Physical symptoms such as, scarring, fatigue and lymphedema were reported by patients. The impact of patient's condition on their family and social life was also noted; family members also face anxiety regarding the lack of treatment options for their loved ones, in addition to facing financial stress due to costs of treatments.

Therapies with which patients had previous experience included surgery, interferon, ipilimumab, dabrafenib and trametinib, and watch and wait. Common side effects included flu-like symptoms, weight loss, depression, hair loss, and nausea and vomiting. Of patients responding to MNC's survey, 14% received nivolumab in the adjuvant setting, while 9% received it in the metastatic setting. Fifteen percent of patients responding to SYSF's survey reported receiving nivolumab, however it is not clear in what setting it was received. Compared to previous treatments, patients seemed to prefer nivolumab for its better tolerance and improved effectiveness. Issues related to nivolumab included the large number of hospital visits required for infusions, and the financial impact of having to take time off work for the drug, or having to pay for it out of pocket. Both MNC and SYSF highlighted the lack of accessibility of nivolumab, and treatments in general for patients with melanoma.

Please see below for a summary of specific input received from LCC. Quotes are reproduced as they appeared in the survey, with no modifications made for spelling, punctuation or grammar. The statistical data that are reported have also been reproduced as is according to the submission, without modification.

3.1 Condition and Current Therapy Information

3.1.1 Experiences Patients have with melanoma

MNC mentioned that in every survey previously sent to patients with melanoma, over 70% of patients indicated significant mental health challenges. For this submission, MNC noted that 73% of patients indicated mental health challenges, including suffering from fear and anxiety of recurrence of disease. Pain (43%), scarring (74%), lymphedema (28%), mobility issues (21%), fatigue (56%), depression (48%), negative impact to family and social life (39%), financial impact (31%), negative impact on sexuality (29%), and disrupted sleep (42%) were all aspects of quality of life patients felt were impacted by their condition. Thirteen respondents of MNC's survey indicated experiencing *"other"* symptoms related to melanoma that impacted their quality of life, however it was not reported what these respondents experienced.

SYSF asked respondents to report issues experienced with melanoma (see Table 2). Fear and/or anxiety, scarring and disfigurement, fatigue, pain and depression were reported by at least half of patients as issues experienced with melanoma. Respondents reported the following symptoms as being the most important to control: mental health including fear, anxiety, depression and outlook (72%), fatigue (48%), pain (41%), lymphedema (23%), and scarring and disfigurement (21%). SYSF asked respondents to indicate if they experienced any ongoing symptoms affecting day to day life; respondents indicated physical symptoms such as *"Tiredness and confusion," "nerve damage from surgery,"* and *"lymphedema is an ongoing issues for pain and swelling. Fatigue slows e down at work and with my kids."* Respondents also indicated a number of ongoing issues affecting their day-to-day lives, including fear and anxiety related to recurrence of disease:

- *" Fear of return of the disease is frequent, which results in anxiety"*
- *"Most affected by PTSD especially after treatment during ongoing follow up."*
- *"I am 5 years post diagnosis of Stage 2c melanoma and I still worry it will come back"*

- *"My work suffers as do relationships since not sleeping well, scared and depressed"*
- *"Fear of dying had to retire from work."*
- *"Have had issues with relationships with those close to me due to frustration and anger since being diagnosed."*

SYSF mentioned that the majority of patients (90%) were able to manage ongoing symptoms, and were not limited by their disease. However, 10% of patients reported being limited due to their disease or treatment making them unable to work.

Table 2: Symptoms Experienced by Patients

Aspect of Patient's Disease Experience	n (%)	
	MNC, N=113	SYSF, N=NR
Fear and/or anxiety	82 (72)	55 (88)
Scarring and disfigurement	84 (74)	45 (71)
Fatigue	63 (56)	41 (65)
Pain	48 (43)	32 (50)
Depression	54 (48)	32 (50)
Disrupted sleep	47 (42)	30 (48)
Weight loss or weight gain	33 (29)	30 (48)
Nausea or vomiting	15 (13)	20 (31)
Negative impact to family or social life	44 (39)	25 (39)
Financial loss or job loss	35 (31)	20 (31)
Headaches	19 (17)	20 (31)
Loss of/gain of appetite	NR	18 (29)
Lymphedema	32 (28)	17 (27)
PTSD	24 (21)	14 (23)
Cognitive impairment	16 (14)	14 (23)
Damage to organ	15 (13)	13 (21)
Mobility issues[a]	24 (21)	12 (19)
Breathing problems	9 (8)	4 (6)
Negative impact on sexuality	33 (29)	NR
Edema or fluid retention	21 (19)	NR
Gastrointestinal issues	21 (11)	NR
Peripheral neuropathy	21 (19)	NR
No side effects	3 (29)	4 (6)
Other	13	NR

NR: Not reported
[a]MNC described this as being unable to walk or having impaired movement

MNC provided the following quotes from respondents in regards to their experience with melanoma. Five of the six quotes indicate mental or emotional distress related to respondents' disease experience, and all quotes provided by MNC indicate some sort of physical impairment due to respondents' condition. The quotes also indicate the strain on friends and families of patient's with melanoma with one patient indicating having to *"adjust [their] standards for what type of people [they] are willing to have in [their] life."*

- *"Impact on family planning and unsure if we can have another child"*
- *"lymphedema limits physical; Lymphedema has affected activities Cancer has created anxiety and impacted relationships; My physical limitations include not being able to walk*

because of 3 surgeries in the year. Showering and daily care was also affected. I do wear a compression stocking to eliminate the swelling in my leg I am always on the lookout for more spots and at times it can make me a little anxious when a new spot appears;"

- *"I live with constant fear and anxiety my cancer will return/progress. It impacts myself and my family daily, the depression and emotional toll is draining; Work loss severe depression anxiety; Emotional impact; effects on work and daily routine's; limits on activities; Cancer affects all the aspects of your life. It kills your personality and your dreams before killing your body. I am and will never be the same person; The fear of the disease progressing is always at the back of my mind. The mental stress is always there; Couldn't work. Skin grafts wouldn't heal. Family life in tatters. Depressed; Anxiety and major impact to daily routines. Limited outdoor activities in the daytime, increased costs for protective sun gear (sunscreen, UV clothing, etc). Anxiety over physical scars, painful scars. Anxiety over recurrence and cancer paranoia; Anxiety when you have to go for regular visits and scans. Family life is affected; Unable to work. Lots of anxiety regarding recurrence.; Inability to walk after a month after excision/skin graft –general exhaustion limiting daily activities –strain on relationships due to stress on both parts –lost wages for healing/various appointments –anxiety; It impacted me in countless ways. I am lucky to be alive, but the fear of another recurrence will never leave me."*
- *"Got put out of my career due to physical limitations; The fear of the sun is the biggest stress, the financial stress of not able to afford time off work for appointments.; Anxiety and fear to be outside in the sun for more than a few minutes. Fear and anxiety about people seeing my scars. Fear the disease will come back or spread"*
- *"Physical impairment issues, mental and emotional issues, post-traumatic stress that has gotten better but still can't deal with high stress or loud noises, financial impact on my ability to work and was hard on my husband during treatment – the time he had to take off to care for me and the stress was something"*
- *"I had to stop athletic activities before diagnosis due to the fatigue the melanoma was causing me. Pain was manageable, surgery was difficult; there has been isolation and social stress post-cancer, and relationships have changed a lot. It brings out some nasty emotions and beliefs about cancer, so I've had to adjust my standards for what type of people I'm willing to have in my life. I have/had post-traumatic stress from diagnosis and treatment including nightmares, avoiding triggers like hospitals, hypervigilance, emotional numbness. This was the hardest to cope with, besides long term side effects from treatment and the social hardships.*

Over 70% of respondents of both MNC's and SYSF's surveys indicated scarring and disfigurement and fatigue as aspects of the melanoma that greatly affected them. Similar percentages of respondents indicated that these aspects of melanoma as impacting their lives between both SYSF's and MNC's samples of respondents. Respondents from both surveys also voices distress related to their condition, how it has impacted their lives, including their work and relationships with both family and friends, and how it has resulted in a general sense of anxiety.

3.1.2 Impact of melanoma and Current Therapy on Caregivers

Input from caregivers was provided by both MNC and SYSF. MNC highlighted the extreme levels of stress and anxiety experienced by caregivers related to a lack of available treatment options for patients in the adjuvant setting after surgery. Caregivers mentioned feeling fatigue due to increased responsibilities of care, having to take time off work for appointments and home care, the financial impact on their household due to lost income and increased medical costs, uncertainty regarding the future, and fear of losing their loved ones. MNC also pointed out that caregivers expressed concern about how the diagnosis affected their family dynamics. In some

cases the diagnosis brought about greater togetherness for families, however MNC mentioned that most caregivers indicated a negative impact on their families due to greater feelings of stress on their children.

SYSF provided quotes from caregivers and patients on behalf of the caregiver experiences. These quotes were similar to statements from the MNC's surveys and relate feelings of fear and anxiety, missing work to take care of loved ones, the financial impact of caregiving, and the consequences it can have on relationships.

- *"My family continues to have fear of recurrence."*
- *"In 2013 first diagnosed with stage 2, removed with little follow up. 2017 stage 4, whole lot of issues, lots of appointments. Trying to work and take care of my spouse and manage all the appointments. As caregiver I am physically and emotionally exhausted."*
- *"Had to move provinces, leave school, find a job, and ultimately our new marriage ended in divorce."*
- *"My spouse had to deal with my anxiety and fears, difficult to talk about."*
- *"Lost time at work because of appointments, surgery and treatment."*
- *"Financially drained because my husband misses work to take care of me and I have to travel 4 hours each way to my melanoma specialist."*
- *"Strain on our relationship"*
- *"Lost time at work, arguing over the disease, just not knowing enough about treatment options or disease in general."*
- *"The entire family is still in shock! We do not know what to do and where to seek help. The doctor told us that the only drug that would help the cancer not advance to stage IV is not approved. She offered that we could pay $100,000 or wait until the cancer gets to Stage IV. We all feel helpless and powerless because we do not have the money. We were told there is a 60% chance that it will go to stage IV."*
- *"Just knowing how much time I have left, planning for my stage 4, hard on relationship and financial worry!"*

3.1.3 Patients' Experiences with Current Therapy for Melanoma

Information regarding patients' experiences with current therapies for melanoma was provided by SYSF. According to SYSF, surgery, interferon (38%), and nivolumab (Opdivo) (15%), ipilimumab (Yervoy), or dabrafenib-trametinib (Tafinlar-Mekinist) (6%) via clinical trials were previously reported therapies by patients. "Watch and wait" was also reported by 38% of patients.

Respondents indicated a number of side effects related to their previous or current treatment options. For patients with experience receiving interferon, all reported experiencing severe fatigue and flu-like symptoms. Nearly all respondents indicated experiencing weight loss (95%), some form of depression (90%), hair loss or hair thinning (90%), and nausea and vomiting (90%). All respondents receiving interferon indicated their symptoms as unmanageable, and 95% reported that the side effects were not worth the result as they all experienced disease recurrence in stage 4 melanoma.

Respondents with experience with "watch and wait" express regret about the lack of treatment options, as they felt that if they had another treatment option their condition might not have worsened. SYSF provided the quotes below to portray the feelings of regret and worry that patients experienced in having limited or no treatment options for their condition:

- "It would have been important to have a drug therapy as I wanted to do everything possible to fight"

- "We did not have any treatment. If we would have gotten something, maybe we would not have gone to Stage 4"
- "It would have meant the world to me to be offered treatment. It would have been a game changer!"
- "Having a treatment option would have given me Peace of Mind."
- "It would have meant to not have to worry as much"
- "I could feel like I was getting treatment and I might have a chance to stop it before it comes back"
- "Less fear that we'd miss something between appointment with dermatologist and I would be less likely to end up terminal or massive spreading before it is found again"
- "The possibility of not having to have another surgical procedure and the fear that the next diagnosis wouldn't be caught early enough."
- "I would have tried anything"

SYSF did not provide specific input from patients who underwent treatment with ipilimumab or the combination of dabrafenib-trametinib.

3.2 Information about the Drug Being Reviewed

3.2.1 Patient Experiences with Nivolumab

MNC indicated that 28 (14%) of the 205 patients were receiving adjuvant therapy for stage □□□ melanoma, while 19 (9%) were receiving treatment in the metastatic stage. The majority of patients (n=25, 89%) were receiving nivolumab as part of a clinical trial, while the remainder (n=3, 11%) were paying approximately $6200 every two weeks out of pocket. For patients in the adjuvant setting, there are no current therapies available at this time; therefore, most patients did not have another treatment to compare with nivolumab. MNC stated that a couple of patients had previously received interferon prior to nivolumab, and that the side effects of interferon were worse than those experienced with nivolumab. MNC provided the following quotes from patients comparing interferon with nivolumab; both patients considered nivolumab to be more tolerable and effective:

- *"It is black and white comparing interferon with the new drug. The new drug is so much more tolerable, it also because it's the gold standard of treatment it makes us feel much more confident about our future. We've actually started planning."*
- *"I received treatment with interferon in 2012 and currently being treated with Opdivo. Thus I have had experience with both of those drugs. The Opdivo treatment has had minimal side effects more tolerable than interferon. Interferon was not sustainable for more than a few months."*

MNC highlighted that prior surveys that had been conducted and submitted to pCODR indicated that nivolumab was well tolerated by most patients in the metastatic setting. Compared to interferon, MNC stated side effects experienced with nivolumab are fewer and different, contributing to the improvement of patient's quality of life. Fatigue and weakness (53%, n=25), skin rash (35%, n=16), and muscle and joint pain (30%, n=14) were side effects reported by metastatic patients receiving nivolumab through a clinical trial; MNC stated that other side effects were also reported, but in far fewer numbers (Table 3); although it should be noted that 158 respondents did not provide input regarding side effects experienced with nivolumab. Eight patients also indicated having experienced *"other"* side effects, however it was not reported what these patients experienced.

- *"Hyperthyroidism being managed. Kidney issues resolved with prednisone (was off treatment for 6 weeks). Rash managed with steroid cream. Constipation managed with Senekot. Joint pain managed with Aleve. HOPE is most valuable treatment of all!"*
- *"Sides effect are part of your life when you receive or have received Nivolumab. Life will never be the same. The pain is generalized but … I am alive and I thank God or Bristol Myers… everyday!"*

Table 3: Side Effects of Nivolumab as reported by Respondents of MNC's Survey n=47

Side Effect	Frequency (%)
Fatigue or weakness	25 (53)
Skin rash	16 (34)
Muscle or joint pain	14 (30)
Fever or flu-like symptoms	8 (17)
Pain	4 (9)
Shortness of breath, cough or chest pain (pneumonitis)	4 (9)
Hormone or thyroid problem	4 (9)
Sexual impairment	4 (9)
Cognitive impairment	3 (6)
Weight gain	3 (6)
Diarrhea or colitis	2 (4)
Constipation	2 (4)
Headaches	2 (4)
Liver problems	2 (4)
Kidney problems	2 (4)
Bleeding or bruising more easily	1 (2)
Weight loss or loss of appetite	1 (2)
Stomach pain	0 (0)
None	4 (9)
Other	8

Patients indicated that frequent hospital visits to receive infusions of nivolumab created issues for work and impacted them financially; however, regardless of these limitations patients were willing to participate in the trial. Of the total 47 adjuvant and metastatic patients, 46 stated the side effects experienced while on nivolumab were worth it. The following quotes were provided by patients who had to end treatment on nivolumab due to experiencing side effects in a clinical trial; both patients expressed a desire to continue nivolumab treatment even after experiencing side effects:

- *"I was in Study CA209-915. After first treatment I developed a rash that caused the study doctor to withdraw me from further treatment. I would want to continue if the cause of the rash could be eliminated."*
- *"Unfortunately for myself I had a lot of side effects. For others it has been successful with less side effects. If you asked me would I participate in the trial again, I would say yes. One day I hope that they would find a cure for Melanoma."*

MNC asked patients to comment on the outcome of their treatment on nivolumab; 53% indicated that the effect of nivolumab was unknown as their disease had not been eradicated, 30% indicated their cancer being completely eliminated, 6% indicated slowed progression of disease, 6% experienced no impact, and 6% experienced new lingering health issues. One patient mentioned,

"Hard to say- I am alive and my scans are clear 1 year after beginning treatment. Will / would the cancer spread without the treatment? We will never know. I think the treatment is definitely worth it."

MNC also incorporated feedback from caregivers regarding nivolumab therapy. MNC stated that caregivers felt relief to have access to a therapy, and grateful not to have to be concerned with paying out-of-pocket for nivolumab as they accessed it via a clinical trial. *"This trial gives me reassurance that he's doing all that he can to prevent recurrence." "We are very grateful to have the drug available and a positive outcome."*

One of the main concerns among caregivers and patients was the lack of accessibility of nivolumab related to the frequency of and travel to appointments. The frequent travel to appointments, cost of parking and the inability to work were mentioned as concerns. In addition, some patients had to pay for nivolumab out-of-pocket.

- *"Travelling long distance, leaving work, financial."*
- *"Travel long distance and pay lots of money. The drug was not available in our location so we went out of the country."*
- *"Due to the issue I had, I had to travel to the hospital few times a week and I was unable to work."*
- *"Time involved taking treatment at hospital and 2 hours way travel time round trip plus appointments for bloodwork and scans – a full time job saving one's life."*
- *"Only in that it's difficult to watch your loved ones undergo treatment for a year…. and my having a reduced sex drive would be an issue, although he would never say that. Being off on LTD has impacted his earnings (and household income) by 40% which we have felt."*

SYSF also provided input regarding patient experiences with nivolumab. Among patients providing input with SYSF, 15% (n=9) reported having received nivolumab, all of whom accessed nivolumab through a clinical trial. Six patients reported not having experienced any side effects, 2 experienced fatigue, 1 reported shortness of breath, 1 reported diarrhea, and 1 patient experienced slight nausea. Similar to patient responses in MNC's survey, all patients reported that the benefits of nivolumab outweighed the side effects experienced, and reported the side effects as manageable. All patients reported that they were thankful to have been included in the clinical trial.

3.2.2 Companion Diagnostic

While there is currently no companion diagnostic test for this indication, MNC stated that they believed it would be very useful for all stakeholders if a test that could indicate what therapy would be best for a patient in order to provide patients with the most clinically and cost effective option.

3.3 Additional Information

MNC provided feedback on the patient and caregiver survey speaking to improved outcomes. MNC mentioned that patients feel the current level of side effects from immunotherapies and targeted therapies are manageable, with some patients even being able to return to work. MNC compared the tolerability of immunotherapies and targeted therapies to interferon, which they mentioned as being mostly intolerable, with approximately 70% of patients ending treatment before they complete a year-long regimen. MNC further suggested that interferon does not provide patients with a net benefit in terms of OS, and that interferon is no longer offered in most centres. In addition, the epi-pens for administration are no longer manufactured. Therefore, MNC strongly

believes that current immunotherapies and targeted therapies are much more tolerable for patients compared to interferon, and that newer therapies can better impact quality of life for patients. However, they emphasized the need for therapies with greater effectiveness, the availability of a greater variety of therapies, better accessibility of therapies, and cost coverage by either the Canadian government or private insurance.

SYSF provided a number of quotes regarding the expectations patients had for a new drug. The quotes indicate expectations for effective therapies, quick and long-lasting results, minimal side effects, cost effective, and better quality of life. Similar to statements from MNC, the quotes provided by SYSF mirror expectations for greater effectiveness and management of treatment cost.

- *"Longer overall survivorship."*
- *"Maybe a cure."*
- *"Minimal side effects, prolonged treatment results."*
- *"Lessening spread or minimizing it so I can have as much time as possible with my toddler. Getting ahead of the fight before I get sick."*
- *"Treatments that work, work quickly, that have minimal side effects and are cost manageable."*
- *"Promise, evidence based data for decision making, safety (limited risk of adverse effects)."*
- *"Less side effects, or at least manageable side effects."*
- *"Possible eradication of the disease."*
- *"Tolerable treatment that provides better than a 50% chance of survival."*
- *"Hopefully if treated in stage 3 disease will not progress."*

Both MNC and SYSF provided additional information highlighting patients' and caregivers' desperate need for nivolumab. MNC emphasized the unfortunate circumstance of patients diagnosed with melanoma, due to extreme delays in access to therapy for patients in both the metastatic and adjuvant settings. MNC posits that providing access to therapy for patients is the least that can be done until diagnostic testing allows for clearer understanding of the most ideal approaches and therapies to prescribe to each patient. Delaying treatment and access costs patients who do not have the luxury of waiting for, or worrying about decisions related to their treatment, their lives. MNC stated that it would be best to provide patients access to treatment, and then figure out a way to make it a more precise treatment.

SYSF stated that over 80% of interviewed patients expressed that, while they could not access nivolumab, they wish they could have. There were limited clinical trials available for these patients; patients with stage □□ or □□□ melanoma expressed anxiety about their limited access to nivolumab, which was made worse when patients were told by their physicians about the benefits of nivolumab and then were told that they could only access it if they paid for it out-of-pocket. Of the patients who did not have nivolumab as a treatment option, 60% experienced progression of disease. The majority of patients interviewed by SYSF (over 91%) mentioned that had they been offered a treatment in the early stages of melanoma, they would take it. The three quotes below were provided by SYSF, and express patient's despair about their lack of available treatment options, and their inability to access nivolumab:

- *"The ability to overcome the cancer earlier at stage 3 would enable me to continue to take care of my children and grandchildren and my husband and work, pay taxes and be a contributing member of society instead of being a burden to the system. It would mean saving a human life. It would mean ability to see grandchildren growing up. It would mean hope for the future and an end of despair."*

- *"Not being offered treatment is terrifying and the mental anguish on my family can not be described."*
- *"My entire family has been looking to find a way to pay for the Opdivo or find a clinical trial. We can't afford it and that's painful."*

Paralleling what MNC included, SYSF also mentioned their discontent regarding patient's experiences and their delayed access to treatment; they mention that since patients being considered for this indication face a higher chance of experiencing recurrence, the long approval process is disadvantageous for patients. SYSF described the current state of drug treatments as being like *"seeing a light at the end of a very dark tunnel,"* but since patients may not be able to use the drugs currently on the horizon, it feels *like " 'a carrot is being dangled' in front of them for survival and they may not be able to reach out and grab it."*

In addition, SYSF stated that treating patients in the adjuvant setting before they experience progression would be more cost-effective.

4 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. PAG identifies factors that could affect the feasibility of implementing a funding recommendation.

Overall Summary

Input was obtained from all nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation:

Clinical factors:

- Sequencing with current therapies
- Re-initiation following treatment interruption

Economic factors:

- Appropriate dosing and infusion times
- Resources required to administer intravenous infusion, monitor and treat infusion related reactions and monitor and treat adverse events

Please see below for more details.

4.1 Currently Funded Treatments

PAG identified that currently, high dose interferon alfa is used for adjuvant treatment of high risk melanoma, or observation for those intolerant to or unwilling to undergo interferon alpha therapy. PAG noted that the comparator in the CA209-238 trial was ipilimumab and that ipilimumab is not publicly funded in any province for adjuvant treatment. PAG is seeking information on data comparing nivolumab with interferon alfa.

4.2 Eligible Population

The funding request is for adjuvant treatment of patients with completely resected stage III and IV melanoma and the CA209-238 trial is for patients who were undergoing complete resection of stage IIIB, IIIC, or IV melanoma.

PAG is seeking clarity on whether patients with BRAF mutation positive disease who are receiving or have been treated with dabrafenib plus trametinib in the adjuvant setting, would be eligible for treatment with nivolumab. PAG is also seeking confirmation that nivolumab would be limited to patients with cutaneous melanoma (e.g., not ocular melanoma).

PAG is seeking guidance for use of adjuvant nivolumab for patients who would have been eligible at the time of diagnosis, but who are currently being treated with interferon alfa or on observation. PAG is seeking guidance on, if recommended these patients transition to nivolumab therapy, what would be considered a maximum time frame since surgical resection to initiate nivolumab.

PAG noted that there is potential for indication creep to use nivolumab in earlier stages (e.g., stage IIIA and earlier). PAG noted that treatment of high risk stage II or earlier melanoma would be out of scope of this review. However, PAG wanted to note that adjuvant interferon alfa is sometimes offered to resected stage IIC patients with T4 lesions (high risk node negative) who are fit and motivated for treatment.

4.3 Implementation Factors

The funding request is for a dose of 3 mg/kg administered IV over 60 minutes every 2 weeks. PAG noted there are new product monograph changes regarding dosing and infusion times. PAG is seeking clarity on dosing, specifically the appropriate dosing interval (i.e., every 2 weeks or 4 weeks), weight-based dosing (i.e., 3 mg/kg or 6 mg/kg), weight-based dosing up to a cap (i.e., 240 mg every 2 weeks or 480 mg every 4 weeks), or flat dosing (i.e., 240 mg every 2 weeks or 480 mg every 4 weeks). It would be an enabler to implementation to align the dosing of nivolumab used for other indications with a weight-based dosing up to a cap. In addition, clarification for use of the faster infusion time of 30 minutes would also be an enabler to implementation.

PAG noted some patients may interrupt treatment with nivolumab due to toxicity or other reasons. PAG is seeking guidance on the appropriateness of re-initiation with nivolumab after toxicity resolution or treatment interruption for other reasons and if this occurs, clarification on the total duration of therapy.

PAG identified that additional resources may be required to monitor and treat immune mediated reactions but noted that cancer clinics already have experience with nivolumab. PAG noted that additional clinic visits and chemotherapy visits throughout the 1 year may be required in this patient population to deliver adjuvant nivolumab therapy, as interferon alpha is not well tolerated, and based on experience, many patients do not complete 1 year of interferon therapy and some patients decline interferon therapy.

4.4 Sequencing and Priority of Treatments

PAG is seeking guidance on the appropriate treatment options in the metastatic setting. For patients who have received nivolumab in the adjuvant setting and then develop metastatic disease,

- What would be the first line treatment options in the metastatic setting? Currently, ipilimumab, nivolumab and pembrolizumab are funded for first line treatment and BRAF targeted therapies are available for BRAF mutation positive disease. Nivolumab plus ipilimumab combination therapy is not yet funded at the time of this PAG input, but should also be considered as a potential option.
- What would be an appropriate timeframe from completion of adjuvant nivolumab therapy and initiation of immunotherapy options for metastatic disease? Would single agent nivolumab or pembrolizumab immunotherapy be viewed differently than combination ipilimumab and nivolumab?
- Patients in the trial were BRAF mutation positive or negative. PAG noted that adjuvant treatment with dabrafenib and trametinib may be available. What would be the best treatment for BRAF mutation positive patients in the adjuvant setting?

4.5 Companion Diagnostic Testing

None identified.

4.6 Additional Information

None provided.

5 SUMMARY OF REGISTERED CLINICIAN INPUT

Two clinician inputs were provided: one from an individual oncologist and one from a group of five oncologists associated with Cancer Care Ontario (CCO).

In summary, there is a significant unmet need for treatment of melanoma, as the currently available treatment options for adjuvant treatment of melanoma is limited to high-dose interferon (IFN), which provides a small benefit alongside significant toxicity. The authors of the clinician inputs believe that the patient population eligible for funding is appropriate and meets the needs of clinical practice; however, it was noted that the clinical trial under review did not address all of the patients that the manufacturer is requesting funding for. It was also noted that this treatment is very important for patients who are stage III or higher, having undergone resection, to avoid a palliative situation. It is believed that nivolumab would replace the currently available treatment of IFN and not have an impact on treatment options for metastatic disease. Please see below for additional details from the clinician inputs.

5.1 Current Treatment(s) for this Type of Cancer

Both of the clinician input documents highlighted that the only currently available funded adjuvant treatment option for patients with resected high risk stage II and stage III melanoma, as well as resected stage IV melanoma, is high-dose IFN. According to clinicians, the high-dose IFN has little benefit for survival or disease metastasis but with significant toxicities including fever, flu-like symptoms, myelosuppression, liver toxicity and depression, which is presumably why it is rarely used globally. The overall survival benefit of high dose-IFN was not seen and further confirmatory studies were negative. As a result, most Stage IIc-IIIc patients tend to choose observation instead of treatment with high dose-IFN, even with the risk of relapse ranging from 40-60%. Clinical trials may be option instead, for some patients.

One of the clinician inputs also noted an option that is specifically for patients with the melanoma BRAF V600 mutation (about 40% of patients) but is not yet funded in Canada: oral combined targeted therapy with dabrafenib-trametinib combination. The clinician input stated that this treatment has proven adjuvant benefit, but also has potential for a different set of acute toxicities that may potentially be more challenging.

5.2 Eligible Patient Population

The CCO group verified that the patient population in the request for funding of nivolumab met the needs of the clinical practice setting, but noted that only patients who were stage IIIb and higher, based on the AJCC 7th edition staging system, were included in the clinical trial. They indicated that prescribing nivolumab to patients with histologically confirmed melanoma and metastases to regional lymph nodes or surgically resected distant metastases was appropriate. Further, they noted that complete dissection should not be a requirement to receive treatment with nivolumab citing an article by Faries, MB et al.[29] The second input from an individual oncologist noted that, considering that the risk of metastatic relapse is higher for stage IIc patients than for stage IIIa patients, there exists a strong possibility of indication creep to include the higher risk group, such as patients with stage IIc disease. This oncologist also indicated that patients with pre-existing autoimmune conditions may not be denied immunotherapies at present.

5.3 Relevance to Clinical Practice

Both of the clinician inputs conveyed that the adjuvant treatment with nivolumab is very important and should be used in patients who are stage III, or resected stage IV, as unresectable stage IV melanoma is a palliative situation and progression to stage IV disease should be avoided.

With current options including observation or adjuvant IFN, which has minimal benefit, there is a high unmet need for the treatment of melanoma. Compared to high-dose IFN, nivolumab has more favorable efficacy and safety profile for the target population. The input from the CCO oncologists provided additional detail about the relevance of nivolumab to clinical practice, suggesting that it is "currently the superior benchmark treatment today" for patients without the BRAF V600 mutation; however a comparison of nivolumab to oral dabrfenib-trametinib combination for the BRAF V600 mutation positive patients is not currently available.

5.4 Sequencing and Priority of Treatments with New Drug Under Review

According to the group of CCO oncologists, nivolumab would replace the currently available treatment of IFN or observation alone. Both set of inputs from clinician groups relayed that treatment with adjuvant therapy should not have an impact on the treatment options for metastatic disease, with one group elaborating to say that restrictions to the medication may affect the funding decision.

According to the individual oncologist input, relapsing while taking nivolumab should not exclude patients from taking the following systemic treatments for metastatic disease: oral targeted therapy for V600 mutations, pembrolizumab, or combination of ipilimumab+nivolumab. Further, the current data does not suggest that any of the therapeutic options after adjuvant treatment with nivolumab should be withheld.

5.5 Companion Diagnostic Testing

The CCO group input suggested that all patients should be eligible for treatment with nivolumab, regardless of PD-L1 status. The individual oncologist stated that nivolumab would be applicable to all melanoma patients at the appropriate disease stage.

5.6 Additional Information

None.

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the efficacy and safety of nivolumab for the adjuvant treatment of patients with completely resected advanced stage melanoma.

Supplemental Question: critical appraisal of manufacturer submitted indirect treatment comparisons providing evidence for the efficacy and safety of nivolumab compared to other therapies as adjuvant therapy for adult patients with resected advanced melanoma.

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the CGP and the pCODR Methods Team. Studies were chosen for inclusion in the review based on the criteria in the table below. Outcomes considered most relevant to patients, based on input from patient advocacy groups are those in bold. The literature search strategy and detailed methodology used by the pCODR Methods Team are provided in Appendix A.

[Table 3]. Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Published or unpublished RCTs In the absence of RCT data, fully published clinical trials investigating the safety and efficacy of nivolumab should be included.	Patients with completely resected stage III and IV melanoma. Subgroups: • Stage of disease (III vs. IV) • ECOG PS (0-1 vs. ≥2) • BRAF status • No brain metastases vs. resected brain metastases	Nivolumab monotherapy, 3 mg/kg administered as an IV infusion every 2 weeks.	CTLA-4 inhibitor • Ipilimumab** PD-1 inhibitor • Pembrolizumab** BRAF and MEK inhibitors • Dabrafenib + trametinib ** Interferon alfa Observation	Efficacy • **OS** • **PFS/RFS** • **HRQoL** • Time to progression Safety • **AEs** • Grade 3 or 4 AEs • SAEs • WDAEs • Immune-related AEs • Immunosuppressant used • Dose adjustment, interruption and/or discontinuation • Time to discontinuation • Surgery for colitis

AE = adverse event; **BRAF** = proto-oncogene B-Raf; **CTLA-4 =** cytotoxic T-lymphocyte-associated protein 4; **ECOG PS** = Eastern Cooperative Oncology Group Performance Status; **HRQoL** = Health related quality of life; **IV =** intravenous**; MEK** = mitogen-activated protein kinase kinase; **OS** = overall survival; **PD-1** = programmed cell death 1; **PFS** = progression-free survival; **RCT =** randomized controlled trial; **RFS** = recurrence-free survival; **SAE** = serious adverse event; **WDAE** = withdrawal due to adverse event.

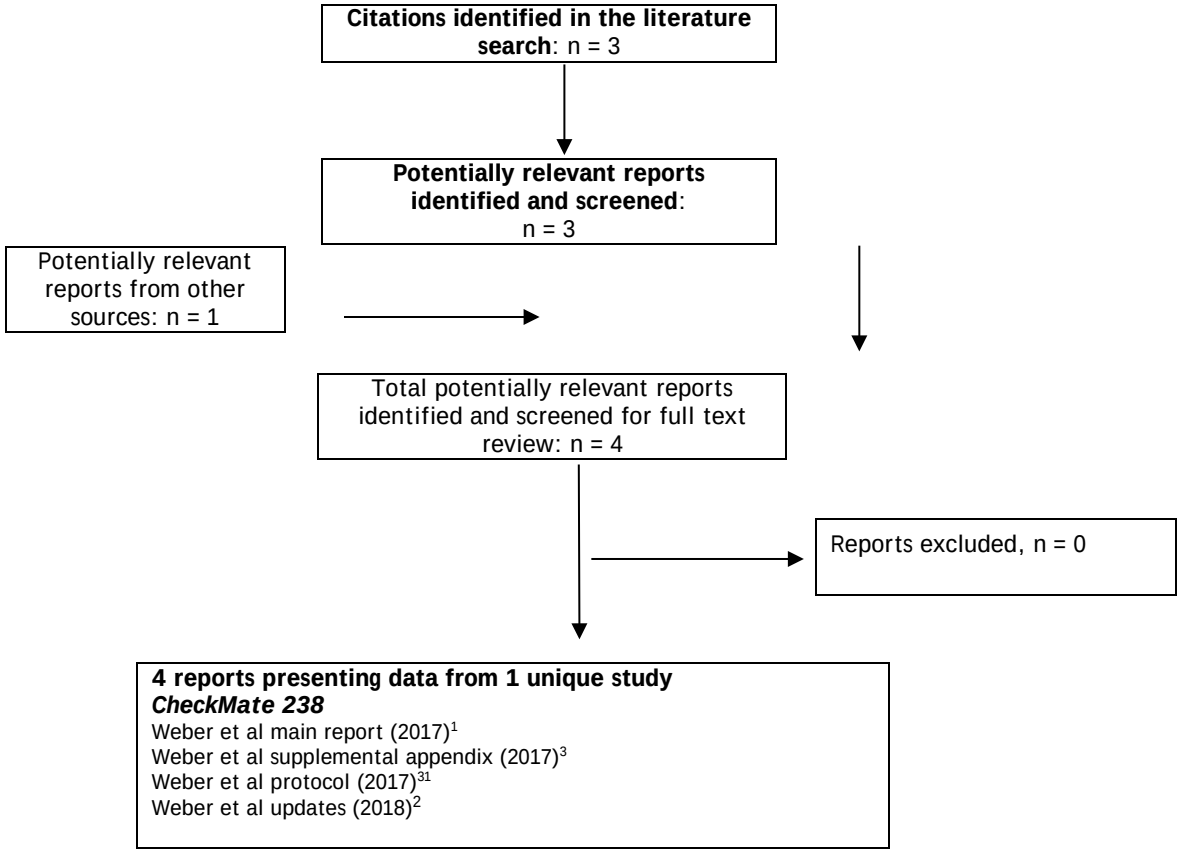
Notes:
Outcomes that were considered important by the patients groups are bold
** Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions)*
*** Identified as agent of interest although not currently reimbursed for this indication in Canada*

6.3 Results

6.3.1 Literature Search Results

Of the three potentially relevant reports identified, one double-blind, phase III randomized controlled trial (RCT) (CheckMate 238), reported in four citations[2,3,30,31] were included in the pCODR systematic review and no studies were excluded. [1-3,31]

Figure 1. PRISMA Flow Diagram for Inclusion and Exclusion of studies



Note: Additional data related to CheckMate 238 were also obtained through manufacturer's submission[2] and requests to the Submitter by pCODR[32]

6.3.2 Summary of Included Studies

The pCODR systematic review identified one RCT that assessed the efficacy and safety of nivolumab for the adjuvant treatment of patients with completely resected advanced stage melanoma.

6.3.2.1 Detailed Trial Characteristics

[Table 4]: Summary of Trial Characteristics of CheckMate 238

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
CheckMate 238 **Other identifiers:** NCT 02388906 Eudra-CT 2014-002351-26 **Characteristics:** Randomized, double-blind, phase III RCT **Sample size:** 906 **Locations:** 130 centres in Australia, Europe, Asia and North America **Patient Enrolment Dates:** March 2015 to November 2015 **Interim Analysis Data cut-off:** May 2017 **Final Analysis Date:** July 2020 (clinical trials.gov) **Sponsor:** BMS	Key Inclusion Criteria: • Patient's ≥ 15 years old except where local regulations and/or institutional policies do not allow for subjects < 18 years of age (pediatric population) to participate. For those sites, the eligible subject population is ≥ 18 years of age. • Completely regional lymphadenectomy or resection within 12 weeks before randomization • Stage IIIb/c or Stage IV before complete regional lymphadenectomy or resection • No previous anti-cancer treatment • ECOG PS of 0 or 1 • Resected brain metastases Key Exclusion Criteria: • Ocular or uveal melanoma • Active, known or suspected autoimmune disease • History of carcinomatosis meningitis • ECOG PS of ≥ 2 • Systemic use of corticosteroids or other immunosuppressive medications < 14 days of randomization • Previous anti-cancer treatment • Treatment directed against the resected melanoma that is administrated after the surgery • previous nonmelanoma cancer without complete remission for more than 3 years	**Intervention:** Nivolumab **Comparator**: Ipilimumab	**Primary:** -RFS **Secondary:** -OS -Safety -RFS based on PD-L1 -HRQoL **Exploratory** -DMFS

DMFS = Distance metastasis-free survival; ECOG PS = Eastern Cooperative Oncology Group performance status; HRQoL = health-related quality of life; OS = Overall Survival; RCT = Randomized controlled trial; RFS = Recurrence-free survival; PD-L1: programmed cell death ligand 1.
Data sources: Weber 2017,[1] Weber 2017 protocol[31]

[Table 5]: Select quality characteristics of CheckMate 238

Study	Treatment vs. Comparator	Primary outcome	Required sample size	Sample size	Randomization method	Allocation concealment	Blinding	ITT Analysis	Final analysis	Early termination	Ethics Approval
CheckMate 238	Nivolumab vs. Ipilimumab	RFS	800	906	Yes [a]	Yes [b]	Yes [c]	Yes	No [d]	No	Yes

ITT = intention-to-treat; **PFS** = Progression-free survival; **OS** = overall survival; **IVRS** = an interactive voice response system; **ORR** = objective response rate.

a: The article indicated that patients were randomized centrally via an Interactive Voice Response System.
b: Details not provided.
c: Study participants, healthcare provider, investigators and outcome assessors were blinded to the treatment assignment until progression of disease or treatment discontinuation.
d: The data cutoff of May 15, 2017 represents a minimum follow-up of 18 months. This was the time of interim analysis. The date of final analysis was not available at the time of the published article.

a) *Trials*

One RCT (CheckMate 238) met the inclusion criteria for this pCODR systematic review. The characteristics of the trial design are presented in Table 4.

CheckMate 238 was a double-blind, multicentre, phase III RCT that assessed the efficacy and safety of nivolumab versus ipilimumab in patients with resected stage III and IV melanoma.[1] In total, 906 patients from 130 centres in 25 countries, including Australia, Europe, Asia and North American, were enrolled. Two Canadian centres participated in the trial.

Patients were accrued between March 30, 2015 and November 30, 2015. The trial included patients aged 15 years and older with histologically confirmed but resected stage IIIB, IIIC or IV melanoma. Cancer stage was determined according to the 2009 classification of the American Joint Committee on Cancer (AJCC), seventh edition. Complete regional lymphadenectomy or resection was required within 12 weeks before randomization. Patients with resected brain metastases were eligible to participate in the trial. Patients were required have a programmed death ligand 1 (PD-L1) expression classification (positive/negative/indeterminate) as determined by a central lab. In addition, patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Patients were excluded from study enrolment if they had ocular or uveal melanoma, had active/known/suspected autoimmune disease, had previous nonmelanoma cancer without complete remission for more than three years, had systemic use of glucocorticoids or other immunosuppressive medications less than 14 days prior to randomization, or previous systemic therapy for melanoma.

Eligible patients were centrally randomized (1:1) by the trial sponsor, Bristol-Myers Squibb to receive nivolumab or ipilimumab, via an Interactive Voice Response System (IVRS). Randomization was stratified by cancer status (stage IIIB or IIIC, stage IV M1a or M1b, or stage IV M1c) according to the AJCC criteria and centrally tested tumour PD-L1 status (negative or indeterminate versus positive).[1,31] Study participants, healthcare provider, investigators and outcome assessors were blinded from the treatment allocation. Upon recurrence of disease and treatment discontinuation of each study participant, investigators could be unblinded to the participant's treatment assignment via IVRS to inform the appropriate subsequent

treatment, however the Sponsor's central protocol team (including but not limited to clinical, statistics, data management) will remain blinded to treatment assignment.[31]

In CheckMate 238, the primary outcome measure was recurrence-free survival (RFS), which was defined as the time from randomization until the date of the first recurrence (local, regional or distant metastasis), new primary melanoma, or death from any cause. The occurrence of 450 events of RFS was needed to provide 85% power to detect a hazard ratio (HR) of 0.75 for disease recurrence or death, using a significance alpha level of 0.05 (two-sided) for a minimum of 36 months follow-up period. An interim analysis was planned after all participants had a minimum of 18 months of follow-up. At the time of the interim analysis, 350 RFS events were anticipated, while 360 (80%) had actually occurred. The critical HR was 0.78 (350 anticipated events out of 450 planned events at 18-month follow-up, approximately 78% information fraction). The primary RFS analyses were conducted using a two-sided log-rank test stratified by PD-L1 status and disease stage at baseline in all randomised study participants. The HR for having an RFS event in the nivolumab arm compared with the ipilimumab group and the corresponding 97.56% CIs (using an adjusted alpha of 0.0244 at 18-month follow-up; a rationale of using alpha = 0.0244 at this particular time point was not provided) were calculated using a Cox proportional hazards model stratified by AJCC disease stage and PD-L1 status at baseline. Median time to RFS distributions along with 95% CIs were estimated using the Kaplan-Meier method. The stopping boundary was derived on the basis of the 360 events. Multiplicity was controlled for in the primary analysis of RFS in the interim analysis - a hierarchical approach to testing the hypotheses that nivolumab and ipilimumab differ with respect to RFS and overall survival (OS), respectively, was adopted. Following a positive test of RFS (overall significance level of 0.05), the main secondary endpoint (OS) was tested (overall significance level of 0.05). No multiplicity adjustment for other secondary analyses was made. Subgroup analyses for RFS based on AJCC cancer stage and PD-L1 were performed; however, multiplicity was not adjusted for in the subgroup analyses.[31]

Secondary efficacy outcomes included overall survival, safety and side-effect profiles, RFS according to tumor PD-L1 expression and health-related quality of life (HRQoL). Adverse events were evaluated according to the Common Terminology Criteria for Adverse Events, version 4.0. Selected adverse events with a potential immunologic cause were analyzed according to organ category.[3] HRQoL was assessed using the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 Questionnaire and the European Quality of Life-5 Dimensions (EQ-5D). The final RFS analysis will be performed after all patients have a minimum of 36 months of follow-up.

The main analyses of the efficacy endpoints were conducted in the intention-to-treat population, which consisted of all the patients who had undergone randomization. Safety analysis was conducted in all the patients who had received at least one dose of the study drug, between the receipt of the first dose and 30 days after the last dose of that drug.

The patients were assessed for recurrence every 12 weeks for the first two years after randomization and every six months thereafter until the end of Year 5. The assessments included physical examination, imaging examination of the chest, abdomen, pelvis, and brain. Recurrent lesions were histologically confirmed.

As of the data cutoff in May 2017, the minimum follow-up was 18 months (median 19.5 months) for all the study participants, and all 905 treated patients were no longer receiving the study drug. An interim analysis on Overall Survival (OS) will be conducted at the time of the final RFS analysis. This comparison of OS will allow for early stopping for superiority. The stopping boundaries at the interim and final analyses will be derived based on the exact number of deaths using a Lan-DeMets alpha spending function with O'Brien-Fleming

boundaries. The final OS analysis will take place after all patients have a minimum of 48 months of follow-up, which will take place approximately 56 months from the start of the study. At the time of the final OS analysis, 302 deaths are expected.[31]

The trial was sponsored by Bristol-Myers Squibb (BMS) and Ono Pharmaceutical. BMS was involved in trial design, data collection, data analysis and report writing. An independent data and safety monitoring committee oversaw the safety and efficacy of the study drugs, as well as the conduct of the trial.

b) ***Populations***

A total of 906 patients with resected stage IIIB, IIIC or IV melanoma were included in the study. Patients were randomized to receive either nivolumab (N = 453) or ipilimumab (N = 453). Baseline characteristics are presented in Table 6. Patient characteristics were generally balanced between the two treatment groups.

The majority of patients were male and had a stage III disease.[1] ECOG performance status of 0 and 1 was reported in 90.3% and 9.7% of the study participants at baseline, respectively.[32]

Table 6: Baseline characteristics of patients enrolled in CheckMate 238, ITT population

Characteristic	Nivolumab (N=453)	Ipilimumab (N=453)
Sex — no. (%)		
Male	258 (57.0)	269 (59.4)
Female	195 (43.0)	184 (40.6)
Median age (range) — yr	56 (19–83)	54 (18–86)
Disease stage — no. (%)		
IIIB	163 (36.0)	148 (32.7)
IIIC	204 (45.0)	218 (48.1)
IV	82 (18.1)	87 (19.2)
Other or not reported	4 (1.0)	0
Type of lymph-node involvement in stage III — no./total no. (%)		
Microscopic	125/369 (33.9)	134/366 (36.6)
Macroscopic	219/369 (59.3)	214/366 (58.5)
Not reported	25/369 (6.8)	18/366 (4.9)
Tumor ulceration in stage III — no./total no. (%)		
Yes	153/369 (41.5)	135/366 (36.9)
No	201/369 (54.5)	216/366 (59.0)
Not reported	15/369 (4.1)	15/366 (4.1)
Metastasis status in stage IV — no./total no. (%)		
M1a	50/82 (61.0)	51/87 (58.6)
M1b	12/82 (14.6)	15/87 (17.2)
M1c	20/82 (24.4)	21/87 (24.1)
Tumor PD-L1 expression — no. (%)		
<5%	275 (60.7)	286 (63.1)
≥5%	152 (33.6)	154 (34.0)
Could not be determined or not reported	26 (5.7)	13 (2.9)
BRAF status — no. (%)		
Mutation	187 (41.3)	194 (42.8)
No mutation	197 (43.5)	214 (47.2)
Not reported	69 (15.2)	45 (9.9)

* Percentages may not total 100 because of rounding. PD-L1 denotes programmed death ligand 1.

Source: Weber 2017[1]

a) *Interventions*

In this trial, patients were randomized (1:1) in a double-blind fashion to receive either nivolumab or ipilimumab.

Patients randomized to the nivolumab arm were given a 3 mg/kg dose of nivolumab intravenously every two weeks, along with placebo matching ipilimumab. In contrast, patients randomized to the ipilimumab arm were given a 10 mg/kg dose of ipilimumab intravenously every three weeks for four doses, and then every 12 weeks along with placebo matching

nivolumab. Both treatments continued for up to one year or until documented disease recurrence, unacceptable toxic events or withdrawal of consent. Dose delays or dose reductions were not permitted for both treatment arms, according to the study protocol.[31,33]

Subsequent anticancer therapy for study participants in CheckMate 238 included radiotherapy, surgery and systemic therapy (Table 7). In total, 28.5% of patients on the nivolumab arm and 37.7% on ipilimumab received subsequent anti-cancer therapy.[3] For patients originally randomized to the nivolumab arm, some of them switched to ipilimumab (7.7%) or pembrolizumab (2.2%), BRAF inhibitor (9.1%) or MEK inhibitor (6.8%); on the contrary, some patients originally in the ipilimumab arm switched to nivolumab (9.5%), pembrolizumab (13.9%), BRAF inhibitor (8.8%) or MEK inhibitor (8.8%).

Table 7: Subsequent Anti-Cancer Therapy in CheckMate 238, ITT population

Treatment	Nivolumab (N = 453)	Ipilimumab (N = 453)
	number of patients (percent)	
Any	129 (28.5)	171 (37.7)
Surgery†	69 (15.2)	64 (14.1)
Radiotherapy	24 (5.3)	26 (5.7)
Systemic therapy	90 (19.9)	136 (30.0)
Chemotherapy	25 (5.5)	24 (5.3)
Immunotherapy	50 (11.0)	104 (23.0)
Anti-PD-1 agent	1 (0.2)	2 (0.4)
Nivolumab	17 (3.8)	43 (9.5)
Pembrolizumab	10 (2.2)	63 (13.9)
CTLA-4 inhibitor	1 (0.2)	1 (0.2)
Ipilimumab	35 (7.7)	15 (3.3)
Ipilimumab/nivolumab combination	3 (0.7)	1 (0.2)
BRAF inhibitor	41 (9.1)	40 (8.8)
MEK inhibitor	31 (6.8)	40 (8.8)
BRAK/MEK combination	3 (0.7)	1 (0.2)
Other (experimental agents)	9 (2.0)	8 (1.8)
Unassigned	2 (0.4)	4 (0.9)

*Patients may have received more than one type of postprotocol therapy, and more than one agent within each type. All percentages are based on total number of patients in each arm. CTLA-4 denotes cytotoxic T-lymphocyte antigen 4; PD-1 programmed death 1.
†Includes tumor resection for diagnostic purposes and biopsies.

Source: Weber 2017 Supplementary Appendix[3]

Treatment interruption was not reported in this study.

b) *Patient Disposition*

For this review, the reported patient disposition of CheckMate 238 was obtained from the May 15, 2017 data cutoff (Table 8), when the minimum follow-up was 18 months (median 19.5 months). In total, 1264 patients were screened for enrollment and 906 patients were randomized on a 1:1 ratio to receive nivolumab (N = 453) or ipilimumab (N = 453). One patient randomized to nivolumab did not receive the assigned treatment.[1,3]

During the treatment phase, fewer patients in the nivolumab group discontinued treatment as compared to the ipilimumab group (39.1% versus 73.1%, respectively). The primary reasons for discontinuation in the nivolumab arm were disease recurrence (26.7%) and drug toxicity (9.1%). In contrast, the primary reasons for discontinuation in the ipilimumab arm were drug toxicity (45.9%) and disease recurrence (22.3%). Finally, 86.8% of patients in the nivolumab group and 83.7% in the ipilimumab group remained on the study at the time of interim analysis (Table 8).[1]

Table 8: Summary of patient disposition in CheckMate 238 at the data cutoff of May 15, 2017

	Nivolumab	Ipilimumab
Randomized	**453**	**453**
Treated, n (%)	452 (99.8)	453 (100)
Not treated, n (%)	1 (0.2)	0
Completed treatment period, n (%)	275 (60.7)	122 (26.9)
Discontinued treatment, n (%)	177 (39.1)	331 (73.1)
Disease recurrence, n (%)	121 (26.7)	101 (22.3)
Drug toxicity, n (%)	41 (9.1)	208 (45.9)
Adverse events unrelated to study drug, n (%)	5 (1.1)	5 (1.1)
Patient request, n (%)	5 (1.1)	9 (2.0)
Withdrawal of consent, n (%)	2 (0.4)	3 (0.7)
Poor/non-compliance, n (%)	0	1 (0.2)
Patient no longer met study criteria, n (%)	0	1 (0.2)
Other, n (%)	3 (0.7)	3 (0.7)
Patients remained on the study, n (%)		
Continued study	393 (86.8)	379 (83.7)
Discontinued study	59 (13.0)	74 (16.3)
Data source: Weber 2017 supplementary appendix[3]		

c) *Limitations/Sources of Bias*

- Multiple comparisons were not adjusted for in subgroup analyses. Therefore there is a risk of inflated type 1 error.
- Overall survival was immature at the time of interim analysis. Although this estimate was immature, it is most likely confounded because patients who progressed could start a subsequent anti-cancer therapy or those randomized to nivolumab could cross over and receive ipilimumab. Furthermore, overall survival was a secondary outcome and it may not be powered to detect an effect.
- At Week 49, HRQoL data were unavailable for substantial proportion of study participants in the two treatment groups (approximately 62% in the nivolumab group and 28% in the ipilimumab group were available for HRQoL assessment, and 53% and 23% respectively completed the questionnaires). The quality of life in patients who did not complete the HRQoL assessment was unknown. Furthermore, except for global quality of life in EORTC QLQ-C30, there were no data provided on any of the functional or symptom subscales of this questionnaire; thus the reviewers were not able to assess the changes in these subscales.
- Study participants were required to have an ECOG performance status score of 0 or 1 at study entry, and approximately 90% of them had a performance status of 1. The generalizability of the study results to a broader patient population may be limited.

- There is still a lack of direct evidence comparing nivolumab to other active treatment, such as pembrolizumab, or BRAF inhibitor + MEK inhibitor.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

Efficacy Outcomes

Overall Survival (OS)

This was a secondary efficacy outcome in CheckMate 238. OS was not mature at the time of interim analysis.

Recurrence-Free Survival (RFS)

RFS was a primary efficacy outcome in CheckMate 238. The analysis of RFS was conducted in the ITT population. The data cutoff date for the interim RFS analysis was on May 15, 2017. At this time point, the median RFS had not been reached in either treatment group.

At 12 months, the rates of RFS were 70.5% (95% CI 66.1% to 74.5%) for patients on nivolumab and 60.8% (95% CI 56.0% to 65.2%) for those on ipilimumab. At 18 months, the rates of RFS were 66.4% (95% CI 61.8% to 70.6%) for nivolumab and 52.7% (95% CI 47.8% to 57.4%) for ipilimumab. Adjuvant therapy with nivolumab was associated with a prolonged RFS as compared to ipilimumab in patients with resected stage III or IV melanoma (HR: 0.65; 97.56% CI 0.51 to 0.83; P < 0.001).[1] Results of RFS at 24 months were reported in an update of CheckMate 238.[2] The median (95% CI) of RFS was 30.8 (30.8, not reached) months for nivolumab and 24.1 (16.6, not reached) months for ipilimumab (HR: 0.66; 95% CI 0.54 to 0.81; P < 0.0001) (Table 9; Figure 2). The median RFS of 30.8 months in the nivolumab group was considered not reliable or stable by the investigators due to few patients at risk.

Study findings of subgroup analyses of RFS based on disease stage were consistent with the primary analyses (Table 9), higher RFS rates were observed for patients in the nivolumab group compared with those in the ipilimumab group at 12 months, 18 months and 24 months. Multiple comparisons were not adjusted for in the subgroup analyses. Subgroup analysis may not have sufficient power to detect a statistically significant between-group difference.

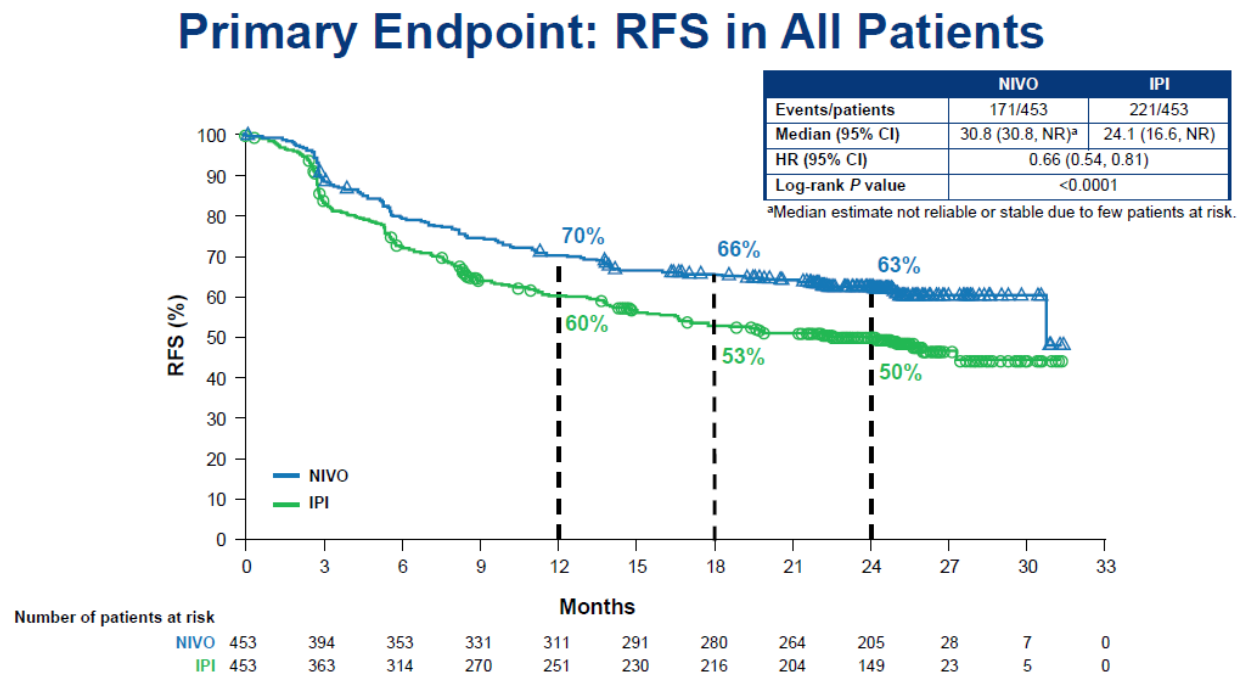
Table 9. Rates of Recurrence-Free Survival in CheckMate 238, ITT population and Subgroups

	Nivolumab (N=453)	Ipilimumab (N=453)
ITT population		
12 months, % (95% CI)	70.5 (66.1-74.5)	60.8 (56.0-65.2)
18 months, % (95% CI)	66.4 (61.8-70.6)	52.7 (47.8-57.4)
24 months, % (95% CI)	63 (NR)	50 (NR)
Median RFS, months (95% CI)	30.8[a] (30.8, not reached)	24.1 (16.6, not reached)
HR (95% CI)	0.66 (0.54-0.81), p < 0.0001 at 24 months	
Subgroup of Disease Stage: Stage IIIB or IIIC		
12 months, % (95% CI)	72.3 (67.4-76.7)	61.6 (56.3-66.5)
18 months, % (95% CI)	67 (NR)	55 (NR)
24 months, % (95% CI)	64 (NR)	52 (NR)
Median RFS, months (95% CI)	not reached	25.5 (16.6, not reached)
HR (95% CI)	0.68 (0.54-0.85), p NR	
Subgroup of Disease Stage: Stage IV		
12 months, % (95% CI)	63.0 (51.6-72.5)	57.5 (46.0-67.4)

18 months, % (95% CI)	61 (NR)	47 (NR)
24 months, % (95% CI)	58 (NR)	44 (NR)
Median RFS, months (95% CI)	30.8 [a] (15.9, not reached)	15.4 (8.5, not reached)
HR (95% CI)	0.68 (0.44-1.06), p NR	

CI = confidence interval; **HR** = hazard ratio; **ITT** = intention-to-treat; **NR** = not reported; **RFS** = recurrence-free survival.
[a] The median RFS of 30.8 months in the nivolumab group was considered not reliable or stable by the investigators due to few patients at risk.
Data source: Weber 2017[1], Weber 2018 updates[2]

Figure 2. Recurrence-Free Survival in CheckMate 238, Kaplan-Meier estimates



Data source: Weber 2018 updates[2]

Distant metastasis-free survival (DMFS)

This was an exploratory outcome measure in CheckMate 238. DMFS was evaluated in patients who were stage IIIb or stage IIIc at study entry. The median DMFS was not reached in either treatment group at 24 months. But longer distant metastasis-free survival was observed in the nivolumab group compared to the ipilimumab group.

Table 10. Rates of Distant Metastasis-Free Survival in CheckMate 238, patients with Stage III melanoma

	Nivolumab (N=370)	Ipilimumab (N=366)
12 months, % (95% CI)	80.2 (75.6-83.9)	73.4 (68.4-77.7)
18 months, % (95% CI)	75 (NR)	67 (NR)
24 months, % (95% CI)	71 (NR)	64 (NR)
Median DMFS, months (95% CI)	not reached	not reached
HR (95% CI)	0.76 (0.59-0.98), p = 0.034	

CI = confidence interval; DMFS = distant metastasis free survival; HR = hazard ratio; NR = not reported.
Data source: Weber 2017[1], Weber 2018 updates[2]

Health-related Quality of Life (HRQoL)

HRQoL was measured using the European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire – Core 30 (EORTC QLQ-C30) Global Health status, European Quality of Life-5 Dimensions (EQ-5D) utility index, and EQ-5D visual analogue scale (VAS). The EORTC QLQ-C30 comprises five functional scales (physical functioning, cognitive functioning, emotional functioning, social functioning and global quality of life), nine symptom scales (fatigue, pain, nausea/vomiting, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties) and a global health/quality of life scale. Raw scores for the EORTC QLQ-C30 are transformed to scores ranging from 0 to 100 such that higher scores for all functional scales and Global Health Status indicate better HRQoL, and an increase from baseline indicates improvement in HRQoL compared to baseline. Lower scores for symptom scales indicate better HRQoL, and a decline from baseline for symptom scales indicates improvement in symptoms compared to baseline.[34] A difference of 10 points on a 100 point scale between the two treatment arms is considered clinically significant.[35] The submitter only provided data for global quality of life for EORTC QLQ-C30 and no data were available on any of the functional or symptom scales.

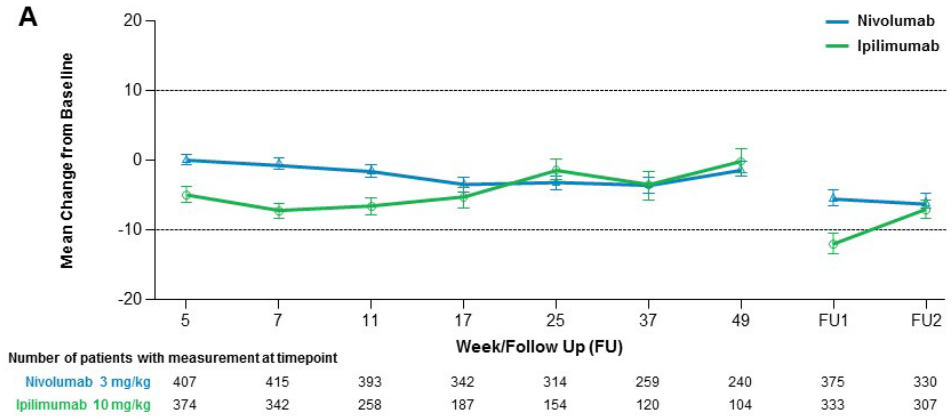
Overall, for patients who completed the questionnaires at Week 49 of the study, the HRQoL scores remained close to baseline values in the two treatment groups (Table 11).[3,32] There were no clinically meaningful changes with respect to the scores observed on any of the HRQoL instruments.

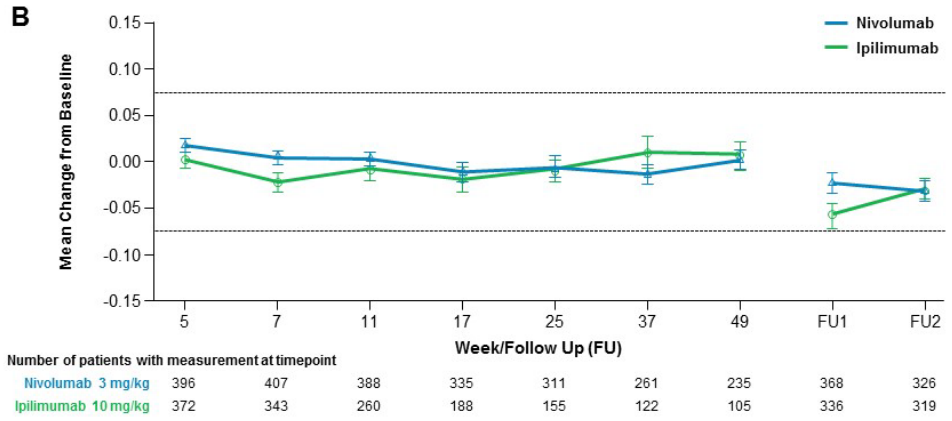
Table 11: Results of Health-Related Quality of Life in CheckMate 238 (number of patients who filled the questionnaire/number of available patients)

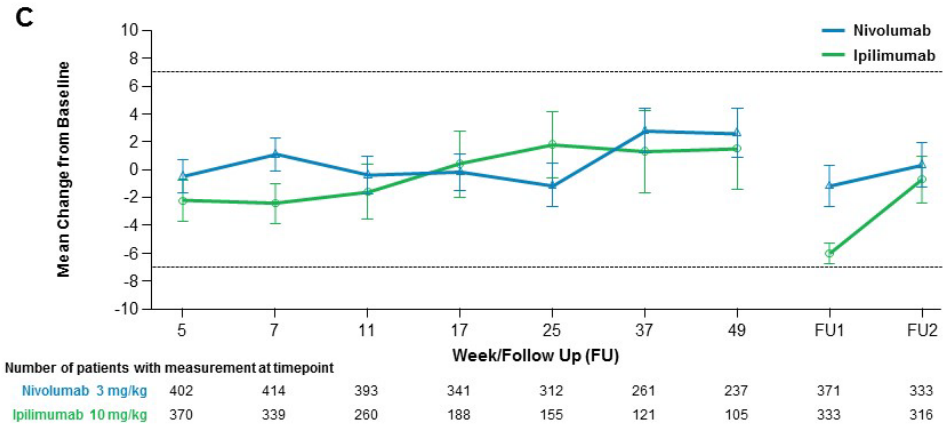
	Nivolumab (N=453)	Ipilimumab (N=453)
EORTC QLQ-C30 global health status summary score, n/N, mean (SD)		
Baseline	443/453 79.74 (17.72)	435/453 78.84 (17.86)
Week 49	243/280 78.55 (18.26)	105/125 79.84 (17.21)
Change from baseline	-1.25 (17.70)	-0.08 (17.28)
EQ-5D health index score, n/N, mean (SD)		
Baseline	436/453 0.856 (0.181)	437/453 0.848 (0.173)
Week 49	240/NR 0.866 (0.167)	106/NR 0.879 (0.131)
Change from baseline	0.003 (0.168)	0.009 (0.168)
EQ-5D VAS score, n/N, mean (SD)		
Baseline	444/453 76.96 (25.42)	439/453 74.80 (26.48)
Week 49	241/280 80.64 (22.15)	107/125 78.72 (22.64)
Change from baseline	2.66 (27.10)	1.53 (29.88)

EORTC = European Organisation for Research and Treatment of Cancer; **EQ-5D** = European Quality of Life-5 Dimensions; **NR** = not reported; **QLQ-C30** = Quality of Life Questionnaire - 30-item core; **SD** = standard deviation; **VAS** = visual analog scale.
Data source: checkpoint meeting[32]

Figure 3. Change in Health-related Quality of Life in CheckMate 238 (A. EORTC QLQ-C30 Global Health Status; B. EQ-5D utility index; C. EQ-5D VAS).







Data source: Weber 2017 Supplementary appendix[3]

Harms Outcomes

Safety outcomes in the CheckMate 238 trial were evaluated in 905 patients who received at least one dose of the study drug, 452 in the nivolumab arm and 453 in the ipilimumab arm. The reported safety data obtained from the May 15, 2017 data cutoff are presented in this section.

Deaths

Two deaths were reported for the ipilimumab group, both occurred more than 100 days after the last dose of ipilimumab. Both cases were considered to be treatment-related.[32]

Adverse Events (AEs)

All grades:

The proportion of patients reporting at least one AE of any cause was similar between the two treatment arms, 96.9% for nivolumab and 98.5% for ipilimumab. The investigators determined whether an AE was related to a study drug (Table 12).

The commonly reported (>10%) AEs of any grades which were considered treatment-related included fatigue (34.5% for nivolumab vs. 32.9% for ipilimumab), diarrhea (24.3% vs. 45.9%), pruritus (23.2% vs. 33.6%), rash (19.9% vs. 29.4%), nausea (15.0% vs. 20.1%), arthralgia (12.6% vs. 10.8%), asthenia (12.6% vs. 11.7%), hypothyroidism (10.8% vs. 6.8%), headache (9.7% vs. 17.4%), abdominal pain (6.4% vs. 10.2%), increased ALT level (6.2% vs. 14.6%), increased AST level (5.5% vs. 13.2%), maculopapular rash (5.3% vs. 11.0%), hypophysitis (1.5% vs. 10.6%), and pyrexia (1.5% vs. 11.9%). Patients treated with nivolumab were less likely to report an AE than those in the ipilimumab group.[3]

Grade 3 or 4:

Patients in the nivolumab group were less likely to report a Grade 3 or 4 AE (25.4%) when compared to those in the ipilimumab group (55.2%).

Serious Adverse Events (SAEs)

The risk of SAEs was lower in the nivolumab group (17.5%) compared with the ipilimumab group (40.4%) (Table 12).

Any Adverse Events leading to Discontinuation

Patients in the nivolumab were less likely to report an AE which led to treatment discontinuation compared to those in the ipilimumab group, 9.7% versus 42.6%, respectively (Table 12).

Immune-related Adverse Events

In general, incidence of selected AEs involving the skin, gastrointestinal tract, liver, and lungs that were deemed to be related to the study drug was lower in the nivolumab group compared with the ipilimumab group (Table 12).

Table 12. Safety Analysis in CheckMate 238, safety population

Event	Nivolumab (N=452)		Ipilimumab (N=453)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients with event (percent)			
Any adverse event	438 (96.9)	115 (25.4)	446 (98.5)	250 (55.2)
Treatment-related adverse event†	385 (85.2)	65 (14.4)	434 (95.8)	208 (45.9)
Fatigue	156 (34.5)	2 (0.4)	149 (32.9)	4 (0.9)
Diarrhea	110 (24.3)	7 (1.5)	208 (45.9)	43 (9.5)
Pruritus	105 (23.2)	0	152 (33.6)	5 (1.1)
Rash	90 (19.9)	5 (1.1)	133 (29.4)	14 (3.1)
Nausea	68 (15.0)	1 (0.2)	91 (20.1)	0
Arthralgia	57 (12.6)	1 (0.2)	49 (10.8)	2 (0.4)
Asthenia	57 (12.6)	1 (0.2)	53 (11.7)	4 (0.9)
Hypothyroidism	49 (10.8)	1 (0.2)	31 (6.8)	2 (0.4)
Headache	44 (9.7)	1 (0.2)	79 (17.4)	7 (1.5)
Abdominal pain	29 (6.4)	0	46 (10.2)	1 (0.2)
Increase in ALT level	28 (6.2)	5 (1.1)	66 (14.6)	26 (5.7)
Increase in AST level	25 (5.5)	2 (0.4)	60 (13.2)	19 (4.2)
Maculopapular rash	24 (5.3)	0	50 (11.0)	9 (2.0)
Hypophysitis	7 (1.5)	2 (0.4)	48 (10.6)	11 (2.4)
Pyrexia	7 (1.5)	0	54 (11.9)	2 (0.4)
Any adverse event leading to discontinuation	44 (9.7)	21 (4.6)	193 (42.6)	140 (30.9)
Treatment-related adverse event leading to discontinuation	35 (7.7)	16 (3.5)	189 (41.7)	136 (30.0)

* The safety population included all the patients who had received at least one dose of a trial drug. Listed are events that were reported between the first dose and 30 days after the last dose. The severity of adverse events was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. ALT denotes alanine aminotransferase, and AST aspartate aminotransferase.
† The investigators determined whether adverse events were related to a trial drug. The events that are listed here were reported in at least 10% of the patients in either treatment group.

Data source: Weber 2017[1]

Table 13. Treatment-related Select Adverse Events

Event	Nivolumab (N = 452)		Ipilimumab (N = 453)	
	Total	Grade 3 or 4	Total	Grade 3 or 4
	number of patients with event (percent)			
Treatment-related select adverse event†				
Skin	201 (44.5)	5 (1.1)	271 (59.8)	27 (6.0)
Pruritus	105 (23.2)	0	152 (33.6)	5 (1.1)
Rash	90 (19.9)	5 (1.1)	133 (29.4)	14 (3.1)
Rash maculopapular	24 (5.3)	0	50 (11.0)	9 (2.0)
Gastrointestinal	114 (25.2)	9 (2.0)	219 (48.3)	76 (16.8)
Diarrhea	110 (24.3)	7 (1.5)	208 (45.9)	43 (9.5)
Colitis	9 (2.0)	3 (0.7)	45 (9.9)	34 (7.5)
Hepatic	41 (9.1)	8 (1.8)	96 (21.2)	49 (10.8)
Increase in alanine aminotransferase	28 (6.2)	5 (1.1)	66 (14.6)	26 (5.7)
Increase in aspartate aminotransferase	25 (5.5)	2 (0.4)	60 (13.2)	19 (4.2)
Pulmonary	6 (1.3)	0	11 (2.4)	4 (0.9)
Renal	6 (1.3)	0	7 (1.5)	0
Hypersensitivity/infusion reaction	11 (2.4)	1 (0.2)	9 (2.0)	0
Endocrine				
Adrenal disorder	6 (1.3)	2 (0.4)	13 (2.9)	4 (0.9)
Diabetes	2 (0.4)	1 (0.2)	1 (0.2)	0
Pituitary disorder	8 (1.8)	2 (0.4)	56 (12.4)	13 (2.9)
Hypophysitis	7 (1.5)	2 (0.4)	48 (10.6)	13 (2.9)
Thyroid disorder	92 (20.4)	3 (0.7)	57 (12.6)	4 (0.9)
Hypothyroidism	49 (10.8)	1 (0.2)	31 (6.8)	2 (0.4)
Hyperthyroidism	36 (8.0)	1 (0.2)	18 (4.0)	1 (0.2)

*The severity of adverse events was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.
†Specific treatment-related select adverse events listed here were reported in at least 5% of the patients in either treatment arm.

Data source: Weber 2017 supplementary appendix[3]

6.4 Ongoing Trials

Table 13: Ongoing trials of nivolumab and ipilimumab in stage III and stage IV resected melanoma

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
Study CA209-915 or NCT03068455 Phase 3, double-blind RCT Estimated enrolment = 2000 participants 123 study locations Study start date: Apr. 7, 2017 Estimated primary completion date: Nov. 8, 2020 Estimated study completion date: Feb. 17, 2023 Funding: BMS	Key Inclusion Criteria: ≥ 12 years; Completely surgically resected stage IIIb/c/d or stage IV melanoma within 12 weeks of participation in study; Must have full activity or, if limited, must be able to walk and carry out activities such as light house work or office work; No prior anti-cancer treatment for melanoma (except surgery for the melanoma lesion(s) and/or except for adjuvant radiation therapy after neurosurgical resection for central nervous system lesions) Key Exclusion Criteria: History of uveal melanoma Patients with active, known or suspected autoimmune disease Prior treatment with interferon (if complete < 6 months prior to participation in study), 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.	Nivolumab Nivolumab + ipilimumab	Primary: -Recurrence-free survival Secondary: -Overall survival -PD-L1 expression
Source: https://clinicaltrials.gov/ct2/show/NCT03068455			

7 SUPPLEMENTAL QUESTIONS

The following supplemental question was identified during development of the review protocol as relevant to the pCODR review of nivolumab as adjuvant therapy in patients with advanced melanoma.

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

7.1 Critical appraisal of the network meta-analysis of nivolumab and other therapies

7.1.1 Objective

The pCODR-conducted literature search identified one RCT that assessed the efficacy and safety of nivolumab versus ipilimumab in patients with completely resected advanced melanoma.[1] Thus there is a lack of direct evidence comparing nivolumab to other PD-L1 inhibitors (i.e. pembrolizumab), targeted therapies (i.e. dabrafenib with trametinib and/or vemurafenib), or routine surveillance (i.e. placebo). Given the sparse evidence from head-to-head trials, the manufacturer conducted a network meta-analysis (NMA).[2,36] In addition, an indirect treatment comparison (ITC) was carried out by the manufacturer to assess the relative clinical benefit as well as HRQoL between nivolumab and placebo.[37,38]

The objective of this section is to summarize and critically appraise the submitted NMA and ITC that provide evidence for the efficacy and safety of nivolumab as adjuvant therapy versus other active therapies or placebo for adult patients with resected advanced stage melanoma.

7.1.2 Findings

7.1.2.1 ***Network Meta-Analysis***[2,36]

Objectives of manufacturer's NMA

The objectives of the manufacturer's NMA were to systematically review RCTs assessing the efficacy and safety of adjuvant treatment for patients with intermediate and high risk non-metastatic melanoma in a Canada-specific setting, and synthesize the study findings by means of network meta-analysis.

Study eligibility and selection process

The Manufacturer conducted a systematic review to identify eligible studies (criteria in Table 14) for the ITC.[36] The manufacturer indicated that the population in the NMA was selected to be consistent with the population in the CheckMate 238 trial.

Table 14: Population, interventions, and study design criteria for inclusion of studies in the NMA[2]

Criteria	Description
Population	Adults aged ≥18 years with • Nonmetastatic stage III melanoma[a] • Nonmetastatic stage IV melanoma
Interventions	Eligible interventions include adjuvant treatment (given after surgery) with 1 of the following[b]: • NIVO • IPI • PEM • DAB+TRAM • All IFNα (including 2a, 2b, pegylated 2a or 2b, and high and low doses)
Comparators	Eligible comparators include • Any treatment listed as an eligible intervention • Placebo • Standard of care • Watchful waiting
Outcomes	Studies must report ≥1 of the following outcomes at a time point of ≥12 months: • OS • RFS or DFS • DMFS • AEs of grade 3/4 • Overall discontinuations • Discontinuations due to AEs • Global quality of life as measured by EORTC QLQ C-30
Study design	Only RCTs will be included
Language	Limited to studies published in the English language

[a]Studies assessing combined stage II/III patients will be included in the SLR, validity of inclusion in analyses will be assessed in the feasibility assessment
[b]Patients with background therapy (such as chemotherapy) in combination with 1 of the interventions of interest are eligible
EORTC QLQ C-30, European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire

Data source: Toor et al. 2018 poster[36]

The following databases were searched by the manufacturer for the systematic review using predefined search strategies: MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL). In addition, the Manufacturer also searched conference proceedings from the American Society of Clinical Oncology (ASCO), European Association of Dermato-Oncology, European Society of Medical Oncology (ESMO), International Society for Pharmacoeconomics and Outcomes Research (ISPOR), International Society for Quality of Life Research, Society for Melanoma Research (SMR), and Society for Immunotherapy of Cancer. This search was performed in May 2018. Only English-language published articles were searched.

It was stated that two reviewers worked independently to screen titles and abstracts, as well as full text articles. Data extraction and study quality assessment were performed independently by two reviewers. The Cochrane Collaboration's Risk of Bias tool was adopted

to assess risk of bias of all included studies in six domains: sequence generation, allocation concealment, blinding of participants, personnel and outcome assessors, incomplete outcome data, selective outcome reporting, and other sources of bias. There was no description on how the results of risk of bias assessment could have an impact on data analysis. If any discrepancies occurred, a third reviewer was included to reach consensus.[2]

Indirect treatment comparison methods

The Manufacturer reported that if the selected trials were deemed sufficiently similar for each population of interest and an evidence network was connected for each outcome of interest, the study findings were synthesized using a Bayesian approach. Time to event outcomes such as RFS was reported as hazard ratios (HRs), Kaplan-Meier (KM), or both. A subgroup analysis was conducted by removing studies with stage II patients. A sensitivity analysis was conducted whereby the IFN node was split into IFN, high-dose IFN, and pegylated IFN.

For binary outcomes, the NMA was performed based on the proportion of patients experiencing the event of interest. Relative treatment effects were expressed as odds ratios (OR). For continuous outcomes, the NMA was performed based on the mean change from baseline in the outcome and the corresponding standard errors using a regression model with a normal likelihood and identify link. Normal non-informative prior distributions for the parameters were used with a mean of 0 and a variance of 10,000. Relative treatment effects were expressed as differences in the outcome. For time-to-event outcomes (using constant HRs) such as RFS/DFS and OS, the NMA was performed using a regression model with a contrast-based normal likelihood for the log HR (and corresponding standard error) of each trial (or comparison) in the network. Normal non-informative prior distributions for the parameters were estimated with a mean of 0 and a variance of 10,000.

The manufacturer indicated that in order to have modeled survival consistent with the Kaplan Meier curve of CheckMate 238, the ipilimumab 10 mg/kg arm of CheckMate 238 was used as the reference and all other survival curves were estimated relative to it. This was done for RFS/DFS analyses. While CheckMate 238 did not report OS, the placebo arm from EORTC 18071 trial was used as the reference for the analysis of this outcome. For all outcomes, a subgroup analysis was conducted excluding trials which enrolled stage II patients.

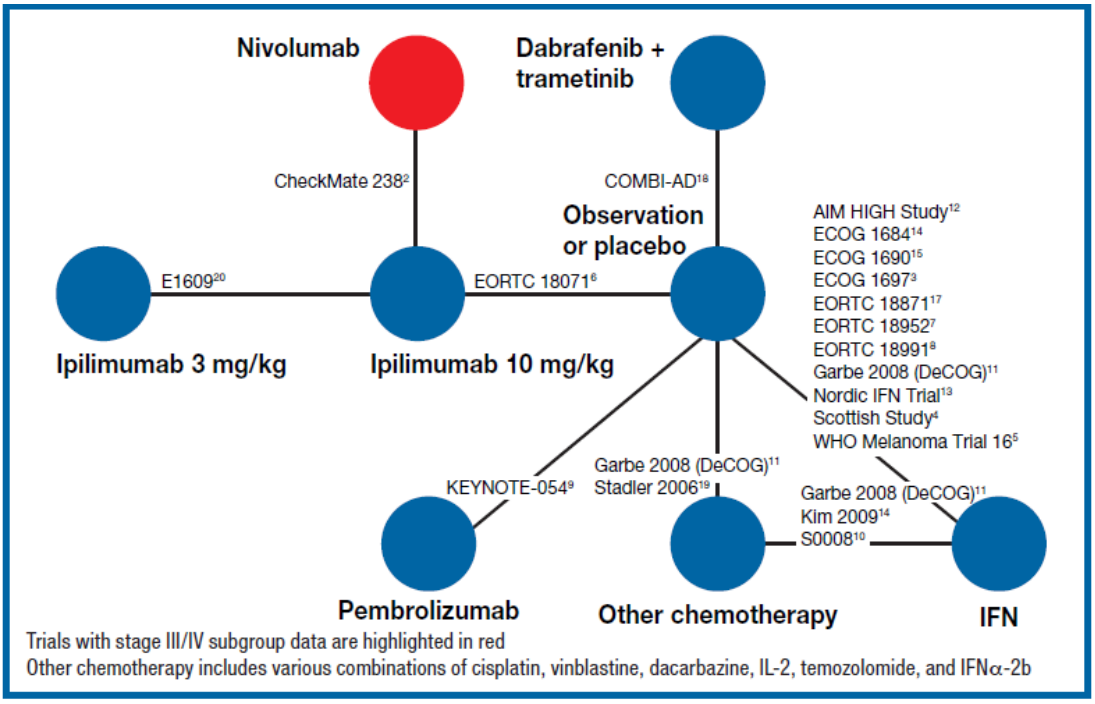
The parameters of the different models were estimated using a Markov Chain Monte Carlo (MCMC) method implemented in the OpenBUGS software package.

Results

Included studies

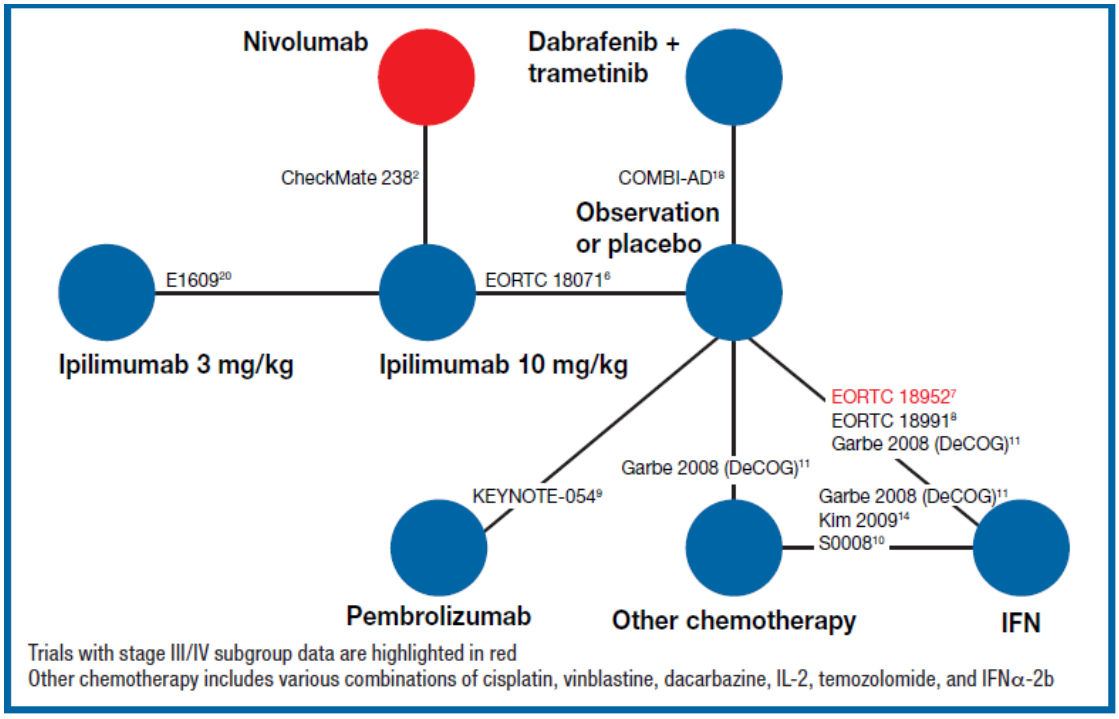
In total, the systematic review identified 25 RCTs. Six of the 25 trials were excluded from the NMA analysis due to differences identified in population (mucosal melanoma or stage I disease included) and treatment definitions (for the primary analysis, all IFN treatment arms were aggregated into a single node; thus for trials comparing various IFN regimens, they were treated as single-arm trials and excluded from the NMA accordingly)[2]. Nineteen RCTs were included in the NMA analysis. Of these, nivolumab was evaluated in one trial (CheckMate 238), IFN regimens in 13 trials, ipilimumab in two trials, dabrafenib+trametinib in one trial, other chemotherapy in four trials, pembrolizumab in one trial, and observation or placebo in 15 trials (Figures 2A and 2B). [36]

Figure 2A. Network of Evidence for Trials included in the NMA, Base Case Analysis (all patients)



Data source: Toor et al. 2018 poster[36]

Figure 2B. Network of Evidence for Trials included in the NMA, Base Case Analysis (stage III/IV subgroup)



Data source: Toor et al. 2018 poster[36]

Trial characteristics

Details of the trial characteristics of the included individual trials are available in a document provided by the submitter.[2] The number of study participants ranged from 96 to 1,455 in the included trials. Patients' baseline demographics, baseline prognostic characteristics or disease characteristics were provided in the included studies. In general, the baseline characteristics were similar across studies. The median age of the study populations ranged from 46 to 56 years old. The majority of the participants were male (52% - 71%). In the majority of the trials, patients had an ECOG performance status of 0 or 1. None of the patients received prior chemotherapy or prior immune-therapy.[2]

RFS was defined differently in the included trials. In most cases, RFS was broadly defined as the time between randomization and first recurrence or death. In CheckMate 238, EORTC 18071, EORTC18952, and EORTC 18991, it was specified that recurrence could be local, regional, or distant metastasis. The AIM HIGH Study was the only trial to explicitly not include death as an endpoint when assessing RFS (disease recurrence and death were measured separately).[2]

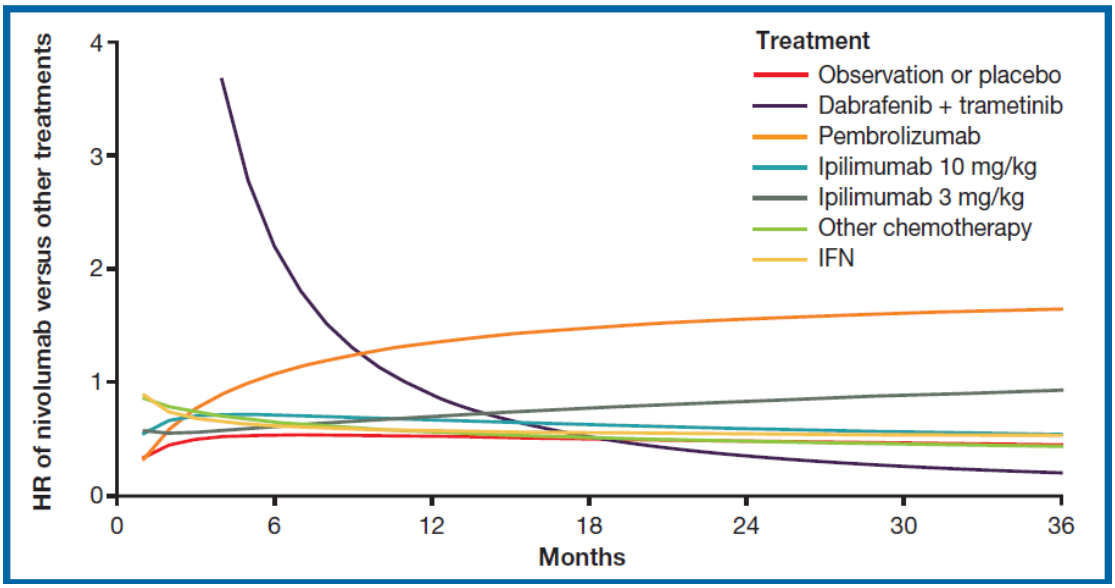
The authors reported that the overall risk of bias of the included RCTs was low, in particular for the domains of "blinding of participants and personnel" and "allocation concealment". Uncertainty was reported for "Sequence generation" and "blinding of outcome assessment" for most of the trials.[2]

Indirect Treatment Comparison

RFS/DFS

Results of the constant HR analysis and time-varying HR analysis suggested that nivolumab was associated with a statistically significant reduction in risk of disease recurrence or death when compared with placebo or interferon (Table 15; Figure 3A). The authors of this analysis stated that the between-group differences in RFS/DFS were not statistically significant between nivolumab and other active treatment, such as pembrolizumab or the combination of dabrafenib+trametinib (Figure 3A).[36] The Methods team noted that pembrolizumab or the combination dabrafenib+trametinib are not currently reimbursed in Canada.

Figure 3A. Time-Varying Hazard Ratios Estimated from Fixed-Effect NMA for RFS (base case, Stage II/III/IV population)



Data source: Toor et al. 2018 poster[36]

OS

OS data for nivolumab were unavailable at the time of analysis.

Grade 3 or 4 AEs

Results of the NMA analysis suggested that nivolumab had similar rates of Grade 3 or 4 AEs as placebo in the study population. It was associated with a statistically significant reduction in the risk of Grade 3 or 4 AEs when compared with interferon (Table 15).[36]

Discontinuation due to AEs

Results of the NMA analysis suggested that nivolumab had similar rates of study discontinuation due to AEs as placebo in the study population. It was associated with a statistically significant reduction in the risk of discontinuation due to AEs when compared with interferon (Table 15).[36]

Table 15: Efficacy and Safety Outcomes for Nivolumab vs. Observation/Placebo and Nivolumab vs. Interferon

Outcome	Time point, months	Primary analysis	Stage III/IV subgroup analysis	Sensitivity analysis	Stage III/IV sensitivity analysis
NIVO vs observation/placebo					
Constant HR analysis					
RFS/DFS	NA	0.50 (0.39–0.65)	0.50 (0.39–0.65)	0.50 (0.38–0.65)	0.50 (0.38–0.65)
Time-varying HR analysis					
RFS/DFS	6	0.54 (0.39–0.74)	0.50 (0.38–0.65)	0.54 (0.39–0.73)	0.51 (0.38–0.65)
	12	0.53 (0.38–0.73)	0.53 (0.38–0.72)	0.52 (0.38–0.72)	0.53 (0.38–0.71)
	18	0.50 (0.33–0.77)	0.54 (0.36–0.81)	0.50 (0.32–0.77)	0.54 (0.36–0.79)
	24	0.48 (0.28–0.83)	0.55 (0.35–0.88)	0.48 (0.27–0.82)	0.55 (0.35–0.87)
AE analyses					
Grade 3/4 AEs	NA	0.92 (0.63–1.37)	0.93 (0.63–1.37)	0.92 (0.62–1.36)	0.93 (0.62–1.37)
Discontinuations	NA	0.68 (0.39–1.22)	0.68 (0.39–1.21)	0.68 (0.39–1.21)	0.68 (0.39–1.21)
DAEs	NA	3.52 (1.95–6.48)	3.54 (1.94–6.60)	3.56 (1.92–6.67)	3.64 (2.04–6.75)

NIVO vs IFN					
Constant HR analysis					
RFS/DFS	NA	0.57 (0.43–0.75)	0.56 (0.42–0.74)	0.58 (0.44–0.76)[a]	0.56 (0.41–0.75)[a]
Time-varying HR analysis					
RFS/DFS	6	0.62 (0.45–0.85)	0.60 (0.45–0.79)	0.68 (0.50–0.95)[a]	0.60 (0.44–0.82)
	12	0.57 (0.41–0.80)	0.61 (0.43–0.86)	0.61 (0.44–0.87)[a]	0.62 (0.43–0.89)
	18	0.56 (0.36–0.86)	0.61 (0.40–0.94)	0.57 (0.37–0.89)[a]	0.63 (0.40–0.97)
	24	0.55 (0.31–0.95)	0.62 (0.38–1.01)	0.54 (0.31–0.93)[a]	0.64 (0.38–1.06)
AE analyses					
Grade 3/4 AEs	NA	0.08 (0.05–0.13)	0.11 (0.07–0.18)	0.16 (0.09–0.31)[a]	17.74 (0.67–311.14)[a]
Discontinuations	NA	0.22 (0.11–0.48)	NA	0.22 (0.10–0.47)[a]	NA
DAEs	NA	0.15 (0.08–0.30)	0.15 (0.07–0.32)	0.20 (0.10–0.40)[a]	0.82 (0.31–2.25)[a]

Data source: Toor et al. 2018 poster[36]

7.1.2.2 ***Indirect Treatment Comparison*** [37] [38]

Objectives of manufacturer's ITC

The objectives of the manufacturer's ITC were to evaluate the relative efficacy and HRQoL of adjuvant treatment with nivolumab to placebo in patients with resected advanced stage melanoma, using data from CheckMate 238 and Study 029 (also known as EORTC 18071 trial).

Study eligibility and selection process

The studies included in this ITC were selected by the manufacturer. A systematic literature review process was not adopted to identify relevant trials. It was unclear whether data extraction and study quality assessment were performed independently by two reviewers.

Indirect treatment comparison methods

Different ITC methods were employed to compare the clinical efficacy for nivolumab and placebo, using ipilimumab as the common comparator. [37]

- Bucher method (unadjusted): cox proportional hazards regression models were fitted to data from both studies separately; each model estimated the within-trial hazard ratio (HR) for treatment effect and was not adjusted for any covariates.
- Bucher method (adjusted): same as the unadjusted Bucher method, except the within-trial Cox proportional hazards regression models were fitted also adjusting for sex, age, disease stage, and ECOG performance status. Further adjustment was also made for the stage IIIb/c population for RFS.
- Pooled Cox analysis (unadjusted): patient-level data from both studies were combined by stacking the patient-level data and adding an additional column in the dataset for trial. A Cox proportional hazards regression was performed on the combined dataset,

including covariates for trial (CheckMate 238 or study 029) and treatment (nivolumab or ipilimumab or placebo).
- Pooled Cox analysis (adjusted): same as the unadjusted pooled Cox method, except the Cox proportional hazards regression model was fit also adjusting for sex, age, disease stage, and ECOG performance status. Further adjustment was also made for the stage IIIb/c population for RFS
- Bayesian network meta-analysis: standard Bayesian NMA on aggregate results from published literature was used to assess the relative efficacy of a number of treatments: nivolumab, ipilimumab, pembrolizumab, dabrafenib + trametinib, interferon, and placebo/standard of care/watchful waiting

The Bucher method was used for the analysis of HRQoL, to compare time to deterioration for nivolumab versus placebo. For analysis of each HRQoL endpoint, time to deterioration was defined as the time from randomization to the time when the specific score reduced from baseline by ≥10. Patients' baseline values were included as covariates. The analyses were performed for both the ITT population and the population of stage IIIb/c patients.[38]

Results

Included studies

CheckMate 238 and Study 029 were included in this ITC.

Trial characteristics

CheckMate 238 (N=906) is a phase 3 RCT comparing nivolumab with ipilimumab in patients with completely resected Stage IIIb, IIIc and IV melanoma. Study 029 (N=951) is a phase 3, double-blind RCT comparing ipilimumab with placebo in patients with completely resected stage IIIa to IIIc melanoma. The two trials were randomized for different stratification factors: by disease stage and by PD-L1 status in CheckMate 238, and by disease stage and geographical region in Study 029. The minimum follow-up was 24 months in CheckMate 238 but 32.4 months in Study 029.[38]

Patients' baseline characteristics were similar between treatment arms within each trial, and also comparable between CheckMate 238 and Study 029, except for the distribution of cancer stage. In both trials, the majority of the study participants (~80%) had Stage IIIb and IIIc disease, while in CheckMate 238, approximately 19% of the participants had Stage IV disease, and in Study 029 around 20% of them had Stage IIIa disease. The treatment duration differed between trials. In CheckMate 238, patients could receive treatment for up to one year. In Study 029, patients could receive ipilimumab treatment for up to three years, and 29% of patients in the ipilimumab group received treatment beyond one year.[39] Outcome measures in the two trials included clinical efficacy such as RFS, safety and patient-reported HRQoL measured with the European Organisation for Research and Treatment of Cancer core quality of life questionnaire (EORTC QLQ-C30). This is a disease-specific measure for assessing the QOL of patients with cancer. It comprises 30 questions measuring 15 multi-item scales: five functional scales (physical, role, cognitive, emotional, and social), nine symptom scales (fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties), and Global health status.

Indirect Treatment Comparison

RFS

The ITC results suggested that patients who received adjuvant therapy of nivolumab had statistically significantly longer RFS compared with those receiving placebo, in both ITT population and subgroup of patients with stage IIIb/c disease (Table 16).

Table 16: Efficacy estimates from the ITC

Method	RFS, HR (95% CI)		DMFS, HR (95% CI)	
	ITT	Stage IIIB/C	ITT	Stage IIIB/C
Bucher (unadjusted)	0.53 (0.41–0.68)	0.52 (0.39–0.69)	0.57 (0.42–0.77)	0.60 (0.43–0.84)
Bucher (adjusted)	0.54 (0.41–0.69)	0.52 (0.39–0.70)	0.62 (0.45–0.86)	0.62 (0.44–0.86)
Pooled Cox (unadjusted)	0.53 (0.41–0.68)	0.52 (0.39–0.69)	0.57 (0.42–0.77)	0.60 (0.43–0.84)
Pooled Cox (adjusted)	0.53 (0.41–0.69)	0.53 (0.39–0.71)	0.62 (0.45–0.86)	0.62 (0.45–0.87)
Bayesian NMA	0.50 (0.39–0.65)	Not performed	0.58 (0.42–0.79)	Not performed

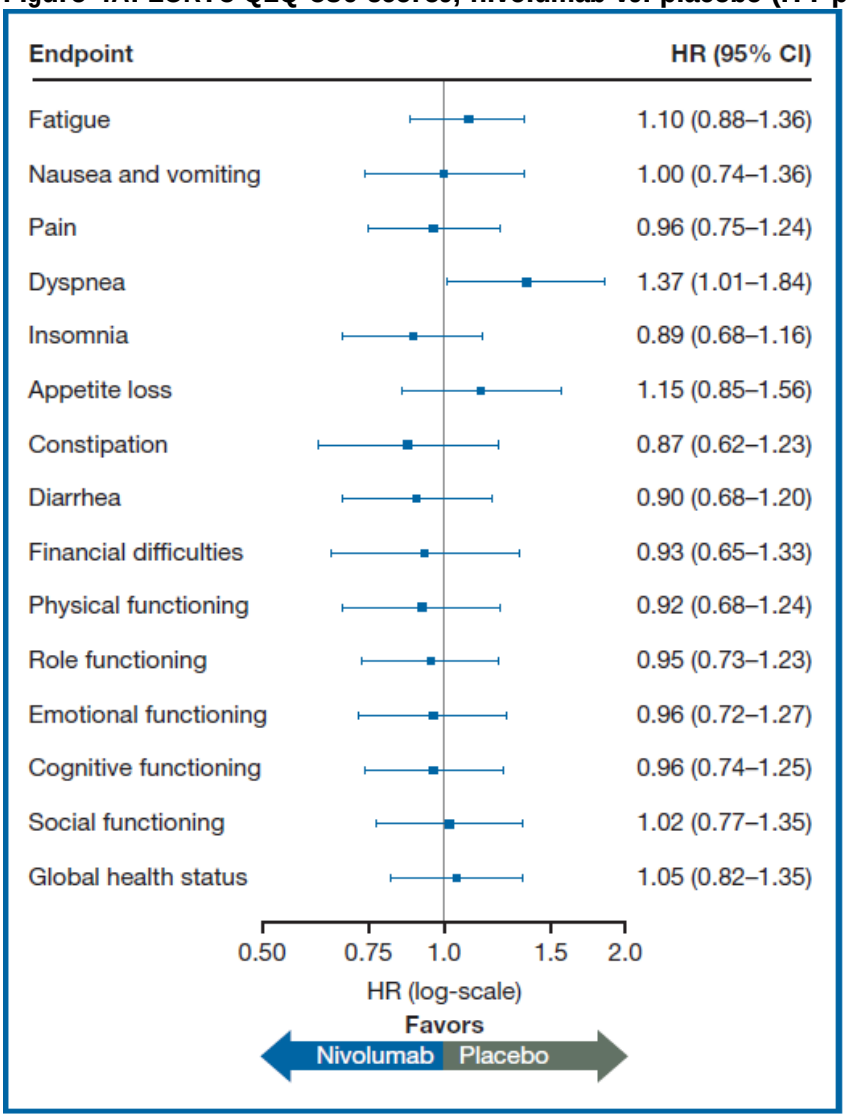
HR <1 favors nivolumab; HR >1 favors placebo

Source: Hemstock et al. 2018[37]

Health-related quality of life

Results of the ITC suggested that HRQoL was similar between nivolumab and placebo. None of the comparisons were statistically significant, except for dyspnea (HR 1.34, 95% CI 1.01 to 1.84, indicating a 34% increased risk in dyspnea for nivolumab compared with placebo). Subgroup results for the stage IIIb/c population were consistent with those of the ITT population (HR 1.42, 95% CI 1.01 to 1.99).

Figure 4A. EORTC QLQ-C30 Scores, nivolumab vs. placebo (ITT population)



Source: Hemstock et al. 2018[38]

Critical Appraisal of the NMA and ITC

The quality of the NMA and ITC was assessed according to the recommendations made by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force on Indirect Treatment Comparisons.[40] Details of the critical appraisal are presented in Table 17.

Table 17: Adapted ISPOR Questionnaire to Assess the Credibility of an Indirect Treatment Comparison or Network Meta-Analysis†

ISPOR Questions	Details and Comments‡	
	NMA	ITC
1. Is the population relevant?	Yes. The indication for this review was to assess the efficacy and safety of nivolumab and other active treatment as adjuvant therapy in intermediate or high risk non-metastatic, stage II/III/IV patients. Patient populations in the included trials, including	Yes. The indication for this review was to assess the efficacy and safety of nivolumab and placebo as adjuvant therapy in resected stage III/IV patients. The study population

ISPOR Questions	Details and Comments‡	
	NMA	ITC
	CheckMate 238, involved patients with intermediate and high or low risk resected melanoma, and aligned with the NMA question.	in CheckMate 238 consisted of resected stage III/IV patients with melanoma, and Study 029 recruited patients with resected stage IIIA–IIIC melanoma. There are some overlaps between the two patient populations.
2. Are any critical interventions missing?	No. Relevant interventions were included in this NMA.	**Yes.** Only nivolumab was compared with placebo in this ITC.
3. Are any relevant outcomes missing?	**Yes.** In the NMA, although OS and HRQoL were planned to be measured, there were no data available for the analysis.	**Yes.** OS and safety were not included in this ITC.
4. Is the context (e.g., settings and circumstances) applicable to your population?	Yes**.** The patient populations in the included trials in this NMA (patients with resected melanoma and required adjuvant therapy) reflect the Canadian population in practice.	Yes. The patient populations in CheckMate 238 and Study 029 reflect the Canadian population in practice.
5. Did the researchers attempt to identify and include all relevant randomized controlled trials?	**Yes, in part.** The Manufacturer provided a summary of the systematic literature review process used in the NMA. In the summary, the Manufacturer described the information sources they used, their search strategy and their study selection criteria. However, only English published articles were included in the systematic review and associated NMA.	**No.** There was no description on study selection. A literature search was not performed.
6. Do the trials for the interventions of interest form one connected network of randomized controlled trials?	Yes. One closed loop for IFN, other chemotherapy and observation/placebo was present, although nivolumab was not included in this loop.	Yes. Indirect comparison between nivolumab and placebo was conducted with ipilimumab being the common comparator.
7. Is it apparent that poor quality studies were included thereby leading to bias?	**Unclear**. Quality of the included trials was assessed. However, the Manufacturer did not elaborate on the potential impact of the risk of bias on data analysis.	**Unclear**. Quality of the included trials was not assessed.
8. Is it likely that bias was induced by selective reporting of outcomes in the studies?	**Unclear**. Two out of 14 trials were labeled as "unclear risk" for the domain of "Selective outcome reporting", while the other trials were of low risk.	**Unclear**. A limited number of outcomes were reported in this ITC.
9. Are there systematic differences in treatment effect modifiers (i.e. baseline patient or study characteristics that impact the treatment effects) across the different treatment comparisons in the network?	**Yes.** The Manufacturer provided patients' baseline characteristics for each included trial; therefore it is possible for us to examine the impact of treatment effect modifiers. However, subgroup analyses were only performed based on inclusion/exclusion of stage II patients. Other treatment effect modifiers such as AJCC staging system or type of surgery were not evaluated. The manufacturer also noted that the definition of RFS differed across the trials.	**Yes.** The distribution of cancer stage was different between the 2 included trials.
10. If yes (i.e. there are such systematic differences in treatment effect modifiers), were these imbalances in effect modifiers across the different treatment comparisons identified prior to comparing individual study results?	Yes, in part. The Manufacturer explored the potential effects of treatment modifiers in a feasibility assessment prior to the actual NMA, to determine the appropriateness of conducting an NMA.	Yes. **S**ex, age, disease stage, ECOG performance status and lymph node involvement were identified as treatment effect modifiers.
11. Were statistical methods	Yes. The Manufacturer used the Bayesian method.	Yes. Different indirect comparison

ISPOR Questions	Details and Comments‡	
	NMA	ITC
used that preserve within-study randomization? (No naïve comparisons)		methods were used, including the Bucher method and a Bayesian NMA method.
12. If both direct and indirect comparisons are available for pairwise contrasts (i.e. closed loops), was agreement in treatment effects (i.e. consistency) evaluated or discussed?	Yes, agreement in treatment effects was observed for both direct and indirect comparisons.	**Not applicable**. Direct comparison was not available.
13. In the presence of consistency between direct and indirect comparisons, were both direct and indirect evidence included in the network meta-analysis?	Yes, both direct and indirect evidence were included in the NMA.	**Not applicable**.
14. With inconsistency or an imbalance in the distribution of treatment effect modifiers across the different types of comparisons in the network of trials, did the researchers attempt to minimize this bias with the analysis?	**Yes, in part.** Subgroup analysis based on disease stage and sensitivity analyses with various IFN regimens were performed to minimize this bias. However, there were no other subgroups evaluated in the NMA.	**Yes, in part.** Subgroup analysis based on disease stage was performed to minimize the bias. However, there were no other subgroups evaluated in the ITC.
15. Was a valid rationale provided for the use of random effects or fixed effect models?	Yes.	Not applicable.
16. If a random effects model was used, were assumptions about heterogeneity explored or discussed?	Yes.	Not applicable.
17. If there are indications of heterogeneity, were subgroup analyses or meta-regression analysis with pre-specified covariates performed?	**Yes, in part.** Subgroup analysis was performed based on disease stage. Method of meta-regression analysis was described in the methodology section of the NMA, but there was no result reported. The Methods Team does recognize that assessment of heterogeneity may have been difficult due to a limited number of studies included in the ITC.	**Yes, in part.** Subgroup analysis was performed based on disease stage. Results were presented in intention-to-treat population as well as patients with stage III disease.
18. Is a graphical or tabular representation of the evidence network provided with information on the number of RCTs per direct comparison?	Yes. This representation was presented in the NMA.	**No.** 2 trials were included for this ITC.
19. Are the individual study results reported?	Yes. The submitter provided the baseline characteristics of the trials used in the NMA as well as the effect estimates of RFS and overall survival.	Yes.
20. Are results of direct comparisons reported separately from results of the indirect comparisons or network meta-analysis?	Consistency check between direct and indirect comparisons was available for the outcome measures within a closed loops containing IFN, other chemotherapy and observation/placebo. However, nivolumab was not included in this closed loop.	**No.**
21. Are all pairwise contrasts between interventions as	**Yes.** The manufacturer provided the hazard ratio and 95% CrI of RFS that was obtained from the	**Yes.** The manufacturer provided the hazard ratio and 95% CI of RFS

ISPOR Questions	Details and Comments‡	
	NMA	ITC
obtained with the network meta-analysis reported along with measures of uncertainty?	indirect comparison between nivolumab and other active treatment.	that was obtained from the indirect comparison between nivolumab and other active treatment.
22. Is a ranking of interventions provided given the reported treatment effects and its uncertainty by outcome?	**No**.	**No.**
23. Is the impact of important patient characteristics on treatment effects reported?	**No**.	**No.**
24. Are the conclusions fair and balanced?	The NMA reported that nivolumab was associated with a protective effect on survival and safety outcome as compared to ipilimumab and interferon. However, health-related quality of life was not assessed in this NMA due to unavailability of data. In addition, there was no comparison available between nivolumab and other potentially relevant comparators (such as pembrolizumab; notably these agents are not reimbursed in Canada). The consistency between direct and indirect comparisons was checked between interferon, other chemotherapies and observation/placebo, but not for nivolumab in the NMA. Some treatment effect modifiers e.g. cancer stage were controlled for in the NMA; other treatment effect modifiers such as AJCC staging system or type of surgery were not evaluated – the heterogeneity across the included trials may have an impact on the study findings and results need to be interpreted with caution. Therefore it is difficult to determine the overall benefit of this drug as compared to currently available adjuvant therapy in the study population.	The ITC showed that nivolumab was associated with a protective effect on survival as compared with placebo. It had similar effect on patient's quality of life as compared with placebo. Safety of the treatment of nivolumab was not included in this ITC.
25. Were there any potential conflicts of interest?	**Not reported.**	**Not reported.**
26. If yes, were steps taken to address these?	**Not applicable.**	**Not applicable.**

CI = confidence interval; CrI = credible interval; HRQoL = health-related quality of life; ISPOR = International Society For Pharmacoeconomics and Outcomes Research; ITC = indirect treatment comparison; NMA = network meta-analysis; RFS = recurrence-free survival.
† Adapted from Jansen et al.[40]
‡ Bolded comments are considered a weakness of the NMA/ITC.

7.1.3 Summary

The Manufacturer submitted a network meta-analysis that compared nivolumab to other active treatments in patients with intermediate or high risk non-metastatic melanoma, as well as an indirect treatment comparison analysis comparing nivolumab with placebo in resected stage III/IV melanoma. The results of the NMA suggested that adjuvant treatment with nivolumab was associated with a reduction in the risk of cancer recurrence or death as compared to interferon or watchful observation/placebo; however there were no statistically significant differences in recurrence-free survival observed between nivolumab and pembrolizumab or the combination of dabrafenib+trametinib. Notably, these two agents are not currently reimbursed in Canada for this indication. In addition, nivolumab had a similar safety profile as placebo, but treatment with

nivolumab was associated with statistically significantly lower risks of Grade 3 or 4 adverse events and discontinuation due to adverse events, as compared with interferon. Effect of nivolumab on health-related quality of life relative to placebo was examined in the indirect treatment comparison analysis, and the between-group differences were not statistically significant, suggesting comparable quality of life for patients who received nivolumab and placebo. Overall survival was not assessed in the comparisons between nivolumab and other active treatments due to the unavailability of data. Subgroup analysis based on disease stage was performed to examine the impact of this treatment effect modifier; other treatment effect modifiers were not evaluated, thus the results of the network meta-analysis and indirect comparison analysis should be interpreted with caution.

8 COMPARISON WITH OTHER LITERATURE

No comparisons were performed to other available literature.

9 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 nivolumab (Opdivo) for adjuvant melanoma. Issues regarding resource implications are beyond the scope of this report and are addressed by the relevant pCODR Economic Guidance Report. Details of the pCODR review process can be found on the 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.

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.

APPENDIX A: LITERATURE SEARCH STRATEGY AND DETAILED METHODOLOGY

1. Literature search via OVID platform

Database(s): EBM Reviews - Cochrane Central Register of Controlled Trials August 2018, Embase 1974 to 2018 September 6, Ovid MEDLINE(R) ALL 1946 to September 06, 2018

#	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 31YO63LBSN).ti,ab,ot,kf,kw,hw,rn,nm.	12084
2	exp Melanoma/ or exp Skin Neoplasms/ or (melanoma* or melanocarcinoma* or melanomalignoma* or naevocarcinoma* or nevocarcinoma* or pigmentary cancer* or skin cancer*).ti,ab,kf,kw.	517350
3	(adjuvant* or adjunct* or add-on or ancillar* or backup or complementary or extra or reserve or secondary or supporting).ti,ab,hw,sh.	3370313
4	exp Neoplasm Staging/	426775
5	(stage III adj15 IV).ti,ab,hw.	42870
6	(tumor* staging or tumour* staging or cancer* staging or neoplasm* staging or carcinoma* staging or adenocarcinoma* staging).ti,ab,hw,sh.	436086
7	(tumor* stage* or tumour* stage* or cancer* stage* or neoplasm* stage* or carcinoma* stage* or adenocarcinoma* stage*).ti,ab,hw,sh.	64226
8	(advanced melanoma or resected melanoma).ti,ab,kw.	6387
9	3 or 4 or 5 or 6 or 7 or 8	3771172
10	1 and 2 and 9	1827
11	10 use medall	341
12	10 use cctr	168
13	*Nivolumab/ or (Opdivo* or nivolumab* or MDX 1106 or MDX1106 or BMS936558 or BMS 936558 or	8322

	ONO4538 or ONO 4538 or 31YO63LBSN).ti,ab,kw.	
14	exp Melanoma/ or exp Skin Tumor/ or (melanoma* or melanocarcinoma* or melanomalignoma* or naevocarcinoma* or nevocarcinoma* or pigmentary cancer* or skin cancer*).ti,ab,kw.	445608
15	(adjuvant* or adjunct* or add-on or ancillar* or backup or complementary or extra or reserve or secondary or supporting).ti,ab,hw,sh.	3370313
16	exp Cancer Staging/	426775
17	(stage III adj15 IV).ti,ab,hw.	42870
18	(tumor* staging or tumour* staging or cancer* staging or neoplasm* staging or carcinoma* staging or adenocarcinoma* staging).ti,ab,hw,sh.	436086
19	(tumor* stage* or tumour* stage* or cancer* stage* or neoplasm* stage* or carcinoma* stage* or adenocarcinoma* stage*).ti,ab,hw,sh.	64226
20	(advanced melanoma or resected melanoma).ti,ab,kw.	6387
21	15 or 16 or 17 or 18 or 19 or 20	3771172
22	13 and 14 and 21	1379
23	conference abstract.pt.	3180578
24	22 and 23	481
25	limit 24 to yr="2013 -Current"	475
26	22 not 23	898
27	25 or 26	1373
28	27 use oemezd	892
29	(Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or Equivalence Trial or Clinical Trial, Phase III).pt.	1101566

30	Randomized Controlled Trial/	978841
31	exp Randomized Controlled Trials as Topic/	275747
32	"Randomized Controlled Trial (topic)"/	147665
33	Controlled Clinical Trial/	550426
34	exp Controlled Clinical Trials as Topic/	286847
35	"Controlled Clinical Trial (topic)"/	9494
36	Randomization/	174980
37	Random Allocation/	191808
38	Double-Blind Method/	392679
39	Double Blind Procedure/	152162
40	Double-Blind Studies/	257173
41	Single-Blind Method/	74202
42	Single Blind Procedure/	32171
43	Single-Blind Studies/	76149
44	Placebos/	322851
45	Placebo/	321895
46	Control Groups/	111324
47	Control Group/	111232
48	(random* or sham or placebo*).ti,ab,hw,kf,kw.	3929337

49	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.	770168
50	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.	2893
51	(control* adj3 (study or studies or trial* or group*)).ti,ab,kf,kw.	2559604
52	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf,kw.	92992
53	allocated.ti,ab,hw.	173353
54	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf,kw.	111870
55	((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.	24074
56	(pragmatic study or pragmatic studies).ti,ab,hw,kf,kw.	914
57	((pragmatic or practical) adj3 trial*).ti,ab,hw,kf,kw.	10652
58	((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.	16795
59	(phase adj3 (III or "3") adj3 (study or studies or trial*)).ti,hw,kf,kw.	124320
60	or/29-59	5625184
61	11 or 28	1233
62	60 and 61	427
63	12 or 62	595
64	limit 63 to english language	571
65	exp animals/	45322390
66	exp animal experimentation/ or exp animal experiment/	2266103
67	exp models animal/	1689028

68	nonhuman/	5511571
69	exp vertebrate/ or exp vertebrates/	44092013
70	or/65-69	47021854
71	exp humans/	36540308
72	exp human experimentation/ or exp human experiment/	423805
73	or/71-72	36542395
74	70 not 73	10480992
75	64 not 74	570
76	(comment or newspaper article or editorial or letter or note).pt.	4003367
77	75 not 76	560
78	remove duplicates from 77	422

2. Literature search via PubMed

A limited PubMed search was performed to capture records not found in MEDLINE.

Search	Query	Items found
#13	Search **#11 AND #12**	13
#12	Search **(randomized controlled trial[pt] OR random*[ti] OR random*[ot] OR Controlled clinical trial[pt] OR clinical trial[pt] OR evaluation studies[pt] OR Cohort studies[Mesh] OR Longitudinal studies[Mesh] OR Prospective studies[Mesh] OR Follow-up studies[Mesh] OR Retrospective studies[Mesh] OR "Comparative Study"[pt] OR Validation Studies[pt] OR Case-control studies[Mesh]) NOT Review[pt] OR ((random*[tw] OR placebo[tiab] OR methods[tiab] OR trial[tiab] OR study[tiab] OR cohort[tiab] OR retrospective[tiab] OR prospective[tiab] OR observational[tiab] OR control*[ti] OR control*[ot] OR nonrandom*[tiab] OR quasirandom*[tiab] OR volunteer[tiab] OR volunteers[tiab] OR cross-sectional[tiab] OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind*[tw] OR dumm*[tw]))) AND (publisher[sb] OR inprocess[sb] OR pubmednotmedline[sb]))**	5283705
#11	Search **#9 AND #10**	26

Search	Query	Items found
#10	Search **publisher[sb]**	531501
#9	Search **#1 AND #2 AND #8**	414
#8	Search **#3 OR #4 OR #5 OR #6 OR #7**	1456769
#7	Search **(advanced[tiab] OR resected[tiab]) AND melanoma[tiab]**	6884
#6	Search **(tumor*[tiab] OR tumour*[tiab] OR cancer*[tiab] OR neoplasm*[tiab] OR carcinoma*[tiab] OR adenocarcinoma*[tiab]) AND (staging[tiab] OR stage*[tiab])**	300936
#5	Search **stage III[tiab OR stage IV[tiab]**	0
#4	Search **Exp Neoplasm Staging[MeSH]**	1076
#3	Search **adjuvant*[tiab] OR adjunct*[tiab] OR add-on[tiab] OR ancillar*[tiab] OR backup[tiab] OR complementary[tiab] OR extra[tiab] OR reserve[tiab] OR secondary[tiab] OR supporting[tiab]**	1191309
#2	Search **Melanoma[mh] OR melanoma*[tiab] OR melanocarcinoma*[tiab] OR melanomalignoma*[tiab] OR naevocarcinoma*[tiab] OR nevocarcinoma*[tiab] OR pigmentary cancer*[tiab] OR skin cancer*[tiab]**	134191
#1	Search **nivolumab[Supplementary Concept] OR nivolumab*[tiab] OR Opdivo*[tiab] 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]**	2553

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

4. 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: Opdivo/nivolumab, melanoma

Select international agencies including:

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

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

Search: Opdivo/nivolumab, melanoma

Conference abstracts:

American Society of Clinical Oncology (ASCO)
http://www.asco.org/

Search: Opdivo/nivolumab, melanoma – last 5 years

APPENDIX B: DETAILED METHODOLOGY OF LITERATURE REVIEW

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-) with in-process records & daily updates via Ovid; Embase (1974-) via Ovid; The Cochrane Central Register of Controlled Trials (August 2018) 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 adjuvant treatment for stage III and stage IV 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 not limited by publication year.

The search is considered up to date as of November 28, 2018.

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. Conference abstracts were retrieved through a search of the Embase database limited to the last five years. Abstracts from the American Society of Clinical Oncology (ASCO) were searched manually for conference years not available in Embase. 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.

Study Selection

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

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

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.

Data Analysis

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

Writing of the Review Report

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

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

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