CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Nivolumab (Opdivo) with Ipilimumab (Yervoy) for Metastatic Melanoma

November 30, 2017

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FUNDING

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

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1 GUIDANCE IN BRIEF

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 in combination with ipilimumab for 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 in combination with ipilimumab for metastatic 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 in combination with ipilimumab for metastatic melanoma, a summary of submitted Provincial Advisory Group Input on nivolumab in combination with ipilimumab for metastatic melanoma, and a summary of submitted Registered Clinician Input on nivolumab in combination with ipilimumab for metastatic 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 in combination with ipilimumab for the treatment of naïve adult patients with advanced (unresectable or metastatic) melanoma. The Submitter, Bristol-Myers Squibb Canada has requested funding of nivolumab in combination with ipilimumab for treatment-naïve adult patients with advanced (unresectable or metastatic) melanoma, regardless of BRAF status. The funding request aligns with the Health Canada indication. A Notice of Compliance with conditions was issued by Health Canada for the use of nivolumab in combination with ipilimumab in previously untreated advanced melanoma patients in October 2016 pending the results of trials to verify its clinical benefit.[1]

The appropriate comparators for nivolumab in combination with ipilimumab include nivolumab monotherapy and ipilimumab monotherapy. It is noted that at the time of this review, nivolumab monotherapy is not currently funded in all provinces in Canada. Current treatments for metastatic melanoma include single agent pembrolizumab, single agent ipilimumab, single agent nivolumab and for BRAF mutated tumours, vemuratenib-cobimetinib and dabrafenib-trametinib.

The combination of nivolumab with ipilimumab combines the actions associated with PD-1 (nivolumab) and cytotoxic T-lymphocyte antigen-4 (CTLA-4 (ipilimumab) checkpoint inhibitors. The recommended dose of nivolumab during the combination phase is 1 mg/kg administered as an intravenous infusion over 60 minutes every 3 weeks for the first 4 doses in combination with ipilimumab 3 mg/kg administered intravenously over 90 minutes, followed by the single-agent phase. In the single agent phase, the recommended dose of nivolumab is 3 mg/kg administered as an intravenous infusion over 60 minutes every 2 weeks. Treatment is continued as long as clinical benefit is observed or until treatment is no longer tolerated by the patient.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

The pCODR systematic review included two RCTs. The first trial was a double-blind, phase III trial (CheckMate 067, N = 945) and the second one was a double-blind, phase II trial (CheckMate 069, N= 142).

CheckMate 067

CheckMate 067 was a double-blind, multicentre, multi-arm phase III RCT that assessed the effect of nivolumab, nivolumab plus ipilimumab and ipilimumab on overall survival and progression free survival (PFS) in 945 patients with unresectable stage III or IV melanoma.[2] Patients, regardless of *BRAF* carrier status, were randomized (1:1:1) to receive nivolumab (N = 316; $N_{BRAF\ carriers}$ = 100 [31.6%]), nivolumab plus ipilimumab (N = 314; $N_{BRAF\ carriers}$ = 101 [32.2%]) or ipilimumab (N = 315; $N_{BRAF\ carriers}$ = 97 [30.8%]). Patients continued to be treated with their assigned therapies until they had documented disease progression, developed unacceptable toxic events or withdrew consent. In addition, patients could be treated beyond progression if they continued to have investigator assessed clinical benefit and they were still tolerant to the study medication. It should be noted that this trial was not designed to compare nivolumab plus ipilimumab to the nivolumab treatment group.[2]

The co-primary outcomes assessed in CheckMate 067 were progression free survival (PFS) and overall survival. The study was designed to have 83% power to reject the null hypothesis of an HR of 0.71 (489 progressive events) using a two-sided significance level of α=0.005 for a nine month follow-up period or the minimum required follow-up of 6 months for all comparisons.[3] The study also had 99% power to reject the null hypothesis of an HR of 0.65 for overall survival (442 deaths) using a two-sided significance level of α=0.02 for a 28 month follow-up period or the minimum required follow-up of 22 months for all comparisons.[3] The secondary efficacy endpoint in CheckMate 067 was objective response rate (ORR) and the exploratory outcomes included median duration of response (DOR), time to objective response (TTR), health related quality of life (HRQoL), safety and tolerability.

Efficacy

At the database lock of 17-Feb-2015, 55.1% (N = 175) of patients in the nivolumab arm, 48.1% (N = 151) in the nivolumab plus ipilimumab arm and 74.3% (N = 234) in the ipilimumab arm had disease progression or had died.[2] Median PFS was 6.9 months (95% CI, 4.3 to 9.5) for patients treated with nivolumab, 11.5 months (95% CI, 8.9 to 16.7) for patients treated with nivolumab plus ipilimumab and 2.9 months (95% CI, 2.8 to 3.4) for patients treated with ipilimumab.[2] Treatment with nivolumab plus ipilimumab was associated with a prolonged PFS as compared to ipilimumab in patients with advanced melanoma (HR: 0.42; 99.5% CI, 0.31 to 0.57; P < 0.001).[2] A similar effect was also observed when nivolumab plus ipilimumab was compared to nivolumab on PFS (HR: 0.74, 95% CI, 0.60 to 0.92). The latter analysis was descriptive and these results should be interpreted with caution.[2]

At the 13-Sept-2016 database lock, 44.9% (N = 142) of patients on nivolumab, 40.8% (N=128) on combination therapy and 62.5% (N=197) on ipilimumab had died.[4] Median overall survival had not been reached for nivolumab or for combination therapy; however, it was 20.0 months (95% CI, 17.1 to 24.6) in the ipilimumab arm.[4] Treatment with nivolumab plus ipilimumab was associated with an increase in survival as compared to ipilimumab (HR: 0.55, 95% CI, 0.42 to 0.72; P < 0.0001).[4] The descriptive analysis comparing the effect of nivolumab plus ipilimumab to nivolumab on overall survival was not significant (HR: 0.88, 95% CI, 0.69 to 1.12).[5]

ORR was a key secondary endpoint in the CheckMate 067 trial. At the 17-Feb-2015 database lock, patients in the nivolumab plus ipilimumab group were more likely to demonstrate an ORR as compared to those in the ipilimumab group (57.6% [95% CI, 52.0 to 63.2] vs. 19.0% [95% CI, 14.9 to 23.8]).[2] The ORR in the nivolumab alone treatment group was 43.7% (95% CI, 38.1 to 49.3).[2] The median DOR for the three treatment groups had not been reached and the TTR was similar for patients treated with nivolumab (2.79 months [range: 2.3 to 32.9]) nivolumab plus ipilimumab (2.76 months [range: 1.1 to 11.6]) and ipilimumab (2.79 months [range: 2.5 to 12.4]).[2]

Harms

The population evaluable for safety in CheckMate 067 consisted of 937 patients who received at least one dose of their assigned therapy (nivolumab arm: 313, nivolumab plus ipilimumab: 313 and ipilimumab arm: 311).[2] At the database cut-off of 13-Sept-2016, more grade 3 to 4 treatment-related adverse events were reported in the nivolumab plus ipilimumab group (58.5%) than in the ipilimumab (27.7%) or the nivolumab treatment groups (20.8%).[5] Similar patterns were reported for grade 3 to 4 treatment-related serious adverse events (nivolumab plus ipilimumab: 36.7%, ipilimumab: 16.7% and nivolumab: 8.0%).[4] Likewise, a higher proportion of select adverse events occurred in the nivolumab plus ipilimumab group as compared to the ipilimumab and the nivolumab groups. These adverse events included: skin (nivolumab plus ipilimumab:61.3%, ipilimumab: 55.3% and nivolumab: 45.7%), gastrointestinal (nivolumab plus ipilimumab: 47.9%, ipilimumab: 37.6% and nivolumab: 22.4% vs.), hepatic (nivolumab plus ipilimumab: 32.6%, ipilimumab: 7.4%, nivolumab: 7.7%) and endocrine (nivolumab plus ipilimumab: 33.2%, ipilimumab: 11.6% and nivolumab: 17.3%).[4] These trends were also observed for grade 3 and 4 events of special interest.[4]

Table 1: Highlights of key outcomes in CheckMate 067

	Nivolumab (N = 316)	**Nivolumab + Ipilimumab (N=314)**	**Ipilimumab (N = 315)**
No. patients on treatment, n (%)[A]	313	313	311
No. PFS events (%)	174 (55.1)	151 (48.1)	234 (74.3)
Median PFS, months (95% CI)	6.9 (4.3-9.5)	11.5(8.9-16.7)	2.90 (2.8-3.4)
HR (95% CI; two-sided p-value)[AC]	0.74 (0.60 to 0.92)[†]	0.42 (0.31-0.57); P < 0.001[‡]	
No. deaths events (%)	142 (44.9)	128 (40.8)	197 (62.5)
Median overall survival months (95% CI)	NR	NR	20.0(17.1, 24.6)
HR (95% CI; two-sided p-value) [BD]	0.88 (0.69-1.12) [†]	0.55 (0.42-0.72); P < 0.0001[‡]	
ORR**,** n	138	181	60
ORR, % (95% CI)[AE]	43.7 (38.1-49.3)	57.6(52.0-63.2)	19.0(14.9-23.8)
TTR**, n**	316	314	315
Median TTR in months, (range)[BF]	2.79 (2.3-32.9)	2.76(1.1-28.8)	2.79 (2.5-17.3)
DOR**, n**	NR	NR	NR
Median DOR in months (95% CI)[AG]	NR	NR	NR

NR: Not reached; PFS = Progression-free survival; HR: Hazard ratio; ORR = Objective response rate; TTR = Time to Response; DOR = Duration of response.
A: Represents the 17-Feb-2015 database lock date for CheckMate 067
B: Represents the 13-Sept-2016 database lock date for CheckMate 067
C: PFS was defined as the time between the date of randomization and the first date of documented progression, as determined by the investigator, or death due to any cause, whichever occurs first.
D: Overall survival was defined as the time between the date of randomization and the date of death due to any cause in all patients
E: Overall response rate was defined as the proportion of patients with the best overall response which is the sum of complete or partial responses.
F: Time to objective response was defined as the time from the date of randomization to the date of the first documented complete or partial response only in patients with confirmed complete or partial response.

G: Duration of response was defined as the time from first documented complete or partial response to the date of first documented tumour progression using RECIST 1.1 or death due to any cause.
† HR represents the effect size estimate of PFS comparing nivolumab plus ipilimumab to nivolumab. This is a descriptive analysis and should be interpreted with caution.
‡ HR represents the effect size estimate comparing nivolumab plus ipilimumab to ipilimumab.
Data sources: Larkin et al (2015);[2] CheckMate 67 CSR[4]

CheckMate 069

CheckMate 069 was a double-blind, phase II RCT that assessed the effect of nivolumab plus ipilimumab and ipilimumab on ORR in 109 *BRAF* V600 wild-type carriers with advanced melanoma.[6,7] All eligible patients (including *BRAF* wild-type and *BRAF* mutation-positive carriers) were randomized (2:1) to receive either nivolumab plus ipilimumab (N= 95 and $N_{BRAF\ WT}$ = 72) or ipilimumab (N = 47 and $N_{BRAF\ WT}$ =37). All analyses conducted in the *BRAF* mutation-positive patients were considered descriptive.[8] Patients continued to be treated with their assigned therapies until they had documented disease progression, developed unacceptable toxic events or they met other withdrawal criteria.

In this trial, patients could be treated beyond progression if they continued to have investigator assessed clinical benefit or they were still tolerant to the study medication. Notably, patients originally assigned to ipilimumab had the option of crossing over to receive nivolumab 3 mg/kg IV every 2 weeks until further progression or they could receive standard of care.[8] Those assigned to the combination arm could only receive standard of care.

The primary outcome assessed in CheckMate 069 was ORR in *BRAF* wild type-carriers. The study was designed to have 87% power with a two-sided α=0.05 to show a significant difference between an ORR of 40% and an ORR of 10% for nivolumab plus ipilimumab and ipilimumab, respectively.[8] The secondary efficacy endpoints included ORR in all randomized patients, PFS in all *BRAF* wild-type carriers and PFS in all randomized patients.[8] Exploratory outcomes included overall survival, median DOR, TTR, HRQoL, safety and tolerability, and pharmacokinetic parameters.

Efficacy

The primary endpoint in CheckMate 069 was ORR assessed by the investigator using RECIST 1.1 criteria in all *BRAF* wild-type carriers. ORR was assessed at the 30-Jan-15 database lock date.[6] The Manufacturer reported that *BRAF* wild-type carriers randomized to nivolumab plus ipilimumab had a higher ORR as compared to those treated with ipilimumab (61% [95% CI, 49 to 72] vs. 11% [95% CI, 3 to 25], respectively).[6] Similar ORR estimates were obtained for all randomized patients (nivolumab plus ipilimumab: 59% [95% CI, 48 to 69]) vs. ipilimumab: 11% [95% CI, 3 to 23]).[9]

PFS was a key secondary outcome in the CheckMate 069 trial. At the 29-Feb-2016 database lock date, 43.1% of *BRAF* wild-type carriers on nivolumab plus ipilimumab and 75.7% on ipilimumab alone had disease progression or died.[9] Median PFS had not been reached for the *BRAF* wild-type carriers who were randomized to nivolumab plus ipilimumab but the median PFS was 4.4 months (95% CI, 2.8 to 5.3) for patients on ipilimumab alone.[9] The Manufacturer showed that nivolumab plus ipilimumab therapy was associated with a prolonged PFS as compared to ipilimumab in *BRAF* wild-type carriers (HR: 0.35; 95% CI, 0.21 to 0.59; P < 0.0001).[9] This was also observed for all randomized patients (HR: 0.36, 95% CI, 0.22 to 0.56; P <0.0001).[9] Overall survival was immature at the database lock.[7]

Harms

The population evaluable for safety in the CheckMate 069 consisted of 140 patients who received at least one dose of their assigned therapies (94 patients in the combination arm and 46 in the ipilimumab arm).[7] Patients in the combination treatment group were more likely to experience a grade 3 to 4 treatment-related adverse event (54.0% vs. 20.0%), a grade 3 to 4 treatment-related

serious adverse event (36.0% vs. 9.0%) or treatment-related death (3.0% vs. 0%) as compared to those in the ipilimumab group.[7] Likewise, a higher proportion of select adverse events of interest occurred in the nivolumab plus ipilimumab group as compared to the ipilimumab group, which included: skin (73.4% vs. 63.0%), gastrointestinal (48.9% vs. 34.8%), hepatic (31.9% vs. 8.7%) and endocrine (30.9% vs. 15.2%).[7] This trend was consistent for grade 3 and 4 events of special interest.

Table 2: Highlights of key outcomes in CheckMate 069

	BRAF wild-type carriers		All patients	
	Nivolumab + Ipilimumab (N=72)	Ipilimumab (N = 37)	Nivolumab + Ipilimumab (N=95)	Ipilimumab (N = 47)
No. patients on treatment, n (%)[A]	23 (10.9)	11 (5.2)	13(13.7)	6(12.8)
No. PFS events (%)	32 (73)	28 (37)	43(95)	35(47)
Median PFS, months (95% CI)	NR (7.23-NR)	4.44(2.76-5.32)	NR (7.36-NR)	3.02(2.69-5.13)
HR (95% CI; two-sided p-value)[AC]	0.36(0.21-0.60); P < 0.0001		0.36(0.22-0.56) ; P = 0.0001	
No. deaths events (%)	24(73)	18(37)	35(95)	22(47)
Median overall survival months (95% CI)	NR	24.8(10.3-NR)	NR	NR (11.9-NR)
HR (95% CI; two-sided p-value) [AD]	0.60(0.21-1.11); P = 0.098		0.74 (0.43-1.26) ; P = 0.262	
ORR**,** n	44	4	56	5
ORR, % (95% CI)[BE]	61(49.0–72.0)	11 (3.0-25.0)	59 (48.0-69.0)	11 (3.0-23.0)
TTR**, n**	72	37	95	47
Median TTR in months, (range)[BF]	2.76 (2.3-5.3)	2.66(2.5-2.7)	2.8 (2.3- 5.3)	2.7(2.5-2.7)
DOR**, n**	NR		NR	
Median DOR in months (95% CI)[AG]				

NR: Not reached; PFS = Progression-free survival; HR: Hazard ratio; ORR = Objective response rate; TTR = Time to Response; DOR = Duration of response.
A: Represents the 29-Feb-2016 database lock date for CheckMate 069
B: Represents the 30-Jan-2015 database lock date for CheckMate 069
C: PFS was defined as the time from randomization to the date of the first documented progression as assessed by the investigator per RECIST 1.1 or death due to any cause.
D: Overall survival was defined as the time between randomization to the date of death.
E: Overall response rate was defined as the proportion of patients with the best overall response which is the sum of complete or partial responses.
F: Time to objective response was defined as the time from the date of randomization to the date of the first documented complete or partial response only in patients with confirmed complete or partial response.
G: Duration of response was defined as the time from first documented complete or partial response to the date of first documented tumour progression using RECIST 1.1 or death due to any cause.
Data sources: Postow et al (2015);[6] Postow et al (2016 AACR)[9] and Hodi et al (2016)[7]

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, symptoms most important to control for respondents were: i) progression of disease, death ii) pain everyday associated with disease progression or treatment; iii) cognitive impairment, fatigue; iv anxiety, fear, depression; and v) gastrointestinal issues, including vomiting and diarrhea. Therapies used to treat this type of cancer include: ipilimumab, trametinib, dabrafenib (as monotherapies or in combination for the BRAF + population) vemurafenib, cobimetinib (as monotherapies or in combination

for the BRAF + population), aldesleukin, pembrolizumab, and nivolumab. Common adverse events experienced on treatment include: fatigue or weakness, followed by skin rash, muscle or joint pain, weight loss or loss of appetite, shortness of breath, cough or chest pain, hormone and thyroid problems, and diarrhea or colitis.

Provincial Advisory Group (PAG) Input

PAG identified the following as factors that could impact the implementation:

Clinical factors:

- Potentially limited comparative data with other PD-L1 inhibitors and with oral targeted therapies for BRAF mutation positive
- Uncertainty regarding post-progression treatments and sequencing

Economic factors:

- Potential for substantial drug wastage with both drugs
- High cost of combination therapy
- Uncertainty in the cost of monitoring and managing toxicities
- Unknown treatment duration

Registered Clinician Input

Clinicians providing input identified that the combination of nivolumab plus ipilimumab showed an improvement in response rate and progression free survival compared to ipilimumab monotherapy or nivolumab monotherapy. They also noted that PD-L1 testing is not required for treatment with this combination and that treating facilities administering combination immunotherapies should have infrastructure in place to manage treatment-related toxicities.

Summary of Supplemental Questions

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

- Critical appraisal of a manufacturer-submitted indirect treatment comparison (ITC) of the relative efficacy and safety of nivolumab plus ipilimumab versus active therapies in treatment-naïve adult patients with advanced (unresectable or metastatic) melanoma.

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 6.3.2.1a and 6.3.2.1b (regarding internal validity).

Table 2: Assessment of generalizability of evidence for the combination of nivolumab plus ipilimumab for metastatic melanoma[2,6,7]

<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>Population</td><td>Stage of disease</td><td>CheckMate 067
• Inclusion: Adult patients ≥ 18 years with histologically confirmed, unresectable, stage III or IV untreated melanoma
<table>
<tr><th>Metastasis stage, n(%)</th><th>Nivo(N= 316)</th><th>Nivo + Ipi (N=314)</th><th>Ipi (N = 315)</th></tr>
<tr><td>M1c</td><td>184 (58.2)</td><td>181 (57.6)</td><td>183 (58.1)</td></tr>
<tr><td>M0, M1a, or M1b</td><td>132 (41.8)</td><td>133 (42.4)</td><td>132 (41.9)</td></tr>
<tr><td>Not reported</td><td></td><td></td><td></td></tr>
</table>
The majority of patients randomized to the combination arm and ipilimumab have a metastasis stage of M1c (57.6% and 58.1%, respectively.)

CheckMate 069
• Adult patients ≥ 18 years with histologically confirmed, unresectable, previously untreated stage III or IV melanoma with measurable disease
<table>
<tr><th></th><th colspan="2">CHECKMATE 069
BRAF wt patients</th><th colspan="2">CHECKMATE 069
All patients</th></tr>
<tr><th>Metastasis stage</th><th>Nivo + Ipi (N=72)</th><th>Ipi (N = 37)</th><th>Nivo + Ipi (N=95)</th><th>Ipi (N = 47)</th></tr>
<tr><td>M1c</td><td>37 (52)</td><td>20 (54)</td><td>44 (46)</td><td>21 (45)</td></tr>
<tr><td>M0, M1a, or M1b</td><td>34 (47)</td><td>16 (43)</td><td>50 (53)</td><td>25 (53)</td></tr>
<tr><td>Not reported</td><td>1 (1)</td><td>1 (3)</td><td>1 (1)</td><td>1(2)</td></tr>
</table>
Among BRAF wt carriers, the majority of patients in both treatment groups have a metastasis stage of M1c (Nivolumab + Ipilimumab: 52% and ipilimumab: 54%). In contrast, among all randomized patients, the majority</td><td>Does stage limit the interpretation of the trial results with respect to the target population (e.g., Canadian clinical practice, patients without the factor, etc.)?</td><td>The majority of patients randomized to the combination arm had a metastasis stage of M1c. The Clinical Guidance Panel (CGP) agree that the majority of patients who are treated in clinical practice are stage M1C. The CGP agree that treatment with the combination of nivolumab plus ipilimumab can be generalizable to disease stage M1c, M0, M1a or M1b metastasis stage. Patients should not have had previous immunotherapy.</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></td><td>of patients have a metastasis stage of M0, M1a or M1b (Nivolumab + Ipilimumab: 53% and ipilimumab: 53%).</td><td></td><td></td></tr>
<tr><td></td><td>Performance Status</td><td>Both trials only included patients with an ECOG (Eastern Cooperative Oncology Group) of 0 to 1. Those with an ECOG > 2 were excluded.

There is also a difference between ECOG across studies, where patients in CheckMate 067 were more likely to have an ECOG of 0 (for all treatment groups) as compared to those in CheckMate 069.

<table>
<tr><th></th><th colspan="3">CHECKMATE 067
All patients</th><th colspan="2">CHECKMATE 069
All patients</th></tr>
<tr><th>ECOG</th><th>Nivo (N = 316)</th><th>Nivo + Ipi (N=314)</th><th>Ipi (N = 315)</th><th>Nivo + Ipi (N=95)</th><th>Ipi (N = 47)</th></tr>
<tr><td>0</td><td>238 (75.3)</td><td>230 (73.2)</td><td>224 (71.1)</td><td>79 (83)</td><td>37 (79)</td></tr>
<tr><td>1</td><td>77 (24.4)</td><td>83 (26.4)</td><td>91 (28.9)</td><td>14 (15)</td><td>10 (21)</td></tr>
<tr><td>2</td><td>1 (0.3)</td><td>0</td><td>0</td><td>2 (2)</td><td>0</td></tr>
<tr><td>NR</td><td>0</td><td>1 (0.3)</td><td>0</td><td></td><td></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 trial was restricted to patients with ECOG 0-1 and specifically excluded patients with ECOG ≥2. However, the CGP noted that in routine clinical practice, most patients with advanced melanoma are ECOG PS 1 or 2. The CGP agrees that treatment may be reasonably extended to patients with ECOG PS 2 and the decision should be left to the discretion of the treating oncologist.</td></tr>
<tr><td></td><td>Age</td><td>Patients in Checkmate 067 and Checkmate 069 were not excluded by age.

<table>
<tr><th></th><th colspan="3">CHECKMATE 067
All patients</th><th colspan="2">CHECKMATE 069
All patients</th></tr>
<tr><th></th><th>Nivo (N = 316)</th><th>Nivo + Ipi (N=314)</th><th>Ipi (N = 315)</th><th>Nivo + Ipi (N=95)</th><th>Ipi (N = 47)</th></tr>
<tr><td>Median (range)</td><td>60 (25-90)</td><td>61.0 (18-88)</td><td>62.0 (18-89)</td><td>64 (27-87)</td><td>67 (31-80)</td></tr>
</table></td><td>Should there be an age restriction on who should be treated with the combination of nivolumab and ipilimumab?</td><td>Both trials did not exclude patient by age. The median age of patients was 61 in Checkmate-067 and 64 in CheckMate-069 respectively. The CGP agrees that the combination of nivolumab and ipilimumab can be considered for all ages, if appropriate in all other medical aspects.</td></tr>
</table>

Domain	Factor	Evidence	Generalizability Question	Clinical Guidance Panel Assessment of Generalizability
	Autoimmune Disorders	Checkmate 067 and Checkmate 069 excluded patients if they had a previous history of autoimmune disorders.	Does the exclusion of patients with autoimmune disorders limit the interpretation of the trial results with respect to the target population?	Although patients with a previous history of autoimmune disorders were excluded from both trials, the CGP agrees that in clinical practice, treatment with the combination of nivolumab plus ipilimumab may be considered in carefully selected patients with well controlled autoimmune disorders and the decision to treat the patient should be left to the discretion of the responsible oncologist. For example, therapy should not be implemented if there is active immune disease (e.g. colitis). However, thyroid disease (hypo/hyperthyroidism) that is clinically managed should not be a contraindication.

<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>Metastatic Sites</td><td>The majority of patients in both trials did not have brain metastases at baseline.
<table><tr><th></th><th colspan="3">CHECKMATE 067 All patients</th><th colspan="2">CHECKMATE 069 All patients</th></tr><tr><th></th><th>Nivo (N = 316)</th><th>Nivo + Ipi (N=314)</th><th>Ipi (N = 315)</th><th>Nivo + Ipi (N=95)</th><th>Ipi (N= 47)</th></tr><tr><td>Yes</td><td>8 (2.5)</td><td>11 (3.5)</td><td>15 (4.8)</td><td>4 (4)</td><td>0</td></tr><tr><td>No</td><td>308 (97.5)</td><td>303 (96.5)</td><td>300 (95.2)</td><td>90 (95)</td><td>47 (100)</td></tr></table></td><td>Did the exclusion of patients with certain sites of metastatic disease limit the interpretation of the trial results with respect to the target population?</td><td>Patients with uncontrolled brain metastases were excluded from the trials. This exclusion criteria is similar to most drugs as systemic therapies have poor CNS penetration. Although there were small proportions of patients with stable brain metastases (3.5% in CheckMate-067 and 4% in Checkmate-069, respectively), the CGP agrees that treatment with the combination of nivolumab plus ipilimumab should be offered to patients with treated stable brain metastases and based on clinical judgement.</td></tr>
<tr><td></td><td>Biomarkers</td><td>Both CheckMate 067 and 069 looked into the effect PD-L1 and lactase dehydrogenase biomarkers.</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>LDH is a biomarker of prognosis but does not define patients who should receive therapy or not.
PD-L-1 is a biomarker that suggests the probability of benefit but does not exclude patients from treatment.</td></tr>
<tr><td>Intervention</td><td>Line of therapy</td><td>Trials CheckMate 067 and CheckMate 069 investigated the combination of nivolumab plus ipilimumab in patients with untreated metastatic melanoma. Neither CheckMate 067 nor CheckMate 069 addressed any issues of sequencing for BRAF mutation-positive carriers.</td><td>Are the results of the trial generalizable to other lines of therapy?</td><td>Both trials investigated the combination of nivolumab plus ipilimumab in treatment naïve patients and therefore, interpretations regarding sequencing can only be</td></tr>
</table>

Domain	Factor	Evidence	Generalizability Question	Clinical Guidance Panel Assessment of Generalizability
				considered for treatment naïve patients with advanced melanoma.
Comparator	Standard of Care	CheckMate 067 and CheckMate 069 only assessed the effect of nivolumab and/or ipilimumab in both BRAF wild-type and mutation-positive carriers. Furthermore, the submitter did not provide any information on the effect of BRAF inhibitors in the indirect comparison.	If the comparator is non-standard, are the results of the trial applicable in the Canadian setting?	Generalizable. The trial comparators are applicable to the Canadian setting. The current standard of care in Canada are: Nivolumab monotherapy, Ipilimumab monotherapy, Pembrolizumab monotherapy
Setting	Location of the participating centres	At the Checkpoint meeting, the Manufacturer stated that "at the time that CheckMate-067 was established, the nivolumab plus ipilimumab regimen was still new and the decision was made to go to sites that had I-O experience. Therefore, the vast majority of the sites were academic institutions." This was similar for the Checkmate 069 trial.	If the trial was conducted only in academic centres are the results applicable in the community setting?	The CGP agrees that treatment should be limited to centres with clinicians who have experience with the combination of nivolumab and ipilimumab. The centres should also be able to manage the adverse events associated with treatment with the combination of nivolumab plus ipilimumab, particularly infusion related reactions and serious immune mediated toxicities.
	Supportive medications, procedures, or care	In the Checkmate 067, the Manufacturer stated that IMM concomitant medications were administered for management of AEs in 55.3%, 84.3%, and 59.5% of subjects in the nivolumab, nivolumab plus ipilimumab, and ipilimumab groups, respectively. Additionally, the most commonly used type of IMMs used in the trial were systemic corticosteroids (41.2% nivolumab group, 78.0% nivolumab plus ipilimumab group, and 49.5% ipilimumab group). Likewise, IMM were also given to patients in Checkmate 069 to manage AEs; however, patients in the nivolumab plus ipilimumab group were more likely to be treated with an IMM as compared to those in the ipilimumab group (89.4% and 54.3%). A similar trend was observed for patients receiving corticosteroids for systemic use (nivolumab + ipilimumab: 79.8% and ipilimumab: 47.8%).	Are the results of the trial generalizable to a setting where different supportive medications, procedures, or care are used?	The CGP agrees that the support medications, procedures and care given in both trials are generalizable to the majority of Canadian treatment centres.

1.2.4 Interpretation

Despite recent treatment advances for metastatic melanoma, patients affected by this disease and their caregivers continue to experience significant challenges, including time lost from work and financial stresses, burden on colleagues and families, anxiety and depression, and physical limitations. As a result, research continues to investigate new therapies for advanced melanoma that can alleviate many of these problems. Specifically, there is a need for treatments that are more effective and less toxic. The introduction of single agent immuno-oncology drugs (e.g. ipilimumab, pembrolizumab, and nivolumab) and combination targeted therapies (e.g. dabrafenib plus trametinib and vemurafenib plus cobimetinib) in the first line setting has improved outcomes significantly and resulted in long-term disease control in a minority of patients. However, there remains a considerable unmet need for more effective and tolerable systemic therapies that can increase the proportion of long term survivors with advanced melanoma.

Two recent double-blind randomized controlled trials have examined the efficacy of nivolumab plus ipilimumab versus ipilimumab monotherapy, including a phase III trial (CheckMate 067, N = 945) and a phase II trial (CheckMate 069, N= 142).

In CheckMate 067, progression free survival (PFS) and overall survival (OS) were co-primary endpoints. Both PFS and OS favored the combination of nivolumab plus ipilimumab. At the database lock of 17-Feb-2015, the median PFS was 11.5 months (95% CI, 8.9 to 16.7) for patients treated with nivolumab plus ipilimumab and 2.9 months (95% CI, 2.8 to 3.4) for patients treated with ipilimumab (HR: 0.42; 99.5% CI, 0.31 to 0.57; P < 0.001). At a subsequent database lock of 13-Sept-2016, the median OS had not yet been reached for the combination of nivolumab and ipilimumab, but was approximately 19.9 months for ipilimumab alone (95% CI, 17.08 to 24.61) (HR: 0.55, 95% CI, 0.42 to 0.72; P < 0.0001). Thus, the combination of nivolumab plus ipilimumab provides a clinically meaningful progression free and overall survival benefit over ipilimumab monotherapy in advanced melanoma.

These positive findings must be interpreted in the context of the safety and potential harms associated with immunotherapy. The vast majority of patients (98.5% of those receiving nivolumab plus ipilimumab, 86.7% of those on nivolumab and 86.2% of those on ipilimumab) experienced an adverse event. Specifically, patients on nivolumab plus ipilimumab were more likely to experience a grade 3 to 4 treatment-related adverse event (58.5% vs. 20.8 vs. 27.7%), a grade 3 to 4 treatment-related serious adverse event (36.7% vs. 8.0% vs. 16.7%) and treatment-related death (0.6% vs. 0.3% vs. 0.3%) compared to those receiving nivolumab alone, and ipilimumab alone, respectively.

Similar findings were observed in the smaller CheckMate 069 trial where the primary outcome was objective response rate (ORR) in BRAF wild type-carriers. ORR was assessed at the 30-Jan-2015 database lock date. BRAF wild-type carriers randomized to nivolumab plus ipilimumab experienced a higher ORR as compared to those treated with ipilimumab (61% [95% CI, 49 to 72] vs. 11% [95% CI, 3 to 25], respectively). Comparable observations were reported for all randomized patients (both BRAF wild-type and mutant carriers), where there was a higher ORR in patients in the nivolumab plus ipilimumab group (59% [95% CI, 48 to 69]) as compared to the ipilimumab group (11% [95% CI, 3 to 23]).

Toxicity profiles were similar to those observed in CheckMate 067 and almost all patients experienced an adverse event. In particular, patients in the combination treatment group were more likely to experience a grade 3 to 4 adverse event (69.0% vs. 44%), a grade 3 to 4 treatment-related adverse event (54.0% vs. 20.0%), a grade 3 to 4 treatment-related serious adverse event (36.0% vs. 9.0%) and treatment-related death (3.0% vs. 0%) compared to those receiving ipilimumab alone.

Patient reported outcomes were assessed in the CheckMate trials. Overall, in CheckMate 067, there was no clinically meaningful difference in health related quality of life for patients in the nivolumab plus ipilimumab group using the minimally important difference of greater than 10 points in the EORTC QLQ-C30. Likewise, there were no clinically meaningful differences using the EQ-5D instrument (MID ≥ 0.08) or the EQ-5D VAS instrument (MID ≥ 7 points). In CheckMate 069, quality of life was also measured using the EORTC QLQ-C30. It was noted that health related quality of life worsened early on in week 7, but improved and remained stable over time for both the nivolumab plus ipilimumab and ipilimumab treatment arms. Similar health related quality of life effect estimates were reported for the EQ-5D instrument (MID ≥ 0.08) and the EQ-5D VAS instrument (MID ≥ 7 points).

Despite the compelling evidence of a survival benefit with the combination of nivolumab and ipilimumab as demonstrated in the CheckMate studies, there remains uncertainty about how the combination should best be used in the real world setting, given the heterogeneity of treatments currently available to be used in routine clinical practice. In particular, it is unclear how best to sequence therapies or to use the combination of nivolumab plus ipilimumab in patients who have been previously treated with or currently on oral BRAF/MEK targeted therapies, or previously on ipilimumab monotherapy, or previously or currently on PD-1 inhibitor monotherapy without disease progression. The role of biomarkers in the form of PD-L1 testing to guide therapeutic decision making remains unclear at this time.

Furthermore, a clinically relevant issue that was not fully addressed in the clinical trials is the important comparison of efficacy between the combination of nivolumab plus ipilimumab and nivolumab monotherapy since PD-1 inhibitor monotherapy has rapidly emerged as the treatment of choice in first-line management of advanced melanoma. CheckMate 067 was not designed to compare the combination of nivolumab plus ipilimumab to nivolumab monotherapy. Numerically, PFS favored the combination of nivolumab plus ipilimumab (HR: 0.74, 95% CI, 0.60 to 0.92) when compared to nivolumab monotherapy, but this analysis must be interpreted with significant caution since it is descriptive, unplanned, and underpowered. Likewise, the ad hoc descriptive analysis comparing the effect of the combination of nivolumab plus ipilimumab to nivolumab monotherapy demonstrated no difference in OS as the confidence interval crossed 1 (HR: 0.88, 95% CI, 0.69 to 1.12).

The PAG provided feedback on the pCODR Expert Review Committee's (pERC's) Initial Recommendation that the combination of nivolumab plus ipilimumab was not compared against pembrolizumab, previously recommended by pCODR as first line immunotherapy over ipilimumab, independent of BRAF mutation status. Pembrolizumab has been implemented as first line, standard of care therapy in most Canadian jurisdictions. Ipilimumab is no longer a valid comparator in Canada and nivolumab is recommended only for BRAF wild type tumors. Pembrolizumab is the most relevant standard of care for advanced melanoma as it is recommended for patients independent of BRAF status and it has a more favorable administration schedule. PAG noted that there were concerns with the use of an indirect comparison against pembrolizumab. However, clinicians have repeatedly indicated that pembrolizumab and nivolumab are considered clinically/therapeutically equivalent. In response to PAG's feedback, the CGP acknowledge that at the time the CheckMate-067 trial was designed, ipilimumab was an appropriate comparator. However, PD-inhibitors, such as pembrolizumab and nivolumab have recently become available in the first line setting for patients with metastatic melanoma who are treatment naive. Specifically, pembrolizumab is available in the first line setting independent of BRAF mutation status and nivolumab is available for patients with BRAF wildtype disease based on provincial funding criteria. It is unlikely that there will be future direct comparative trials comparing the efficacy of pembrolizumab and the combination of nivolumab and ipilimumab. The submitted ITC sought to compare the clinical effectiveness of the combination of nivolumab plus ipilimumab compared to pembrolizumab. However, due to the substantial heterogeneity in the patient characteristics in

the included studies in the indirect treatment comparison, the CGP and Methods team re-iterate that there is uncertainty in the comparative efficacy estimates. Therefore, the CGP could not offer an opinion on the relative efficacy of pembrolizumab and the combination therapy.

The PAG also provided feedback on pERC's Initial Recommendation that the combination was not compared against BRAF/MEK targeted agents, previously recommended by pCODR for first line treatment in patients with BRAF mutated disease. A number of jurisdictions do not allow sequencing of BRAF/MEK inhibitors after immunotherapy, thus BRAF/MEK targeted agents are the first line standard of care for patients with BRAF mutated disease. Registered clinicians provided feedback on pERC's Initial Recommendation indicating that they disagree with the recommendation to limit funding to treatment naïve patients, as the clinicians strongly support the use of nivolumab plus ipilimumab either as a first line immunotherapy or second line post-BRAF targeted therapy. The latter would also be consistent with Ontario's funding for single agent immunotherapies. Furthermore, a patient group, Melanoma Network of Canada, provided feedback on pERC's Initial Recommendation that the combination therapy should be considered in second line as well as first line, for patients that have failed targeted therapies. In response to PAG's feedback, the CGP acknowledge that the current standard of treatment for patients with metastatic melanoma who are BRAF mutation positive are BRAF targeted agents (ex. trametinib, dabrafenib, vemurafenib) based on provincial funding criteria. The CGP are not aware of any trials evaluating the clinical effectiveness of BRAF targeted therapies and the combination in the treatment naïve metastatic melanoma setting. The CGP re-iterate that the submitter attempted to compare the effect of nivolumab plus ipilimumab compared to targeted agents in BRAF mutation-positive carriers in the submitted indirect treatment comparison. However, the submitter was unable to do so. Therefore, the comparative efficacy of the combination compared to targeted agents for BRAF mutation positive carriers is unknown. There is uncertainty as to whether the benefits seen with the combination of nivolumab plus ipilimumab in previously untreated patients with advanced melanoma would be observed in those patients who have already been treated with or are currently being treated with either single agent immunotherapy or BRAF/MEK targeted therapy. Furthermore, the CGP is unaware of any evidence to guide optimal sequencing of immune checkpoint drugs (CTLA-4 and PD1 inhibitors) and BRAF/MEK inhibitors.

1.3 Conclusions

The Clinical Guidance Panel (CGP) concluded that there is a net clinical benefit for patients with advanced melanoma treated with the combination of nivolumab and ipilimumab, compared to ipilimumab alone, based on the findings reported in one large randomized phase III clinical trial supported by the findings from one smaller randomized phase II clinical trial. Both trials were well designed and conducted. The study results reported to date demonstrate a clinically and statistically significant benefit in overall survival, progression free survival, and objective response rate for nivolumab plus ipilimumab compared with ipilimumab alone. Adverse event profiles were more prevalent among those treated with nivolumab plus ipilimumab than those treated with ipilimumab alone but are manageable in the hands of physicians familiar with the use of immunotherapy drugs.

The CGP also considered that:

- There is uncertainty as to whether the benefits seen with the combination of nivolumab plus ipilimumab in previously untreated patients with advanced melanoma would be observed in those patients who have already been treated with or are currently being treated with either single agent immunotherapy or BRAF/MEK targeted therapy.

- In terms of the submitted indirect comparison that compared nivolumab plus ipilimumab to pembrolizumab 2 mg Q3w in patients with advanced melanoma. The CGP and Methods team considered the indirect comparison, and agreed that the comparative efficacy of nivolumab plus ipilimumab and pembrolizumab is uncertain given the substantial heterogeneity in the patient characteristics in the included studies (CheckMate 067, KEYNOTE 002 and KEYNOTE 006), which were used in the submitted indirect treatment comparison.
- Additionally, the effect of nivolumab plus ipilimumab compared to targeted agents in *BRAF* mutation-positive carriers is unknown.
- In addition, based on the current available data, firm conclusions cannot be drawn at this time regarding the clinically pertinent comparison of the combination of nivolumab plus ipilimumab versus nivolumab monotherapy as this comparison was exploratory. Numerically, there may be a trend favoring the combination of nivolumab plus ipilimumab over nivolumab monotherapy with respect to PFS outcomes, but there appears to be no difference between the combination and nivolumab monotherapy in terms of OS.
- The PAG provided feedback on pERC's Initial Recommendation requesting guidance on whether it would be clinically reasonable to use pembrolizumab after induction with the combination of nivolumab plus ipilimumab instead of nivolumab, since pembrolizumab is given every 3 weeks, a more favourable administration schedule, and is used regardless of BRAF status. There is no evidence that pembrolizumab should be used as maintenance therapy after the induction of the combination of nivolumab plus ipilimumab. Maintenance therapy should be administered as per the CheckMate-067 trial, with nivolumab monotherapy.
- The PAG provided feedback on pERC's Initial Recommendation that if nivolumab plus ipilimumab combination therapy is discontinued due to toxicities, treatment with nivolumab monotherapy would likely occur after toxicity resolution. PAG is requesting guidance on clarification of re-starting treatment with nivolumab monotherapy in the clinical scenarios of toxicity resolution with no disease progression, or after disease progression during a treatment break. In response to the PAG feedback, the CGP note that if discontinuation of the combination therapy was due to side effects from ipilimumab and not nivolumab, the re-initiation of nivolumab monotherapy would be reasonable in clinical practice. If there is disease progression on nivolumab during a treatment break, nivolumab monotherapy should not be re-started.
- The PAG provided feedback on pERC's Initial Recommendation requesting guidance on the extrapolation of eligibility for the combination of nivolumab plus ipilimumab to patients with ocular melanoma and whether the results of the CheckMate-067 trial could be extended to include these patients. In response to PAG's feedback, the CGP note that guidance on eligibility for the combination of nivolumab plus ipilimumab to patients with ocular melanoma was not requested during the pCODR review through the PAG input. However, the CGP note that patients with ocular melanoma were excluded from CheckMate-067. Therefore, the results of the trial cannot be extended to patients with ocular melanoma.

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

Melanoma is a malignancy of melanocytes which are distributed throughout the body including skin, eyes, and gastrointestinal tract. Although primary melanomas can occur in a variety of anatomical sites, the skin is the most common, comprising 95% of cases. In Canada, 6,800 new cases of primary melanoma are expected in 2015 and approximately 1,150 patients will die from melanoma.[10] The incidence of melanoma has been steadily increasing over the past several decades, with recent increases of 2.3% per year in men between 2001 and 2010, and 2.9% per year among women between 2001 and 2010. At present, the lifetime probability of developing a melanoma for women is 1 in 85 and for men is 1 in 67.[11] Risk factors for melanoma include a history of sunburns in childhood, fair skin, and the use of tanning beds. There has been a recent spike in the incidence of melanoma in adolescent females. This is thought to be due to the increased use of tanning beds which is more common in adolescent females as opposed to adolescent males.

Staging of melanoma is based on the current AJCC 7th Edition Classification.[12] The tumour characteristics principally involve the Breslow height, mitotic rate and the presence or absence of ulceration in the primary. The detection of microscopic and macroscopic lymph node involvement, serum lactate dehydrogenase and the sites of metastatic disease are integral components to the staging classification. All of these factors have been shown to be important prognostic variables which influence patient outcomes and which help to guide management decisions.

2.2 Accepted Clinical Practice

In early stage melanoma, cures are commonly achieved with surgery alone. The primary tumour is excised with appropriate margins. Depending upon the Breslow height, mitotic rate, presence of ulceration and location of the primary, a sentinel node biopsy may be performed to assess nodal status. If the sentinel node is positive then a completion node dissection of the surrounding nodal basin is often performed in order to reduce the risk of a regional recurrence.[13] Although only 5% of patients actually present with metastatic disease, the majority of patients who die from melanoma, will have developed recurrent and/or distant disease. Approximately one-third of patients with early stage melanoma will develop metastasis whereas half of patients with nodal disease will recur and likely die from the development of metastatic disease.[14] Brain metastases are relatively common in advanced melanoma and occur in up to 75% of patients with overt metastatic disease.[15] They often prove to be relatively refractory to radiotherapy and systemic treatment and are associated with a particularly dismal prognosis.

Highly selected patients with Stage IV disease may benefit from surgical resection of the metastases and 5 year survival in these patients ranges from 15 to 25%. For those patients who are not candidates for surgical resection, systemic treatment with chemotherapy is the most commonly offered treatment outside of a clinical trial. Unfortunately, the prognosis for these patients prior to 2012 remains poor. The median survival is six to nine months and the five-year survival is approximately 6%.[16] In spite of multiple phase II and phase III trials with systemic therapy, the objective response to systemic chemotherapy agents remains low and has generally been less than 15%. Until recently, the median survival rates with both single and multiple drug combinations had not changed in the past several decades and was in the range of six to twelve months.

Over the past 30 years, the standard first line systemic therapy has been dacarbazine (DTIC).[13,17] There were no randomized studies comparing DTIC versus BSC to show either an improvement in overall survival or improvements in quality of life. Although this intravenous alkylating agent is generally well tolerated, complete responses are rare.[18-23] In the 1990's the FDA approved the use of high dose interleukin-2 based on phase II data showing an overall response rate of 16% but also a durable complete response rate of 5%, extending beyond five years.[24,25] Unfortunately, high dose interleukin-2 is accompanied by significant toxicity and requires intense cardiac monitoring and hemodynamic support. Interleukin-2 has been used in only a few centres but is largely unavailable throughout Canada.

A very wide spectrum of chemotherapeutic and immunological treatment approaches have been explored in metastatic melanoma with, until recently, limited to no success. Patient outcomes have not changed significantly over the past three decades.[18] Nevertheless, what has become apparent is that melanoma represents a heterogeneous group of diseases which appear to have varying genetic abnormalities which drive cellular proliferation and metastases.[26-28] The MAP kinase signalling pathway appears to be a key regulatory mechanism for cell growth, and differentiation in melanoma.[29] Mutations in the BRAF protein in this pathway can alter the activity of BRAF and result in uncontrolled cellular proliferation and increased potential for metastatic spread.[30] Approximately 50% of human melanomas appear to have an activating mutation in BRAF and this has become a potential key target for inhibition with new molecular therapies.[31]

Vemurafenib is a BRAF inhibitor that selectively targets the mutated BRAF V600 and was approved in August 2011 by the FDA as a treatment for late stage or unresectable melanoma in patients harbouring a V600E mutation. It was subsequently approved by Health Canada in February 2012.[32-34] Just fewer than 50% of all melanoma patients will harbour a V600 mutation, with the majority being V600E. In the randomized Phase III study (BRIM3,) there was a relative reduction of 63% in the risk of death and a 74% relative reduction in the risk of tumor progression. The overall response rate was 48%.[35] This is now a standard first line treatment for advanced, unresectable melanoma in patients harbouring a V600 Mutation. Since the introduction of vemurafenib into clinical practice, there has been a marked increase in understanding of the pathways of activity and resistance of the BRAF/ MEK pathway. The addition of a MEK inhibitor to a BRAF inhibitor as first line treatment has helped to overcome some of the resistance mechanisms. As of 2016, two BRAF inhibitors have become available: vemurafenib and dabrafenib, and two MEK inhibitors: trametimb and cobimetinib. It is known that individuals will respond to either a BRAF inhibitor as a single agent or a MEK inhibitor as a single agent. Using a MEK inhibitor as second line treatment post progression on a BRAF inhibitor does not result in a significant response. The combination of BRAF and MEK inhibitors has been compared to BRAF inhibitors alone and to MEK inhibitors alone.

There are two phase III studies comparing dabrafenib plus trametimb. The first phase III study (COMBI-d) compared first line treatment with Dabrafenib and trametimb to dabrafenib and placebo.[36] Median progression free survival was 9.3 months in the combination arm and 8.8 months in the dabrafenib arm (HR 0.75, p=0.03). The overall response rate was 67% in the combination arm and 51% in the BRAF inhibitor arm alone, p=0.002. These findings suggest that the combination was superior to BRAF inhibitor alone. This data was updated, with a median follow up of 17 months, median progression free survival for the combination arm was 11 months versus 8.8 months for the BRAF inhibitor arm alone; median overall survival in the combination arm was 25.1 months and 18.7 months in the BRAF inhibitor arm. 47% of patients died in the combination treated arm versus 58% in the BRAF inhibitor arm (HR 0.71, p=0.01).

A second phase III trial (COMBI-v) compared dabrafenib plus trametimb to vemurafenib monotherapy. The median progression free survival for the combination was 11.4 months versus 7.3 months for the monotherapy (HR of 0.5, p <0.001). The overall response rate was 64% for the combination arm compared to 51% for the monotherapy arm. Median overall survival had not been reached for the combination arm but was 17.2 months for the monotherapy arm. Therefore, this

data suggests that a combination of BRAF and MEK inhibitors is superior to either of the BRAF inhibitors alone.[37]

A second combination of drugs has been studied combining the BRAF inhibitor vemurafenib with the MEK inhibitor cobimetinib. There has been one phase III study comparing the combination to a BRAF inhibitor alone. The median progression free survival in the combination arm was 9.9 months versus 6.2 in the single agent arm. The overall response rate was 68% in the combination arm versus 45% in the control arm. Once again, the data suggest that a combination of a BRAF and a MEK inhibitor is superior to a BRAF inhibitor alone.[38] Thus a combination of a BRAF and MEK inhibitor is considered standard treatment for patients with BRAF mutated melanoma.

Ipilimumab is a monoclonal antibody that binds to and blocks the cytotoxic T-lymphocyte associated antigen 4 (CTLA4) located on cytotoxic T-lymphocytes. CTLA4 appears to play an important role in the regulation of the immune response.[39-42] In 2012, ipilimumab received a Health Canada indication for the treatment of unresectable or metastatic melanoma in patients who had failed or did not tolerate other systemic therapy for advanced disease. Since that time, it has been widely used across Canada as second line therapy given at a dose of 3 mg per kg every 3 weeks for a total of 4 doses. Provision for re-induction has been provided for patients who progress following a response to Ipilimumab treatment.

The initial approval was principally based upon the findings of a multi-center, double blind placebo controlled trial consisting of three treatment arms randomly assigned 3:1:1 to ipilimumab 3 mg/kg + cancer vaccine GP100, ipilimumab alone, GP100 alone.[43] The study demonstrated an improvement in overall survival (HR 0.66) in the two ipilimumab containing arms compared to GP100 alone. Median overall survival for the ipilimumab arms was 10 months compared to 6.4 months in GP100 alone arm. Adverse events were primarily immune related, which included diarrhea/colitis, and endocrine problems. Fatigue, rash and anorexia were common but were seldom grade 3 or greater. The study represents the first randomized controlled trial which demonstrated an improvement in survival in patients with metastatic disease. In 2011, Robert and colleagues reported on a randomized controlled trial comparing ipilimumab 10 mg/kg + dacarbazine 850 mg/m^2 versus dacarbazine alone in patients who were previously untreated.[44] Overall survival was improved in the ipilimumab containing arm (HR 0.72) and appeared to extend out to 3 years. The median survival was 11.2 months in the ipilimumab arm compared to 9.1 months in the dacarbazine arm. Immune related events were observed in the ipilimumab arm and grade 3 or 4 adverse events were more common (56.3% vs 27.5%). Rates of elevated liver enzymes appeared to be higher than observed in other studies in which ipilimumab was used alone. Although the progression free survival and overall survival were similar in these trials, the relative impact of the 3 and 10 mg doses of ipilimumab, which were used cannot be directly assessed. Furthermore the positive or negative effect on outcomes and toxicity which the GP100 or dacarbazine had within the combination arms of each trial also remains uncertain.

Due to the futility of chemotherapy, ipilimumab quickly moved into first line treatment. The milestone survival analysis was published by Maio et al. as Five Years Survival Rates for Treatment Naive Patients with Advanced Melanoma Receiving Ipilimumab plus Dacarbazine in Phase III trials.[45] A landmark analysis was conducted to exclude patients with overall survival less than 6 months, marking the maximal time to response observed in the study. The median overall survival for the ipilimumab plus the dacarbazine group was 11.2 months and 9.1 months for the dacarbazine group, (HR 0.69). At a minimum follow up of five years 18.2 % of patients in the ipilimumab plus dacarbazine were still alive compared with 8.8 % of patients in the dacarbazine arm, p=0.002. At a minimum follow up of five years, 40 patients on ipilimumab plus dacarbazine group and 20 patients on the dacarbazine group were alive. Seven patients remained on ipilimumab maintenance therapy at the time of the data lock. Subsequent treatment was received by patients who survived these five years in both of the groups. In the dacarbazine arm, 30% of

patients continued to receive ipilimumab plus Dacarbazine and 55% of patients on the chemotherapy arm received at least one subsequent treatment including chemotherapy, immunotherapy, radiotherapy, and/or surgery.

Schadendorf et al recently published in the Journal of Oncology a Pooled Analysis of Long-Term Survival Data From Phase II and Phase III Trials of Ipilimumab in Unresectable or Metastatic Melanoma.[46] The pooled data included 1,861 patients from ten perspectives trials, 2 retrospective studies, and two phase II trials as well as an EAP program. Most patients had been previously treated. Patients receiving either 3 mg/kg or 10 mg/kg were included. The results showed that the median overall survival was 11.4 months. The survival curve began to plateau around year three. The three year survival rates were 22% for all patients, 26% for treatment naïve patients and 20% for previously treated patients. This data was derived from a pooled database and does have limitations; however, it does provide supporting evidence for the potential durability of the ipilimumab response and survival.

The phase III trial in patients with metastatic melanoma comparing 3mg per kg of ipilimumab versus 10 mg per kg of ipilimumab has completed its accrual. The final data collection for primary outcomes was February 2016 and the estimated study completion date is July 2017. In this study long term adverse effects were also documented and the most common adverse effect of any grade affected was skin toxicity, including rash, vitiligo and pruritus. Low grade adverse effects that affected the gastrointestinal tract were primarily increased liver function tests. Grade 3 to 4 adverse effects were reserved exclusively to the skin and there were no grade 5 adverse effects. This study documents that the overall five year survival observed in the ipilimumab group was approximately double the control group, as well as the historically expected survival for these patients. A plateau in the survival curve begins at approximately three years and has been observed in other data sets.

There are two PD-1 inhibitors that have Health Canada approval for metastatic melanoma: Pembrolizumab and Nivolumab.

Recently, KEYNOTE-001, Three Year Overall Survival with Patient with Advanced Melanoma treated with Pembrolizumab, was presented at ASCO.[47] In this study patients were enrolled in both ipilimumab naive and ipilimumab treated cohorts and received 2 mg/kg of pembrolizumab every 3 weeks versus 10 mg/kg every 3 weeks vs 10 mg/kg every 2 weeks until intolerable toxicity, progression, or investigator decision. The median follow up duration of 32 months. The 36 month overall survival rate was 38% in patients treated with pembrolizumab 2 mg every 3 weeks, 39% in pembrolizumab 10 mg every 3 weeks and 43 % in pembrolizumab 10 mg every 2 weeks. In the ipilimumab treated patients, the 24 month overall survival rate was 46% and the 36 month overall survival rate was 41%. In the ipilimumab naïve group, 24 month overall survival rate was 54%, and the 36 month overall survival rate was 41%. In the treatment naïve group, 24 month overall survival rate was 60% and the 36 month overall survival rate was 45%. The authors concluded that the data supported the use of pembrolizumab in patients with advanced melanoma regardless of prior treatment. The results are consistent across all three arms and thus the recommended dose of pembrolizumab is 2 mg/kg every three weeks.

KEYNOTE-002 compared pembrolizumab to investigator choice chemotherapy for patients with ipilimumab refractory melanoma.[48] The primary end points were progression free survival, as well as overall survival. Most patients had received 2 or more previous lines of therapy and just under a half had received chemotherapy. A quarter of all patients had received BRAF Mek inhibition. Progression free survival was improved in patients assigned to pembrolizumab 2 mg/kg (HR: 0.57, $p < 0.001$), Pembrolizumab 10 mg/kg has (HR: 0.55, $p < 0.001$) compared to chemotherapy. Six month progression free survival was 34 % for pembrolizumab 2mg/kg, 38% for 10 mg/kg group and 16% in the chemotherapy group respectively. The data was recently updated at ESMO in 2016 with

a median follow up of 35 months.[49] Overall survival for patients receiving 2 mg/kg was 13.4 months, 14.7 months for those on 10 mg/kg and 11.0 months for those on chemotherapy. Two-year overall survival rate was 35.9 %, 38.2% and 29.7% (HR: 0.86, p=0.1173 and HR: 0.74, p=0.106, respectively). The improvements in the overall survival with pembrolizumab compared to chemotherapy have not yet met the protocol specified significant threshold as longer follow up is needed. The median progression free survival was three months for each of the groups. The two year progression free survival for pembrolizumab 2 mg/kg was 16%, for pembrolizumab 10 mg/kg was 21.9%, and for chemotherapy was 6%, respectively. Overall response rate was 22.2 % for pembrolizumab 2mg/kg, 27.6% for 10 mg per kg and 4.5% for chemotherapy. At the time of the updated analysis, 50% of patients on 2mg/kg and 58% of patients on 10 mg/kg on pembrolizumab who responded were alive with no subsequent progression or anti-tumor therapy compared to 12% of patients who responded to chemotherapy. The main treatment related immune mediated adverse of grade 3 to 4 severity were pneumonitis, colitis in patients receiving the 10 mg/kg dose. Adrenal insufficiency, skin toxicity, hypophysitis, hepatitis, pancreatitis, myasthenia and nephritis was reported in patients receiving the 2 mg/kg dose. The long term data for overall survival is awaited. Ongoing studies with respect to the analysis of the data based on PD ligand status is also being undertaken. The study authors concluded that pembrolizumab is a new standard of care for the treatment of patients with ipilimumab refractory melanoma. The study would support a dose of 2 mg/kg every three weeks.

KEYNOTE-006 compared pembrolizumab to ipilimumab in advanced melanoma.[50] This phase III trial with a 1:1:1 randomization compared pembrolizumab 10 mg/kg every two weeks, pembrolizumab 10 mg/kg every three weeks, or 4 cycles of ipilimumab at a dose of 3 mg/kg every three week. The primary end points of the study were disease progression and overall survival. There were two planned interim analysis. After the first interim analysis at a data cut-off date of September 2014, the results were released by the data safety monitoring committee to representatives of the study sponsor for regulatory purposes. The second analysis at the data cut off of March of 2015 evaluated the superiority of pembrolizumab over ipilimumab for overall survival. The results were released by the data safety monitoring committee with the recommendation that pembrolizumab be made available to all patients with disease progression on the ipilimumab arm.

Within the study populations the arms were well balanced and 65.8% had received no previous systemic treatment. The BRAF 600 mutation was observed in 36.2% patients and approximately 50% of those have received BRAF inhibitor treatment. 80.5% of patients had PDL-1 positive tumor samples. The median duration of follow up was 7.9 months. The estimated six month progression free survival for pembrolizumab every 2 weeks was 47.3%, 46.4% for every three weeks, and 26.5% for Ipilimumab. Median estimates for progression free survival were 5.5 months for pembrolizumab every 2 weeks, 4.1 months for pembrolizumab every 3 weeks and 2.8 months for ipilimumab. The hazard ratio for disease progression for pembrolizumab compared to ipilimumab was 0.58 for the two week regimen and 0.58 for the three week regimen ($p<0.001$). Benefit for progression free survival was evident in all pre specified sub groups for the two pembrolizumab arms. The benefit of pembrolizumab over ipilimumab was observed both in the PD-L1 positive and PD-L1 negative. There was more significant benefit in the PD positive groups compared to the PD negative group. The one year survival estimate was 74.1% for patients receiving pembrolizumab every 2 weeks, 68.4 % for patients receiving pembrolizumab every 3 weeks and 58.2 % for patients receiving ipilimumab. The hazard ratios were significant for all subgroups. The exception was in the pembrolizumab PD-L1 negative group where the hazard ratio for every three weeks was 0.91 with wide confidence intervals. For pembrolizumab administered every two weeks, the hazard ratio was 1.02 with the confidence interval crossing one. Sample size for this comparison was small. Efficacy between every 2 to 3 week appeared similar with no significant differences and thus the current recommended dose is 2 mg/kg every 3 weeks. Toxicities were as expected grade 3-5 toxicities occurred with pembrolizumab every 2 weeks in 13.3%. It occurred in 10.1% of patients receiving pembrolizumab every 3 weeks, and in 19.9% of patients on ipilimumab. The most

common side effects of pembrolizumab were fatigue, diarrhea, rash, pruritus. For ipilimumab, pruritus and fatigue were the most commonly reported side effects. The authors of this trial concluded that pembrolizumab as compared ipilimumab showed a significantly prolonged progression free survival with less high grade toxicity in patients with advanced melanoma. This trial facilitated pembrolizumab becoming first line treatment for metastatic melanoma and incorporated into clinical practice across Canada.

Nivolumab was previously reviewed by pCODR as single agent treatment and received a positive recommendation in April 2016 for the treatment of patients with unresectable or metastatic BRAF wild-type melanoma who are previously untreated. The first trial investigating nivolumab as treatment for melanoma was a randomized controlled trial between nivolumab compared to investigator choice chemotherapy.[51] This trial was not blinded. The two primary endpoints were objective response rate and overall survival. The published article is the first interim analysis that was preplanned looking at when 120 patients had been randomized to nivolumab out of 272, and followed for 24 weeks. Analysis for objective response and overall survival were planned at different times. The planned analysis for overall response rate was subsequently modified to allow non-comparative estimation of overall response rate in nivolumab arm. At a median follow-up of 8.4 months, the overall response rate for nivolumab was 31.7% compared to 10.6% in the chemotherapy group. Intent to treat objective response analysis was provided by EMA which included all randomized patients to any treatment group. Objective response rate was 25.4% for nivolumab, and 8.3% for chemotherapy. In the subgroups, overall response rates were as follows: BRAF mutated—23.1% nivolumab, 9.1% Chemotherapy, BRAF negative—34% nivolumab, 11.1% Chemotherapy, PDL-1 positive—43.6% Nivolumab, 9.1% Chemotherapy, PDL-1 negative—20.3% Nivolumab, 13.0% Chemotherapy. The median duration of response for ipilimumab was not reached, and was 3.5 months in the chemotherapy group. The median progression free survival was 4.7 months for nivolumab; 4.2 months for chemotherapy which was not significantly different. The explanations offered were the possible imbalance of adverse prognostic features, maturity of data and false positive disease progression based on modulation reactions. Overall survival at 6 months was not statistically different (nivolumab 76.7% compared to Chemotherapy 78.6%). The median overall survival for nivolumab was 15.5 months compared to chemotherapy of 13.7 months. This trial is suggestive of an improvement in overall response rate in patients receiving nivolumab either post ipilimumab for wild type BRAF or ipilimumab and BRAF inhibition, if mutated BRAF.

CheckMate-066 randomized patients with stage 3 unresectable metastatic disease in the first line setting to nivolumab or chemotherapy.[52] The primary end-point was overall survival. The study enrolled wild type BRAF patients. The median progression free survival for nivolumab was 5.1 months and for Dacarbazine 2.2 months (HR 0.43, p<0.001).The median overall survival for nivolumab has not yet been reached. 54.8% of patients in the chemotherapy arm went on to second line treatment which was most commonly ipilimumab. The overall survival rate at one year for nivolumab was 72.9%, p< 0.001, and a progression free survival of 5.1 months compared to chemotherapy which had an overall survival rate at one year of 42.1%, with a p< 0.001, and a progression free survival of 2.2 months. The overall response rate was 44% in the nivolumab group compared to 13.9% in the chemotherapy group. In the PDL-1 positive group the overall hazard ratio was 0.3 with a response rate of 52.7%% compared to 10.9% response rate in the chemotherapy group. In the PDL-1 negative group the overall hazard ratio was 0.48 with a response rate of 33.1% compared to 15.7% response rate in the chemotherapy group. The PD1 positive patient appears to derive more benefit from nivolumab, but the response in the PDL-1 negative group was not clinically insignificant. The withdrawal for grade 3–4 AE was 11.7% in the nivolumab compared to 17,6% in those receiving DTIC demonstrating that this treatment was extremely well tolerated. In summary, in wild type BRAF patients with no prior treatment, the patients receiving nivolumab did significantly better with respect to chemotherapy in terms of response rate, progression free survival rate, median overall survival rate and one year survival.

CheckMate-067 randomized patients to nivolumab monotherapy or nivolumab plus ipilimumab or ipilimumab monotherapy.[2] Primary endpoints were progression free survival and overall survival. There was no direct comparison in the statistical plan to compare nivolumab with nivolumab plus ipilimumab, although the hazard ratio noted is 0.74 (95% CI 0.60–0.92), as compared to the hazard ratio of nivolumab plus ipilimumab compared to ipilimumab which was 0.42, and the hazard ratio of nivolumab compared to ipilimumab which was 0.57. With respect to the first line treatment in this patient population, nivolumab alone or nivolumab plus ipilimumab were both superior to ipilimumab alone. CheckMate-067 demonstrated that the progression free survival rate for nivolumab alone was 6.9 months, for nivolumab plus ipilimumab was 11.5 months, and for ipilimumab alone was 2.9 months. Overall survival data remains blinded. The benefits of nivolumab plus ipilimumab were seen across a number of subgroups with respect to median progression free survival. For BRAF positive patients median PFS was: 5.62 months, 12.7 months and 4.04 months, respectively. In BRAF negative patients, the median PFS was 7.89 months, 11.2 months, 2.83 months respectively. In patients with PD1 positive disease, median PFS was 14 months, 14 months and 3.9 months, respectively. In patients with PD1 negative disease, median PFS was 5.3 months, 11.2 months and 2.8 months, respectively. In all subgroups, nivolumab was favoured compared to ipilimumab alone and nivolumab plus ipilimumab was better than ipilimumab alone. With respect to all patients, the overall response rate in the nivolumab group was 43.7%, nivolumab plus ipilimumab group 57.6% and in ipilimumab group, it was 19%. Complete response rates were 8.9%, 11.5%, and 2.2% respectively. In the PD1 positive group the overall response rate was 57%, 72%, and 21.3% respectively. PD1 negative group they were 41.3%, 54.8%, and 17.8 % respectively. In the PDL-1 analyzed groups, the greatest benefit of nivolumab plus ipilimumab was seen in the PD negative cohort. Within BRAF subsets, results were similar for the combination in wild and mutated cohorts. The wild type cohort may derive more benefit from nivolumab than the BRAF mutated type but a statistical comparison is not available. Overall survival is pending.

The safety profile was as expected from earlier phase I and II studies. Grade 3 to 4 toxicity in the single agent nivolumab was 16.3%, in the combination of nivolumab plus ipilimumab was 55%, and in the ipilimumab alone was 27%. The rate of discontinuation for adverse events, most commonly diarrhea and colitis in the single agent nivolumab was 7.7%, in the combination of nivolumab plus ipilimumab was 36.4% and in the Ipilimumab alone was 14%.

With respect to efficacy, nivolumab alone and nivolumab plus ipilimumab appear to be superior with respect to progression free survival rates as compared to ipilimumab alone. The complete overall survival data will be important to inform the decision of whether in PD1 positive cohort nivolumab single agent is comparable to nivolumab plus ipilimumab as well as to confirm that the combination of nivolumab plus ipilimumab may be superior to single agent in the PD1 negative group. The major limitation of this study was the lack of direct comparison of nivolumab alone to nivolumab plus ipilimumab.

2.3 Evidence-Based Considerations for a Funding Population

There is strong evidence to support the use of PD1 inhibitors as first-line therapy as opposed to ipilimumab or dacarbazine in patients with metastatic melanoma. Randomized studies comparing PD1 inhibitors versus ipilimumab have shown clear superiority in both response rates and progression free survival. The CheckMate- 066 study showed a 31% improvement in one year survival rates compared to dacarbazine. It is no longer ethical to use dacarbazine as a first line therapy. Longer follow-up is required to show if these improvements in response rates and progression free survival translates to an improvement in overall survival. The combination of the PD1 inhibitor plus ipilimumab is very promising but longer follow-up is required to show whether

this translates to improvements in overall survival. The combination arm is associated with greater toxicity than ipilimumab or PD1 inhibitors.

Ipilimumab and BRAF pathway modulators were the first major advances to provide marked improvement in overall results with progression free survival rates and potentially long term survival in patients with metastatic or recurrent melanoma. The programed death inhibitors which exhibit a unique mechanism of action demonstrate exciting results for those patients. Two drugs in that class have shown superiority over chemotherapy as first line as well as in-patients who have been exposed to previous ipilimumab or BRAF inhibitors. The programed death inhibitors appear superior to ipilimumab as single agents with higher response rates in all groups of treatment. PD1 ligand expression on the tumor predicts higher response rates with PD1 inhibitors are utilized; however, patients whose tumors are PD1 ligand negative have still exhibited durable responses. Current research is focusing on genetic signatures to see whether we can predict which patients will respond to PD1 inhibition. With the development of techniques the assays for measurement of the PD ligand will be critical, PDL-1 status may serve as both a prognostic and predictive marker for response to programed death inhibitors, as well as CTLA-4 inhibitors. As there are now multiple assays for PDL, there is work being undertaken to try to establish the criteria for what is considered a positive across all assays. To date the literature suggests that those individuals whose tumors are PD ligand positive have a higher response rate to the inhibitors than PDL-1 negative when used as single agent. This has prompted studies asking the question of whether combining a programed death inhibitors with a CTLA-4 for inhibitor provides improvement in overall survival, disease free progression with acceptable toxicity. Stratification based on PDL ligand status will be critical to interpreting the end results of those studies.

Clinically both pembrolizumab and nivolumab are indicated for first line treatment patients with metastatic melanoma. They are effective in patients with prior ipilimumab exposure, as well as BRAF inhibition when indicated. A direct comparison between these two compounds is not likely to become available. Despite the advances with these agents, patients and clinicians are still pursuing treatments with increased efficacy.

2.4 Other Patient Populations in Whom the Drug May Be Used

PD1 inhibitors are currently being evaluated as an adjuvant therapy in high-risk melanoma patients who have had complete resection of their disease but remain at high risk of recurrence. To date there is no evidence to support their use as adjuvant therapy and longer follow-up of the adjuvant trials is required. However, ipilimumab has secured this indication. Ipilimumab has been studied in the adjuvant setting. EORTC 18071[53] a phase III trial, comparing adjuvant ipilimumab with placebo, in patients with resected stage III melanoma randomized Ipilimumab versus Placebo. Based on the initial results with a median follow up of 2.7 years, ipilimumab was granted FDA approval for that indication. More recently, as reported by Eggermont et al in the New England Journal of Medicine results at a median follow up of 5.5 years demonstrated an overall survival of 65.4% in the ipilimumab arm as compared with 54.4% in the placebo arm (HR 0.72, p=0.001).[54]

3 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

Input on nivolumab in combination with ipilimumab (Opdivo + Yervoy) for treatment-naïve adult patients with advanced (unresectable or metastatic) melanoma, regardless of *BRAF* status was provided by Melanoma Network of Canada (MNC) and Save Your Skin Foundation (SYSF). Their input is summarized below.

MNC conducted a confidential on-line survey from across Canada, the United States, and Australia. Respondents were recruited through the MNC database, a generic email with an on-line link to their survey, and post cards left at major cancer treatment centres to instruct patients to voluntarily contact MNC. MNC requested input from patients that had been treated with nivolumab and as well as patients who had been treated with other drugs or those that had not been treated but who may have an opinion on the unmet need for this therapy in the future. MNC received input from a total of 102 patients from across Canada (82 respondents), the United States (18 respondents) and Australia (2 respondents). Of the total, 20 patients (20%) had been treated with the combination therapy. The survey had a combination of multiple choice and open comment questions. MNC has provided selected commentary from respondents that is reflective of various perspectives.

SYSF obtained information through personal experience, surveys, and one-on-one conversations. A total of 86 respondents were interviewed; SYSF collected information from 51 survey monkey interviewees and 35 one-on-one interviewees. Of the 86 respondents, 76 were patients and 10 were caregivers. 100% of information collected for section 2 included all melanoma patients, while section 3 was information collected from patients treated by drug under review (n=55). Over 60 % of respondents were female, ages of those interviewed ranged between 21 and 60+. Over 40% of respondents are employed and over 30% were retired. Patients from all provinces were interviewed and 20% of those interviewed do not live in Canada.

From a patient's perspective, symptoms most important to control for respondents were: i) progression of disease, death ii) pain everyday associated with disease progression or treatment; iii) cognitive impairment, fatigue; iv) anxiety, fear, depression; and v) gastrointestinal issues, including vomiting and diarrhea. Therapies used to treat this type of cancer include: ipilimumab, trametinib, dabrafenib (as monotherapies or in combination for the *BRAF* + population) vemurafenib, cobimetinib (as monotherapies or in combination for the *BRAF* + population), aldesleukin, pembrolizumab, and nivolumab. Common adverse events experienced on treatment include: fatigue or weakness, followed by skin rash, muscle or joint pain, weight loss or loss of appetite, shortness of breath, cough or chest pain, hormone and thyroid problems, and diarrhea or colitis. According to MNC, with this new combination therapy, results have indicated response rates in the 60% level, which is well above current monotherapies; this number is reflected in our respondents who indicated that over 50% had a complete response and another nearly 40% had slowed progression of the disease (most were continuing on treatment or had recently started treatment). MNC reported that if the combination drug works, it works relatively quickly and within two years patients are off of therapy, if not sooner. In turn, this saves the health system significant dollars from ongoing treatment and allows patients to return to work and their lives. SYSF reported that most patient respondents said that adverse events associated with this treatment option were manageable. SYSF also noted that this drug has higher adverse events than other available treatment options, however it has higher success rates, and patient respondents were willing to undergo side effects for better a chance of survival.

Please see below for a summary of specific input received from MNC and SYSF. 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 asked respondents to identify issues experienced with melanoma. There were a total of 87 respondents that had responded to this part of the survey.

Cancer and the different stages of cancer affect people in different ways. What issues have you experienced with your cancer diagnosis? Please select as many responses as appropriate.		
Answer Options	**Response Percent**	**Response Count**
Fear or anxiety	86.20%	75
Fatigue	66.70%	58
Scarring or disfigurement	63.20%	55
Depression	49.40%	43
Pain	46.00%	40
Disrupted sleep	44.80%	39
Appetite loss or weight gain	37.90%	33
Negative Impact to family or social life	37.90%	33
Financial loss or job loss	32.20%	28
Lymphedema	31.00%	27
Headaches	21.80%	19
Edema or fluid retention	19.50%	17
Nausea or vomiting	19.50%	17
Mobility issues (unable to walk or impaired movement)	18.40%	16
Post traumatic stress	18.40%	16
Gastrointestinal issues	16.10%	14
Peripheral neuropathy (nerve pain or damage)	12.60%	11
Damage to organs, such a lungs, liver, brain	11.50%	10
Cognitive Impairment	10.30%	9
Breathing problems	8.00%	7
None	2.30%	2
Other (please explain)		13
	answered question	**87**

Similarly, SYSF reported aspects of melanoma experienced by patients (from most important to least important). There were a total of 76 respondents that had responded to this part of the survey.

Aspects of Melanoma Experienced by Patients (From Most Important to Least Important)	
Fear and/or anxiety	75%
Fatigue	67%
Financial loss or job loss	53%
Scarring and disfigurement	50%
Pain	50%

Weight loss or weight gain	50%
Disrupted sleep	48%
Nausea or vomiting	42%
Negative impact to family or social life	39%
Depression	39%
Loss of/gain of appetite	32%
Nerve pain or damage	28%
Lymphodema	25%
Gastro Issues	25%
PTSD	25%
Cognitive Impairment	18%
Damage to organ	18%
Breathing problems	17%
Mobility Issues	14%
Headaches	10%
No side effects	4%
Answered question	76

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

- *"I am young 29 - with a potentially deadly stage IV cancer. Enough said."*
- *"Exhausted....mentally...physically and socially.....one big nightmare"*
- *"Trouble sleeping, diminished sex drive, now on thyroid medication, high anxiety"*
- *"The depression and anxiety effected my family members, my job and my social life. It took a couple of years to get everything under control and regain my life."*
- *"Fear. Uncertainty. Surgery. Pain. Fear."*
- *"Vision loss means no more driving. Bowel issues are being dealt with by a gastroenterologist. Headaches were very painful."*
- *"It has affected my entire life. I have gone from being a happy, working, family man to being depressed and anxiety ridden, off work, unable to cope with daily life."*
- *"I have to limit my exercise and activities because of fear of lymphedema and other fluid retention because if groin dissection."*
- *"Melanoma has had a profound impact on my life; disruption to family life, my work, my ability to travel, and indirectly on my physical mobility."*
- *"Living in constant fear and anxiety of dying but probably more leaving my 14 old daughter behind. Loss of income has destabilized my whole life so far and the diagnosis of is devastating in limbo Stage 3b like mine..."*
- *"I don't want to live if it has to be like this. I have tumours all over my head and had so many skin grafts, they can't do anymore. I had radiation that has wiped out my salivary glands. I can eat, swallow and am throwing up phlegm all the time. They should have let me die rather than live like this. It hasn't stopped the cancer and the combo is my only hope to have my 3 year old remember me."*

Common complaints from MNC respondents include: pain, disfigurement, depression and anxiety, nausea, headaches and dizziness from brain metastases.

MNC expressed that melanoma is such a widespread cancer with so many symptoms, but symptoms that impair mobility or daily functioning, other than death, are the symptoms that most respondents feel are important to control. Reported symptoms that were consistently most important to control for respondents include:

- progression of disease, death

- pain everyday associated with disease progression or treatment
- cognitive impairment, fatigue
- anxiety, fear, depression
- gastrointestinal issues, including vomiting and diarrhea.

Similarly, the most important symptoms to control for respondents surveyed by SYSF were:

- pain
- fatigue
- gastro-intestinal issues
- mental health including fear, anxiety, depression, outlook.

SYSF also reported the ongoing symptoms (if any) affecting respondent's day to day life:

- nothing (40%)
- fatigue (25%)
- depression (25%)
- pain (10%)

Below are some of the key comments gathered from SYSF respondents:

- *"Nothing really-- I can do as much as I could before to some degree but not as fast and with less strength."*
- *"Fear after diagnosis Depression during treatments PTSD after surviving"*
- *"Severely effected my life and my family, couldn't look after my grandchildren. A lot of things in the home, plus social e.g. Friends"*
- *"It has affected my ability to be employed, the type of employment I choose, my marital status, my activity level, the location where I live and it is something I think about daily. "*
- *"They don't". (side-effects affecting day to day life)*
- *"I'm concerned about what treatment will be available next if needed"*

Lastly, SYSF noted that 10% of patients interviewed found that they were limited due to disease, or treatment and were unable to work and that 90% of patients interviewed were able to manage ongoing symptoms through side effect management, support, etc.

3.1.2 Patients' Experiences with Current Therapy for Melanoma

According to MNC, stage III patients are currently still using interferon as the only approved therapy for this stage in Canada. Of these patients, more than 50% will become metastatic. MNC noted that targeted therapies are available for stage IV unresectable patients with a *BRAF* mutation, including vemurafenib, and dabrafenib and trametinib. For other metastatic patients, ipilimumab has been approved and funded. Nivolumab has been approved for wild type melanoma, but is under current negotiations in the provinces.

Similarly, SYSF reported that therapies used to treat this type of cancer include: ipilimumab, trametinib, dabrafenib (as monotherapies or in combination for the *BRAF* + population in about 50% of melanoma patients) vemurafenib, cobimetinib (as monotherapies or in combination for the *BRAF* + population in about 50% of melanoma patients) aldesleukin, pembrolizumab, and nivolumab.

MNC expressed that current therapies (interferon, targeted therapies, and immunotherapies) may add to the fatigue and some side effects for patients during treatment, but if working, they can control the disease or eliminate it entirely for a small portion of metastatic patients. MNC stated that the majority of patients still do not respond to treatment. According to MNC, those treated with targeted therapies indicated a variety of milder side effects including rash, additional skin cancers, fatigue, sun sensitivity, abdominal pain and diarrhea, headaches, edema. Respondents

treated with ipilimumab indicated side effects were commonly diarrhea (several had severe colitis that required steroids), headaches, chills, rashes, stomach cramps, fatigue, nausea and vomiting. A total of 92% of respondents indicated that the side effects were tolerable and short lived, once therapy ceased. One respondent indicated significant side effects with ipilimumab with a perforated bowel, which was treated; while another respondent on targeted therapy experienced damage to the eye from swelling and side effects. Most respondents indicated that these drugs were well tolerated, but eight patients had dose reductions and/or were removed from treatment because of side effects.

When MNC asked respondents if they would be willing to put up with side effects if the benefits were only short term, all but one indicated that they would be willing to tolerate side effects for the potential of living longer. MNC added that as the responses to therapies are so different from one to the other that side effects are difficult to predict and often not lingering after therapy is discontinued.

SYSF reported that the most common adverse events experienced on treatment include: fatigue or weakness (71.43%), followed by skin rash (50%), muscle or joint pain (42.86%), weight loss or loss of appetite (42.86%), shortness of breath, cough or chest pain (35.71%), hormone and thyroid problems (28.57%), and diarrhea or colitis (28.57%).

SYSF noted the following:

- 90.91% of patients felt that side effects were manageable
- 66.67% of patients felt that their quality of life was improved on treatment
- 90.91% felt that the benefits of treatment outweighed the side effects
- 75% of patients did not complete full course of treatment
- 87.5% are no longer receiving treatment
- 40% are presently cancer free
- 30% experienced slowed disease progression
- 10% did not respond
- 0% of those who have had a response to treatment have had a progression of the disease
- 55.56% of patients who have had a response to treatment have not been treated in the last six months

Below are some of the key comments gathered from SYSF respondents:

- *"Aside from my weight loss and fevers I suffered, it's been positive! I believe these miracle drugs are the reason I am here."*
- *"It has had a positive impact because the treatment appears to be working. This has significantly reduced stress levels."*
- *"It as a positive impact because i need less care."*

MNC noted that the most common issue for access was that of travel time and expense. Approximately 30% of respondents had to travel more than two hours to be treated. Moreover, approximately 32% of respondents indicated loss of job, loss of income and significant financial impact as a result of diagnosis and treatment.

Similarly, SYSF reported on the hardships faced by respondents: travel to centres for treatment, access to treatments, paying out of pocket for treatment and necessity to endure other treatments in order to have access to appropriate treatment and emotional hardships related to the disease and impact on the family.

Below are some of the key comments gathered from SYSF respondents:

- *"I had to travel to the cross cancer institute in Edmonton from Kamloops BC and still do every two weeks as I am still on treatment! My parents had to rent a house for us while I was there. I am very fortunate to have been able to be on the study and am forever grateful. If it*

happened this year with the new protocol I'm not sure the outcome would have been so good."

- *"I had to privately pay for the 10mg/kg treatment of Ipilumimab (Yervoy) at $200 000. I also had to do one treatment of chemotherapy in order to qualify for the 3mg/kg ipi treatment."*
- *"My insurance was responsible to pay for the 1/2 the cost and I was denied. My wife did crowd funding which yielded media attention … Once the local news began airing how an insurance company was denying him coverage- they reversed their denial."*
- *"None, other than needing to travel further to access the treatment."*
- *"Unmet needs for Patients in the adjuvant and advanced/metastatic setting include treatment options available for them. Access to available treatments without delays"*
- *"WANT TO HAVE OPTIONS APPROVED THAT WOULD BE BEST FOR ME IF I MOVE ONTO STAGE 4. KNOWING THERE WERE SOME PROVEN THERAPIES THAT ARE AVAILABLE WOULD HELP MY ANXIETY THAT I DEAL WITH DAILY."*
- *"Seeing the success of the current treatment i am on it would be fantastic if in the future, should the need arise, that i could have access to any treatment that has shown success with as little side affects. But then again every patient reacts to treatment differently and i consider myself very luck to not have suffered any serious side affects."*
- *"I think that this treatment is going to revolutionize how cancer is treated in the future. I wish that everyone being treated got as lucky as me with having no side effects."*
- *"Treatments that can be used for people who already had treatment that hasn't worked. "*
- *"I would support anything that worked to eliminate cancer."*
- *"Knowing there are better treatment options for cancer patients is very encouraging because we have all seen the dreaded side effects that cancer patients experience."*
- *"Of course the ideal scenario is minimal side effects. But if the treatment is one that can bring hope for me to live my life, I am open minded to whatever that entails."*
- *"Being able to stay relatively healthy and involved in my families life was important. Looking well to my children helped them cope."*

3.1.3 Impact of Melanoma and Current Therapy on Caregivers

MNC did not collect caregiver responses separately; therefore, of the 102 respondents, it is unknown the number of caregiver respondents. SYSF collected information from a total of 10 caregivers.

According to MNC, caregivers and families experience huge challenges, including: time lost from work and significant financial impact, increased burden of caregiving and responsibilities for the family, anxiety and depression, and physical challenges of assistance and lifting. A number of caregivers indicated that the frequency of travel and associated costs to attend appointments and receive treatment on an ongoing basis was difficult.

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

- *"My spouse has been left with his own version of PTSD that has held him back professionally. He is so terrified about how much longer I have to live he prefers to spend all the time he can with me."*
- *"Financially, emotionally and in every way, her life has been impacted hugely! My wife could no longer work full time as she had to look after me, take me to appointments, treatments, deal with side effects. She was also active and hasn't been able to do the things lately that she enjoys ie hiking etc."*
- *"Big effect on daughter, as she is sole caretaker. Has to take care of house, pets, cook, do transport to various medical appointments. She had to cancel a trip to Europe due to a surgery."*
- *"It took away his "happily ever after". He has suffered great stress at work at different times, he lost one job, took a sabbatical from one and quit another to be with me. I was at stage 4*

with melanoma and so before Ipilimumab I was given 6 months to live. This takes away any dream for "growing old together"".

- *"Sadness, stress, exhaustion and disappointment. Loss of work due to caring for me and taking me to appts and surgeries. Hard to stay positive and non-emotional. We have had to cut out family functions and outings due to my pain or fatigue."*

MNC noted the challenges with current therapy include the frequency of hospital visits and associated costs, and fatigue associated with treatment. According to MNC, however, the treatment side effects are minimal, thus improving the quality of life for all:

- *"very positive with no side effects and it worked and my family couldn't be happier"*
- *"Drug side effects no major impact on partner so far apart from driving me to infusions- frustration at treatment inefficiencies- delays and waits. Positive- gives hope for a longer future together. Negative- infusions tying/ time consuming/ fear of side effects- feeling need to be near treatment centre for first 15weeks"*
- *"I would say that maybe by my girlfriend and family members have been impacted negatively, because they are not going to see their inheritance any time soon. But realistically, those close to you and/or your caregiver would have experienced a more severe impact if the patient was allowed to degenerate further, ultimately ending in bereavement."*
- *"It has made it a bit easier as the side effects are pretty minimal. They also are hopeful now and starting to think I may survive this thing".*

SYSF reported the following quotes from respondents related to impact of melanoma and current therapy on caregivers:

- *" t has had a positive impact because the treatment appears to be working. This has significantly reduced stress levels."*
- *"It has had a 100% positive outcome! It saved my life we couldn't be more happy!"*
- *"There had been no impact so far. I have continued to work full time and I'm feeling good except for the rash I had after the first treatment."*
- *"The hospitalization following the treatment affected my family and caregiver/ spouse because it showed the severity of the disease and created fear that this treatment, which was so promised to work, did not work at all and created negative side effects."*
- *"This combo had a very positive effect on me and my family because I responded so quickly to the drugs."*
- *"From a mental persepective definately Yes. I believe myself and my family appreciate every day more."*
- *"I began to feel so much better so got stronger and became engaged in life again. "*

3.2 Information about the Drug Being Reviewed

3.2.1 Patient Expectations for and Experiences To Date with Nivolumab in combination with Ipilimumab

When MNC asked respondents about unmet need, the responses tended to reflect a common theme – that access to this new therapy provides hope to stop progression or eliminate the disease and to provide another option for treatment if and when their current therapy stops working. According to MNC, with this new combination therapy, results have indicated response rates in the 60% level, which is well above current monotherapies; this number is reflected in our respondents who indicated that over 50% had a complete response and another nearly 40% had slowed progression of the disease (most were continuing on treatment or had recently started treatment).

According to the input provided by MNC, there are patients that were "facing imminent death, that are now living cancer-free". MNC noted that most respondents would accept progression-free

survival. Patients are able to resume their lives, practically symptom free after treatment, if it works. The benefits most definitely outweigh the risk, as death is final and survival rates for metastatic disease are very low. MNC reported that if the combination drug works, it works relatively quickly and within two years patients are off of therapy, if not sooner. In turn, this saves the health system significant dollars from ongoing treatment and allows patients to return to work and their lives.

Below are key comments gathered from MNC respondents with no experience with nivolumab in combination with ipilimumab (some of which are currently taking therapy):

- *"Ideally long term complete response - but only for small percentage. BUT treatment might buy time to see daughter graduate- to put affairs in order-treatment gives hope of a longer term future- maybe even time to see children wed even if denied opportunity to see grandchildren"*
- *"I look at the therapy as not optional... it is a question of potential life with it or certain progression and eventual death without it."*
- *"All I can think of is that these lifesaving drugs could be my next line of treatment. I am currently on pembrolizumab, but I have been told by oncologist that the alternative to this drug and potentially if the cancer returns, is a combination therapy of Nivolumab and Ipilimumab ---lines of therapy that could save my life!!"*
- *"I want a chance to live longer with a quality of life. Currently this is not the case. I wish I had been put on this combination right away and spared myself the mental and physical anguish I currently have. My life is not worth living."*
- *"This therapy could provide the exact combination that may stop my disease. Melanoma is not the same in every patient, so a variety of treatment availability is what is best for the patient."*
- *"I am currently on BRAF/MEK inhibitors which most often quit working after a period of time. Nivo/Ipi would be my next approach. I feel there is hope in this treatment as it works with the immune system. I have a friend in Western Canada who just had a complete response with this exact therapy combination. I am hopeful."*

MNC surveyed a total of 20 respondents with experience with nivolumab in combination with ipilimumab. According to MNC, the combination therapy is eliminating the cancer or stopping progression for the majority of treated patients. MNC noted that the combination is challenging and the side effects must be managed by experienced oncologists. According to MNC, side effects are managed or minimal less than 60% of respondents indicated fatigue; 50% of respondents reported a skin rash; 30% of respondents indicated diarrhea; 25% of respondents reported liver problems, headaches and joint aches as common side effects. One respondent indicated the side effects were not worth it.

Below are key comments gathered from MNC respondents with experience with nivolumab in combination with ipilimumab (of note, it is unclear if nivolumab was taken in tandem with ipilimumab or sequentially):

- *"I had worse problems with IPI than Nivolumab - with IPI I had red eyes, rashes, sore joints, some diarrhea - went on steroids and quickly got it turned around.....The Nivolumab was a wonder drug for me...minor manageable side effects (hypothyroid and vitilogo - piece of cake to manage those issues)....I returned to work full time, am able to do everything I want to....I travelled to Toronto from North Bay over times in 6 months to receive Nivolumab.....often drove myself....no problem.....worth every trip, every single kilometre. I am cancer free!!!"*
- *"I received both Ipilimumab and Nivolumab. Both gave me and my family hope. Doing nothing was not an option. I am otherwise a very healthy vibrant person. It was insane to simply wait and see.....taking both of the immunotherapies has given me faith to continue living out my life without despair."*

- *"Fever - took Motrin every 4 hours, dry mouth - chewed gum. At 14 weeks all 7 tumors in my lung were gone or smaller."*
- *"Hepatic toxicity was without symptoms and readily reversed with steroids. Skin rash was tolerable and migratory arthritis bothersome but also tolerable with reduced activity."*
- *"Categorically yes; as noted above this has been a simple binary decision: LIFE OR DEATH. My oncologist was clear from the beginning; without the immunotherapy my very aggressive disease would have killed me."*
- *"Not manageable at times but worth it – I am alive and cancer free."*
- *"From advanced Stage 4 with significant tumor burden in head, neck, lungs, spine & legs I became NED (no evidence of disease) after four infusions of the combo over three months. I am now almost three years out from treatment and remain NED."*

SYSF noted that not all patients will respond to the current treatment and need to have options available to them. Patients with high LDH levels and high tumour burden are also less likely to respond and represent an unmet medical need.

- *"I would like the appropriate drug for me, but as we are not there yet, I want any and all treatments that will keep me alive."*
- *"Treatments that can be used for people who already had treatment that hasn't worked."*

SYSF received input from a total of 55 respondents with experience with nivolumab in combination with ipilimumab. The combination of nivolumab and ipilimumab is being used for curative intent for these patient respondents.

Below are key comments gathered from SYSF respondents with experience with nivolumab in combination with ipilimumab:

- ***"****Feeling comfortable that the treatments might work far outweighed the experience of side effects. In my case presently the treatments seem to be working. So i feel very fortunate."*
- *"I began to feel so much better so got stronger and became engaged in life again."*
- *"After only 1 treatment I experienced shrinking of visible tumours"*
- *"I would mean everything!! A chance of survival and living! "*

SYSF reported that 90.91% of patient respondents felt that the benefits of the treatment outweighed the side-effects and that most patient respondents did not complete the full course of the treatment but still received benefit. A total of 45.95% of respondents are working full-time, 35.14% of respondents are retired and 8.11% of respondents are not able to work. SYSF noted that most patient respondents reported that quality of life was affected by the disease, increased anxiety and depression and difficulty performing daily activities. Treatment has decreased need for care, increased ability to work and productivity, decreased stress and anxiety and increased quality of life.

- *"I can do as much as I could before to some degree but not as fast and with less strength."*

SYSF reported that the new treatment (nivolumab in combination with ipilimumab) has positive effects, regardless of side-effects for patients who respond; it provides hope for survivorship.

SYSF expressed that there are no treatment options for those patients who had severe adverse side effects, or that did not respond to treatment.

There are adverse events associated with this treatment option, but most patient respondents said they were manageable and were willing to deal with the side-effects for the possibility to decrease or eliminate the cancer.

According to SYSF, patient respondents were willing to deal with side-effects for benefit of the treatment.

SYSF noted that this drug has higher adverse events than other available treatment options, however has higher success rates, and patient respondents were willing to undergo side effects for better a chance of survival.

SYSF reported that most patient respondents did not complete the full course of treatment and that most patients had a response, either eliminated cancer or slowed progression of the disease-decreasing anxiety, depression, stress and fear, the need for care outside of the hospital setting. Almost 50% of patient respondents are working full-time. SYSF stated that this therapy is being used for curative intent, increasing long-term health and well-being and decreasing burden on the health care system in the long-term.

3.3 Additional Information

MNC expressed that it would be unimaginable and unethical, not to approve a therapy combination that has such a significant result and impact for patients across Canada. MNC stated that nivolumab in combination with ipilimumab is a remarkable treatment and is the foundation of what they are hoping for – a cure.

SYSF is concerned with time delays from the time pCODR provides a recommendation for the therapy, to the time the treatment gets listed on the formulary. SYSF expressed that there needs to be a streamlining of the HTA process with less siloes. SYSF also stated that patients are aware that the provincial process is slow and that with a disease that has a 3-6 month rate of survival, time is of the essence. SYSF would like to see more transparency and communication in and throughout the approval process.

Moreover, SYSF expressed that they would like to see a patient guidance panel along with the clinical guidance panel.

Lastly, SYSF and patient respondents are concerned with disparities and inequalities in the system. According to SYSF, respondents are worried; they know that there are a number of new treatments on the horizon, but also know that they may not get to see them.

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 eight of 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:

- Potentially limited comparative data with other PD-L1 inhibitors and with oral targeted therapies for *BRAF* mutation positive
- Uncertainty regarding post-progression treatments and sequencing

Economic factors:

- Potential for substantial drug wastage with both drugs
- High cost of combination therapy
- Uncertainty in the cost of monitoring and managing toxicities
- Unknown treatment duration

Please see below for more details.

4.1 Factors Related to Comparators

PAG identified that nivolumab monotherapy and ipilimumab monotherapy would be appropriate comparators. However, at the time of the PAG input, nivolumab was not yet funded in any provinces.

As the CheckMate-069 trial demonstrated overall survival for the combination therapy when compared to ipilimumab monotherapy, PAG indicated that nivolumab plus ipilimumab combination therapy would be an alternate option to ipilimumab or PD-1 (nivolumab or pembrolizumab) monotherapy. PAG is seeking overall survival data comparing nivolumab plus ipilimumab combination therapy to monotherapy with PD-1 inhibitors.

PAG noted that nivolumab plus ipilimumab is indicated in treatment-naïve patients, regardless of *BRAF* mutation status. PAG is seeking data on nivolumab plus ipilimumab compared to oral targeted therapies for *BRAF* mutation positive patients.

4.2 Factors Related to Patient Population

PAG identified that patients with adequate performance status and advanced (unresectable or metastatic) melanoma would be considered eligible for treatment with nivolumab plus ipilimumab combination therapy.

PAG noted that the trial enrolled previously untreated patients and is seeking guidance and data on the appropriate use and patient eligibility for nivolumab plus ipilimumab in the following clinical situations:

- Previous or current treatment with oral *BRAF* targeted therapies

- previous treatment with ipilimumab monotherapy, and if considered, what time interval between prior ipilimumab treatment and combination therapy at the time of disease relapse would be reasonable
- previous or current treatment with PD-1 inhibitor therapy (either nivolumab or pembrolizumab) in the first line setting without disease progression, and if considered to add ipilimumab in combination, would there be any reasonable timeline restriction and, for those receiving pembrolizumab, a requirement to switch to nivolumab
- the same questions as above for those patients previously treated with ipilimumab monotherapy and who currently being treated with PD-1 inhibitor therapy in the second line setting

PAG noted that treatment with nivolumab plus ipilimumab can be given until treatment is no longer tolerated. PAG indicated there may be requests to replace nivolumab in the monotherapy maintenance phase with pembrolizumab as the administration schedule of pembrolizumab is every three weeks compared to every two weeks for nivolumab. PAG is seeking if there is any data or guidance on the use of pembrolizumab instead of nivolumab in the maintenance phase.

PAG is also seeking information and guidance on the sequencing of treatments for patients with *BRAF* mutation positive disease: would treatment with nivolumab plus ipilimumab followed by treatment with oral *BRAF* targeted therapies or treatment with oral *BRAF* targeted therapies followed by nivolumab plus ipilimumab be more beneficial?

For patients with *BRAF* wild-type, PAG is seeking whether there is information from the trial on the benefits of post-progression treatments.

PAG also noted that the trial enrolled patients with performance status of ECOG 0 or 1. Given the higher rates of adverse events with combination therapy, PAG indicated that combination therapy should be limited to patients with performance status of ECOG 0 or 1.

4.3 Factors Related to Dosing

PAG noted that there may be the potential for dosing errors with the different dose and administration schedule for nivolumab when administered with ipilimumab and when administered as monotherapy.

PAG noted that the U.S. Food and Drug Administration recently approved a modified dosage regimen for nivolumab for renal cell carcinoma, metastatic melanoma and non-small cell lung cancer. PAG is seeking information from the manufacturer on if and when the flat dose of nivolumab 240mg intravenously every two weeks would be approved in Canada. PAG noted that the flat dose would impact the economic analysis.

Nivolumab monotherapy is continued at long as clinical benefit is observed. PAG is seeking guidance on discontinuation criteria as treatment could potentially be continued beyond progression.

PAG is also seeking information on whether combination treatment should restart when treatment is temporarily interrupted due to toxicity and within what timelines.

4.4 Factors Related to Implementation Costs

PAG identified that the barriers to implementation are the costs of combination therapy. PAG has concerns for incremental costs due to drug wastage, specifically in centers where vial sharing would be difficult. There are two vial sizes of nivolumab and two vial sizes of ipilimumab available to minimize drug wastage but doses of both drugs are based on weight. PAG noted that use of the flat dose of nivolumab at 240mg would minimize wastage when two 100mg vials and one 40mg vial are used.

4.5 Factors Related to Health System

PAG noted that the frequency of grade 3 and 4 adverse events is higher with the combination therapy than with monotherapy and that it may occur with higher frequency in clinical practice than reported in the trial. Patient selection criteria should be clearly defined.

PAG also noted a recent publication in the New England Journal of Medicine reporting deaths due to myocarditis associated with treatment with the nivolumab and ipilimumab combination. PAG indicated that more resources, including use of emergency room visits and hospitalization, may be required to monitor and treat toxicities. This would be a barrier to implementation.

PAG indicated that patients will need access to centres with the resources to monitor and manage adverse events, particularly infusion related reactions and serious toxicities.

The administration of nivolumab and ipilimumab requires significant chemotherapy chair time as nivolumab is a 60 minute infusion followed by 90 minutes for ipilimumab infusion in the combination phase and the administration of nivolumab every two weeks in the monotherapy phase.

4.6 Factors Related to Manufacturer

PAG identified that there are patients who have participated in clinical trials and received immune checkpoint inhibitor therapies in the adjuvant setting. PAG is seeking guidance on the use of nivolumab plus ipilimumab for metastatic disease in patients who have been treated with immune checkpoint inhibitor therapies in the adjuvant setting.

5 SUMMARY OF REGISTERED CLINICIAN INPUT

One clinician input was provided from the Ontario Skin Cancers Leads at Cancer Care Ontario.

Overall, the clinicians providing input identified that the combination of nivolumab plus ipilimumab showed an improvement in response rate and progression free survival compared to ipilimumab monotherapy or nivolumab monotherapy. They also noted that PD-L1 testing is not required for treatment with this combination and that treating facilities administering combination immunotherapies should have infrastructure in place to manage treatment-related toxicities.

Please see below for a summary of specific input received from the registered clinician(s).

5.1 Current Treatment(s) for Melanoma

The clinicians providing input indicated that the current treatments include:

- Single agent pembrolizumab or single agent ipilimumab
- Dabrafinib-trametinib (*BRAF* combination for mutated status)
- Nivolumab single agent (via expanded access program)
- Cobimetinib-vemurafenib (via patient access program)

5.2 Eligible Patient Population

The clinicians providing input noted that the melanoma patient cohort is considered small compared with lung, breast and prostate cancers as well as lymphoma, accounting for approximately only 3% of all cancer incident cases. Combination immune therapy only applies to metastatic melanoma patients and only a subgroup of patients with metastatic melanoma would be considered for the combination of ipilimumab and nivolumab based on their overall health status and disease status. Hence a very small population of metastatic melanoma patients would be receiving this therapy.

5.3 Identify Key Benefits and Harms with Nivolumab in combination with Ipilimumab

The clinicians providing input identified that the combination of nivolumab plus ipilimumab showed an improvement in response rate (RR) and progression free survival (PFS) compared to ipilimumab and Nivolumab alone. The combination of nivolumab and ipilimumab showed a RR of 57.6% compared to 43.7% for nivolumab and 19% for ipilimumab. The PFS was also longer for the combination (11.5 months) compared to nivolumab (6.9 months) and ipilimumab (2.9 months).

Some clinical data suggests more durable long-term responses with ipilimumab + nivolumab compared to single agent anti-PD1 and targeted therapies. The combination is however more toxic with 55% of patients experiencing grade 3/4 toxicity with 36% of patients discontinuing due to toxicity. However the majority of the patients still derived benefit despite discontinuing therapy. The toxicity for nivolumab and ipilimumab was similar to what was seen in previous trials (16% and 27%).

They also identified that there currently is no biomarker or criteria available for patient selection. PDL-1 status should not be used for patient selection as patient's respond to therapy is independent of PDL-1 status.

5.4 Advantages of Nivolumab in combination with Ipilimumab Over Current Treatments

The combination is superior to the current treatment regimen. Phase I/II and Phase III Data have shown better response rates with combination of nivolumab plus ipilimumab compared to single agent of either ipilimumab or nivolumab, as well as improved PFS with combination. However, the clinicians providing input noted that PFS has not been shown to be a reliable marker for the superiority of ipilimumab-based regimens. PFS was not superior in the ipilimumab studies; the overall response rate was. More recently, in the ipilimumab 3mg vs 10mg, study PFS was the same but OS was different. OS data for the combination is still pending.

5.5 Sequencing and Priority of Treatments with Nivolumab in combination with Ipilimumab

The clinicians providing input indicated that the combination can be given as first line immunotherapy or second line post *BRAF* targeted therapy. The combination is equally efficacious in both *BRAF* wild type and *BRAF* mutated disease. Response rate is just as high as targeted therapies.

For sequencing post pembrolizumab or nivolumab, studies are currently on-going and there should be data coming in the future.

5.6 Companion Diagnostic Testing

Testing is not required. Based on current data, companion testing is not required at present time. However, nivolumab (brand: OPDIVO)'s submission to Health Canada indicates that PD-L1 status may impact on response rate, and we are waiting on the data regarding PFS and OS.

Although PFS is superior only in patients with PD-L1 expression less than 5% ("PD-L1 low" patients), overall response rate (ORR) is superior with the combination regardless of PD-L1 staining. Data on PDL-1 testing is not consistent and even patients with low PDL-1 can respond, hence should not be used for patient selection at this time.

5.7 Additional Information

The clinicians providing input indicated that with respect to the type of support patients would need to receive this type of combination therapy – treating facilities administering combination immunotherapies should have infrastructure in place to manage treatment-related toxicities.

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the efficacy and safety of nivolumab, in combination with ipilimumab, in treatment-naïve adult patients with advanced (unresectable or metastatic) 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

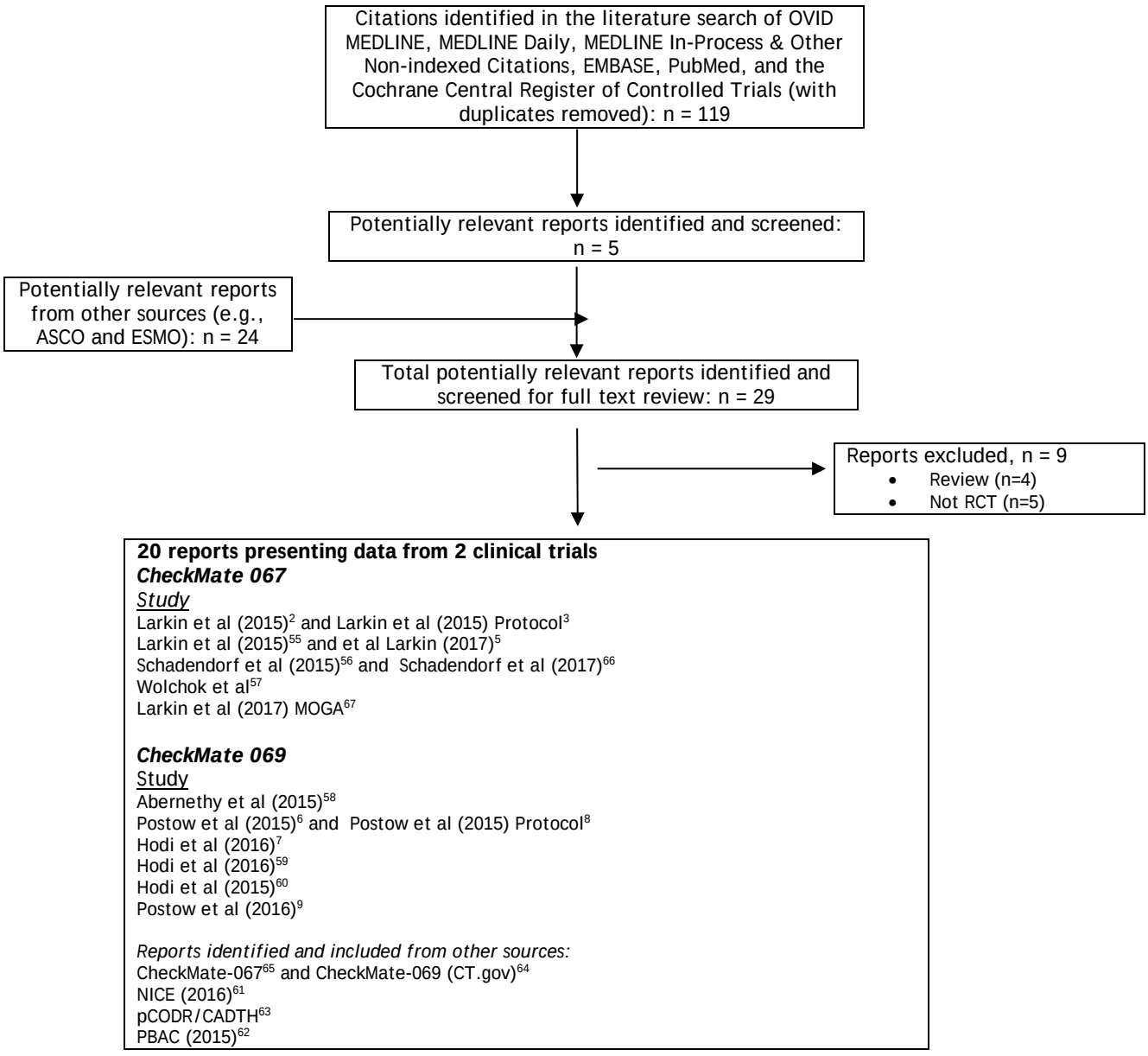
Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Published or unpublished RCTs In the absence of RCT data, fully published clinical trials investigating the safety and efficacy of nivolumab plus ipilimumab should be included.	Treatment-naïve adult patients with advanced (unresectable or metastatic) melanoma, regardless of *BRAF* status. Subgroups: • ECOG PS (0—1 vs. ≥2) • Age (< 65 years vs. ≥65 years) • Sex • *BRAF* status (wild-type vs mutation-positive) • Metastasis stage at entry (M0,M1a, M1b, M1c) • Lactate dehydrogenase (≤ULN, ≥ULN, ≤ 2x ULN, ≥ 2 x ULN) • PD-L1 status (positive vs negative)	Nivolumab plus ipilimumab	CTLA-4 inhibitor • Ipilimumab PD-1 inhibitor • Nivolumab • Pembrolizumab *BRAF* and MEK inhibitors • Cobimetinib • Vemurafenib • Cobimetinib with vemurafenib • Trametinib • Dabrafenib • Dabrafenib with trametinib	Primary • OS • PFS • HRQoL Secondary • ORR • DOR • DCR Safety • AEs • SAEs • WDAEs • Dose adjustment, interruption and/or discontinuation • Time to discontinuation • Autoimmune AEs • Endocrine AEs • Skin related AEs
RCT=randomized controlled trial; ECOG PS=Eastern Cooperative Oncology Group Performance Status; ULN = Upper limit of the normal range; OS = overall survival; PFS = progression-free survival; HRQoL=Health related quality of life; ORR=objective response rate; DOR=duration of response; DCR=disease control rate; AE=adverse events; WDAE=withdrawals due to adverse events; SAE=serious adverse events				
Notes: * Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions).				

6.3 Results

6.3.1 Literature Search Results

Of the 26 potentially relevant reports identified, one double-blind, phase III randomized controlled trial (RCT) (CheckMate 067) and one double-blind, phase II RCT (CheckMate 069), reported in 20 citations,[2,3,5-9,55-67] were included in the pCODR systematic review and 9 studies were excluded. These studies were excluded because they were reviews or they did not use a RCT design.

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



Note: Additional data related to CheckMate 067 and 069 were also obtained through requests to the Submitter by pCODR[4,68,69]

6.3.2 Summary of Included Studies

The pCODR systematic review identified two RCTs that assessed the efficacy and safety of nivolumab, in combination with ipilimumab, in treatment-naïve adult patients with advanced (unresectable or metastatic) melanoma.

6.3.2.1 Detailed Trial Characteristics

Table 4: Summary trial characteristics for CheckMate 067 and CheckMate 069

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
CheckMate 067 **Other identifiers:** NCT01844505 **Characteristics:** Randomized, double-blind, phase III RCT **Sample size:** 945 **Locations:** 137 centres in Australia, Europe, Israel, New Zealand and North America **Patient Enrolment Dates:** 7/2013 to 3/2014 **Primary Analysis Data cut-off:** 2/2015 **Secondary Analysis Data cut-off:** 9/2016 **Final Analysis Date:** Pending **Sponsor:** BMS	<u>Key Inclusion Criteria:</u> • Adult patients ≥ 18 years with histologically confirmed, unresectable, stage III or IV untreated melanoma • ECOG PS of 0 or 1 • Known *BRAF* V600 mutation status • Tumor tissue samples from a metastatic or unresectable site • Measurable disease assessed by CT or MRI according to RECIST 1.1 <u>Key Exclusion Criteria:</u> • ECOG PS of ≥ 2 • Presence of active brain metastases, ocular melanoma, or autoimmune disease.	**Intervention:** Nivolumab with ipilimumab **Comparator:** Ipilimumab Nivolumab	<u>**Co-primary:**</u> PFS OS <u>**Secondary:**</u> ORR <u>**Exploratory**</u> DOR TTR Tumor PD-L1 expression HRQoL Safety and tolerability
CheckMate 069 **Other identifiers:** NCT01927419 **Characteristics:** Randomized, double-blind, phase II RCT	<u>Key Inclusion Criteria:</u> • Adult patients ≥ 18 years with histologically confirmed, unresectable, previously untreated stage III or IV melanoma with measurable disease	**Intervention:** Nivolumab with ipilimumab **Comparator:** Ipilimumab	<u>**Primary:**</u> ORR by IA in *BRAF* wild-type patients <u>**Secondary:**</u> ORR in all patients

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
Sample size: 142 **Locations:** 21 sites in USA and France **Patient Enrolment Dates:** 09/2013 to 02/2014 **Primary Analysis Data cut-off:** 01/2015 **Secondary Analysis Data cut-off:** 02/2016 **Final Analysis Date:** Pending **Sponsor:** BMS	• Known *BRAF* V600 mutation status • ECOG PS of 0 or 1 • Tumor tissue samples from a metastatic or unresectable site <u>Key Exclusion Criteria:</u> • Presence of active brain metastases, uveal melanoma, or serious autoimmune disease.		PFS in *BRAF* wild-type patients PFS in all patients <u>Exploratory</u> Safety and tolerability PK parameters HRQoL Overall survival DOR and TTR
RCT = Randomized controlled trial; **ECOG PS** = Performance Status; **RECIST** = Response Evaluation Criteria In Solid Tumours; **CT** = computed tomography; **MRI** = magnetic resonance imaging; **PFS** = Progression-free survival; **OS** = Overall Survival; **IA** = Investigator assessment; **ORR** = Overall response rate; **DOR** = Duration of response; **TTR** = Time to objective response; **PRO** = Patient reported outcome; **PK** = pharmacokinetics.			

Table 5: Select quality characteristics of CheckMate 067 and CheckMate 069

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 067	Nivolumab + ipilimumab vs Ipilimumab vs Nivolumab[A]	PFS and OS[B]	915[C]	945	IVRS	Yes	Yes[D]	Yes	No[E]	No	Yes
CheckMate 069	Nivolumab + ipilimumab vs Ipilimumab	ORR[F]	100[G]	142	IVRS	Yes	Yes[D]	Yes	Yes	No	Yes
ITT = intention-to-treat; **PFS** = Progression-free survival; **OS** = overall survival; **IVRS** = an interactive voice response system; **ORR** = objective response rate. A: CheckMate 067 was designed to make formal statistical comparisons between the nivolumab and the nivolumab plus ipilimumab treatment groups.											

B: The co-primary endpoints in CheckMate 067 were PFS and OS. The ITT population includes treatment-naïve patients with advanced melanoma.
C: 915 progressive events were expected to provide 83% power for PFS to reject the null hypothesis of an HR of 0.71 using a two-sided significance level of α=0.005 for a 9 month follow-up or the minimum required follow-up of 6 months for all comparisons. For overall survival, the protocol stated that a total of 644 deaths were projected to occur at 28 months, which would provide the study with 99% power to reject the null hypothesis of an HR of 0.65 using a two-sided significance level of α=0.02 for a 28 month follow-up or the minimum required follow-up of 22 months for all comparisons.
D: Patients, study investigator, site staff and sponsor were blinded to the treatment assignment until progression of disease or treatment discontinuation.
E: The database lock of 13-Sept-2016 represents a minimum follow-up of 28 months. At this point, the Manufacturer reported that the actual number of observed events was 28% lower than anticipated, and therefore, this analysis had 95% power to detect a HR of 0.65.
F: The primary endpoint for CheckMate 069 was ORR. The primary analysis was conducted in *BRAF* wild-type carriers with treatment-naïve advanced melanoma. The Manufacturer stated that the ITT includes all randomized patients.
G: 100 *BRAF* wild-type carriers were required to provide 87% power using a two-sided significance level of α=0.05 to show a difference in ORR of 40% for nivolumab plus ipilimumab and 10% for ipilimumab for a 28 month follow-up or the minimum required follow-up of 22 months.

a) Trials

Two RCTs met the inclusion criteria for this pCODR systematic review. These trials include a phase III, double-blind RCT (CheckMate 067, N = 945) and a phase II, double-blind RCT (CheckMate 069, N= 142). The characteristics of the trial designs are presented in Table 4 and Table 5.

CheckMate 067

CheckMate 067 was a double-blind, multicentre, multi-arm phase III RCT that assessed the effect of nivolumab, nivolumab plus ipilimumab or ipilimumab on overall survival and PFS in 945 patients with unresectable stage III or IV melanoma.[2] The trial was conducted in 137 centres in such countries as Australia, Europe, Israel, New Zealand and North America.[2] The database was locked at two planned time points: 17-Feb-2015[2] and 13-September-2016.[4] An additional database lock was performed on Nov-2015, which provided a descriptive analysis at 18 months of follow-up.[57] There were no interim analyses planned for this trial.[3] The trial was sponsored by Bristol-Myers Squibb.

Patient enrolment occurred between July 2013 and March 2014.[2] The trial included patients aged 18 years and older with histologically confirmed, unresectable, stage III or IV untreated melanoma and a known *BRAF* V600 mutation status.[2] In addition, patients were required to have an ECOG performance status of 0 or 1, tissue samples from a metastatic or unresectable tumour and measurable disease assessed by CT or MRI according to the Response Evaluation Criteria In Solid Tumours (RECIST) version 1.1.[2] Patients were excluded from study enrolment if they had an ECOG performance status greater than 2 and presence of active brain metastases, ocular melanoma, or an autoimmune disease.[2]

Eligible patients were randomized (1:1:1) by an interactive voice response system (IVRS) to receive nivolumab, nivolumab plus ipilimumab or ipilimumab. Randomization was stratified by tumour PD-L1 status (positive, negative or intermediate), *BRAF* carrier status (V600 mutation-positive vs. wild-type) and American Joint Committee on Cancer (AJCC) metastasis stage (M0, M1a or M1b vs M1c). It should be noted that this trial was not designed to compare nivolumab plus ipilimumab to the nivolumab treatment group[2] and the results of this comparison will be considered as descriptive only. Patients continued to be treated with their assigned therapies until they had documented disease progression, developed unacceptable toxic evets or withdrew consent.

Patients were evaluated for response according to RECIST 1.1 for the first 12 weeks after randomization and then every six weeks for the first 12 months followed by every 12 weeks until disease progression or treatment discontinuation.[3] It was noted that investigator assessment of disease progression was required within the first 12 weeks of starting the study therapies because patients who receive immunomodulating agents may experience documented pseudo-progression.[62] Patients that had disease progression as defined by RECIST 1.1 could remain on their assigned therapies if they continued to demonstrate investigator-assessed clinical benefit and they were still able to tolerate the study therapy. However, patients who discontinued their assigned therapies due to disease progression or other withdrawal criteria, entered the follow-up phase, where they were monitored for tumour progression. Furthermore, in this phase, randomization assignment was only unblinded after patients had both disease progression and discontinued their assigned treatment.[3] After patients were unblinded they could then receive subsequent therapies, such as anti-PD1s, ipilimumab and/or *BRAF* inhibitors.

The co-primary outcomes assessed in the CheckMate 067 Trial were PFS and overall survival. For PFS, the study was designed to have 83% power to reject the null hypothesis of an HR of 0.71 (489 progressive events) using a two-sided significance level of α=0.005 for a 9 month follow-up period or the minimum required follow-up of 6 months for all comparisons.[3] For overall survival, the protocol stated that a total of 644 deaths were projected to occur at 28 months, which would provide the study with 99% power to reject the null hypothesis of an HR of 0.65 using a two-sided significance level of α=0.02 for a 28 month follow-up or the minimum required follow-up of 22 months for all comparisons for all comparisons.[3,8] PBAC noted that the type I error was shared between overall survival and PFS (α = 0.04 and α = 0.01) and statistical significance could be used for either outcome.[62] However, at the database lock of 13-Sept-2016, the Manufacturer reported that the actual number of observed events was 28% lower than anticipated, and therefore, this analysis had 95% power to detect a HR of 0.65.[4] The secondary efficacy endpoint in this trial was objective response rate (ORR) in all patients and the exploratory outcomes were median duration of response (DOR), time to objective response (TTR), health related quality of life (HRQoL) assessment and safety and tolerability measures.

The protocol was amended seven times. These amendments were made in order to collect radiological or biological samples from patients, comply with country-specific regulations, continue to follow patients who discontinued from the study drug for overall survival and include PFS as a co-primary endpoint as opposed to having overall survival as the original primary endpoint.[63] The amendment to include PFS as a co-primary endpoint occurred prior to the randomization of study participants.

CheckMate 069

CheckMate 069 was a double-blind, phase II RCT that assessed the effect of nivolumab plus ipilimumab and ipilimumab on ORR in 109 *BRAF* V600 wild-type carriers with advanced melanoma.[6,7] The trial was conducted in 21 sites in the United States and France.[62] There were two database locks in this trial. The first database lock occurred on 30-Jan-2015[6] and the second occurred on 29-Feb-2016.[7] These dates represent 11 months and 24.5 months post follow-up, respectively. No interim analyses were planned for this study. The trial was sponsored by Bristol-Myers Squibb.

Patient enrolment occurred between September 2013 and February 2014.[6] The trial enrolled patients who were 18 years and older with histologically confirmed, unresectable, previously untreated stage III or IV melanoma with measurable disease. These patients also had known *BRAF* V600 mutation status, an ECOG of 0 or 1 and tissue samples from metastatic or unresectable tumours. Patients were excluded if they had active brain metastases, uveal melanoma, or serious autoimmune disease.[6]

Eligible patients were randomized (2:1) by an IVRS to receive either a combination of nivolumab plus ipilimumab or ipilimumab. Randomization was stratified by tumour PD-L1 status (positive, negative or intermediate), *BRAF* mutation status (V600 mutation-positive vs. wild-type) and AJCC metastasis stage (M0, M1a or M1b vs M1c).

Patients were evaluated for tumour response according to RECIST 1.1 for the first 12 weeks after randomization, followed by every six weeks for the first 12 months and then every 12 weeks until disease progression, treatment discontinuation or other reasons.[8] Patients that had disease progression could remain on their assigned therapies if they continued to experience investigator-assessed clinical benefit and they were still tolerant to the study therapy.[8] Patients also had the option to discontinue their blinded therapy. Unblinded patients, originally randomized to ipilimumab, could cross-over and receive a 3 mg/kg dose of open-label nivolumab every two weeks until further disease progression. In contrast, unblinded patients assigned to nivolumab plus ipilimumab were required to discontinue treatment.

The primary outcome in CheckMate 069 was ORR in *BRAF* wild-type carriers. It was indicated that the analyses conducted in the *BRAF* mutation-positive carriers were descriptive and this subgroup was not included in the power and sample size calculations.[8] The Manufacturer also provided the Clinical Guidance Panel with a rationale for why *BRAF* wild-type carriers were used in the primary analysis: "…these patients (*BRAF* WT) are considered to have only ipilimumab monotherapy as an approved standard of care. As a result, if the combination of nivolumab and ipilimumab can demonstrate a significant improvement in response rate and quality of responses compared to ipilimumab alone, this would represent a significant clinical advancement for subjects with *BRAF* WT disease and thus potentially warrant an accelerated regulatory approval."[69]

The study was designed to have 87% power with a two-sided α=0.05 to show a significant difference between an ORR of 40% and an ORR of 10% for nivolumab plus ipilimumab and ipilimumab, respectively.[8] Using a hierarchical testing approach, the secondary efficacy endpoints included ORR in all randomized patients, PFS in all *BRAF* wild-type carriers and PFS in all randomized patients.[8] Exploratory measures include overall survival, median DOR, TTR, HRQoL, safety and tolerability, and pharmacokinetic parameters.

The protocol was amended [redacted] times. These amendments were made in order to clarify the protocol and update the study and statistical analysis plan. These amendments included: [redacted].[69] (*Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by manufacturer that it can be publicly disclosed*.) Although there were major revisions made to the protocol, the Manufacturer stated that these changes occurred prior to the first visit of the first study participant.

b) Populations

CheckMate 067

A total of 945 untreated patients with unresectable stage III or IV melanoma were included in the study. Patients were randomized to receive either nivolumab (N = 316), ipilimumab (N = 314) or the combination of nivolumab plus ipilimumab (N = 315). The study baseline characteristics are presented in Table 6. Patient characteristics were generally balanced between the three groups. The majority of patients were male, had an ECOG status of 0, a negative PD-L1 status and brain

metastases at baseline. In addition, approximately two-thirds of the patient population were *BRAF* wild-type carriers.

CheckMate 069

A total of 142 untreated patients with advanced melanoma were included in the study (Table 6). Patients were randomized to receive either a combination of nivolumab plus ipilimumab (N = 95 and $N_{BRAF\ wt}$ = 72) and ipilimumab (N = 47 and N $N_{BRAF\ wt}$ = 37). Among the *BRAF* wild-type carriers, patient characteristics were generally balanced between the two groups. As previously reported, the majority of patients were male, had an ECOG status of 0 and brain metastases at baseline. Notably, more than three-fourths of all randomized patients were *BRAF* wild-type carriers. Similar results were observed for all randomly assigned patients in the trial.

Table 6: Baseline characteristics of patients enrolled in CheckMate 067 and CheckMate 069

	CHECKMATE 067 All patients			**CHECKMATE 069** *BRAF* wild-type carriers		**CHECKMATE 069** All patients	
	Nivolumab (N = 316)	**Nivolumab plus Ipilimumab (N=314)**	**Ipilimumab (N = 315)**	**Nivolumab plus Ipilimumab (N=72)**	**Ipilimumab (N = 37)**	**Nivolumab plus Ipilimumab (N=95)**	**Ipilimumab (N = 47)**
Age							
Median (range)	60(25-90)	61(18–88)	62(18-89)	66(27–87)	69 (46–80)	64 (27–87)	67 (31–80)
Sex - n (%)							
Male	202(63.9)	206 (65.6)	202 (64.1)	48 (67)	23 (62)	63 (66)	32 (68)
Female	114(36.1)	108 (34.4)	113 (35.9)	24 (33)	14 (38)	32 (34)	15 (32)
ECOG – n (%)							
0	238 (75.3)	230 (73.2)	224 (71.1)	62 (86)	30 (81)	79 (83)	37 (79)
1	77 (24.4)	83 (26.4)	91 (28.9)	9 (12)	7 (19)	14 (15)	10 (21)
2	1 (0.3)	0	0	1 (1)	0	2 (2)	0
Not reported	0	1 (0.3)	0				
Metastasis stage - n (%)							
M1c	184 (58.2)	181 (57.6)	183 (58.1)	34 (47)	16 (43)	44 (46)	21 (45)
M0, M1a, or M1b	132 (41.8)	133 (42.4)	132 (41.9)	37 (52)	20(54)	50 (53)	25 (53)
Not reported				1 (1)	1 (3)	1 (1)	1(2)
Lactate dehydrogenase - n (%)							
≤ULN	196 (62.0)	199 (63.4)	194 (61.6)	57 (79)	30 (81)	70 (74)	36 (77)
>ULN	112 (35.4)	114 (36.3)	115 (36.5)	15 (21)	7 (19)	24 (25)	11 (23)
≤2× ULN	271 (85.8)	276 (87.9)	279 (88.6)	69 (96)	36 (97)	88 (93)	46 (98)
>2× ULN	37 (11.7)	37 (11.8)	30 (9.5)	3 (4)	1 (3)	6 (6)	1 (2)
Unknown	8 (2.5)	1 (0.3)	6 (1.9)				
Brain metastases - n (%)							
Yes	8 (2.5)	11 (3.5)	15 (4.8)	4 (6)	0	4 (4)	0
No	308 (97.5)	303 (96.5)	300 (95.2)	67 (93)	37 (100)	90 (95)	47 (100)
PD-L1 tumour expression - n (%)							
PD-L1 ≥ 5%	80 (25.3)	68 (21.7)	75 (23.8)	NR		24 (25)	11 (23)
PD-L1 < 5%	208 (65.8)	210 (66.9)	202 (64.1)			71 (75)	36 (77)

Could not be determined	28 (8.9)	36 (11.5)	38 (12.1)				
BRAF status - n (%)							
Mutation	100 (31.6)	101 (32.2)	97 (30.8)	0	0	23 (24)	10 (21)
No mutation	216 (68.4)	213 (67.8)	218 (69.2)	72 (100)	37 (100)	72 (76)	37 (79)
NR= Not reported Data sources: Larkin et al (2015)[2]; PBAC[62]; Postow et al (2015)[6] and Hodi et al (2016)[7]							

c) Interventions

CheckMate 067

In this trial, patients were randomized (1:1:1) in a double-blind fashion to receive either nivolumab, a combination of nivolumab plus ipilimumab or ipilimumab. As reported in the protocol, patients must have received their first dose three days after randomization.[3] Regardless of randomization assignment, patients received intravenous nivolumab or placebo-matched nivolumab followed by intravenous ipilimumab or placebo-matched ipilimumab no sooner than 30 minutes following the completion of nivolumab.[3]

Patients randomized to the nivolumab plus ipilimumab arm were given a 1mg/kg dose of nivolumab plus a 3mg/kg dose of ipilimumab every three weeks for four doses followed by a 3mg/kg dose of nivolumab every two weeks. In contrast, patients randomized to the ipilimumab arm were given the placebo-matched nivolumab plus a 3mg/kg dose of ipilimumab every three weeks for four doses followed by the placebo-matched nivolumab every two weeks.[3] Dose delays were permitted but dose escalations and/or reductions were not.[3]

CheckMate 069

Patients enrolled in CheckMate 069 were randomized (2:1) in a double-blind fashion to receive a combination of nivolumab plus ipilimumab or ipilimumab. As previously mentioned, patients received their first study dose three days after randomization and patients were given intravenous nivolumab or placebo-matched nivolumab followed by intravenous ipilimumab or placebo-matched ipilimumab no sooner than 30 minutes following the completion of nivolumab.[8]

Patients assigned to the nivolumab plus ipilimumab arm received 1 mg/kg of nivolumab followed by 3 mg/kg of ipilimumab every three weeks for four doses followed by 3 mg/kg of nivolumab every two weeks.[8] On the other hand, those assigned to the ipilimumab arm received 1 mg/kg of nivolumab-placebo followed by 3 mg/kg of ipilimumab every three weeks for four doses and then 3 mg/kg of nivolumab-placebo every two weeks.[8] Patients were unable to receive dose escalations and/or reductions but they were permitted dose delays.[8]

d) Patient Disposition

CheckMate 067

For this review, the reported patient disposition of CheckMate 067 was obtained from the 13-Septmeber-2016 database lock (Table 7). In total, 1296 patients were screened for enrollment and 945 patients were randomized on a 1:1:1 ratio to receive nivolumab (N = 316), nivolumab plus ipilimumab (N = 314) or ipilimumab (N = 315).[2] Three patients randomized to nivolumab, one patient randomized to nivolumab plus ipilimumab and four patients randomized to ipilimumab did not receive their assigned study treatment.[2]

During the treatment phase, more patients in the ipilimumab group discontinued treatment as compared to the nivolumab plus ipilimumab group and the nivolumab group (94.9% vs. 85.9% vs. 79.6%, respectively).[70] The primary reasons for discontinuation in the nivolumab plus ipilimumab arm were drug toxicity (41.9%) and disease progression (28.1%).[70] In contrast, the primary reasons for discontinuation in the nivolumab arm and the ipilimumab arm were disease progression (54.3% and 72.0%) and drug toxicity (12.8% and 16.1%).[70] There were no major differences in patient disposition across the two treatment groups for *BRAF* wild-type and mutation positive carriers.[69] Finally, 53.4% of patients in the nivolumab group, 57.8% in the nivolumab plus ipilimumab group and 34.1% in the ipilimumab group remained on the study (Table 7).

Table 7: Summary of patient disposition in the CheckMate 067 Trial at the database lock of 13-September-2016

	Nivolumab (N=313)	Nivolumab plus Ipilimumab (N=313)	Ipilimumab (N=311)
Patients in the treatment period — no. (%)			
Continuing	64 (20.4)	44 (14.1)	16 (5.1)
Not continuing	249 (79.6)	269 (85.9)	295 (94.9)
Reason for not continuing the treatment— no. (%)			
Disease progression	170 (54.3)	88 (28.1)	224 (72.0)
Study drug toxicity	40 (12.8)	131 (41.9)	50 (16.1)
Adverse event unrelated to study drug	7 (2.2)	15 (4.8)	6 (1.9)
Patient request to discontinue treatment	17 (5.4)	14 (4.5)	8 (2.6)
Death	1 (0.3)	3 (1.0)	1 (0.3
Maximum clinical benefit	8 (2.6)	11 (3.5)	2 (0.6)
Poor/non-compliance	1 (0.3)	1 (0.3)	1 (0.3)
Patient withdrew consent	0	3 (1.0)	0
Lost to follow-up	1 (0.3)	0	0
Patient no longer meets study criteria	0	1 (0.3)	0
Other	4 (1.3)	2 (0.6)	2 (0.6)
Not reported	0	0	1 (0.3)
Patients in the study — no. (%)			
Continuing	167 (53.4)	181 (57.8)	106 (34.1)
Not continuing	146 (46.6)	132 (42.2)	205 (65.9)

Data source: CSR CheckMate 067[4]

Among patients who had progressive disease in the nivolumab plus ipilimumab treatment group, 18.8% were treated beyond progression for a median of 2.40 months (range: 1.15 to 3.91).[69]

Table 8: Subsequent anticancer therapies after discontinuation

	Nivolumab (N = 316)	Nivolumab and ipilimumab (N=314)	Ipilimumab (N=315)
Any subsequent therapy[a]	169 (54.0)	129 (41.0)	225 (71.0)
Systemic therapy	140 (44.0)	100 (32.0)	196 (62.0)
Anti-PD-1 agents	32 (10.0)	30 (10.0)	132 (42.0)
Anti-CTLA-4	83 (26.0)	19 (6.0)	12 (4.0)
BRAF inhibitor	57 (18.0)	40 (13.0)	68 (22.0)
MEK inhibitor	38 (12.0)	30 (10.0)	39 (12.0)

Investigational agents[b]	6 (2.0)	8 (3.0)	15 (5.0)
A: Subject may have received more than one type of subsequent therapy. B: Other than investigational immunotherapy, BRAF inhibitor, and MEK inhibitor Data source: Larkin et al (2017)[5]			

Larkin et al (2017) reported that 54.0% of patients on the nivolumab arm, 41.0% of on nivolumab plus ipilimumab and 71.0% on ipilimumab received a subsequent cancer therapy once they discontinued their initial therapy (Table 8).[5] For those randomized to the ipilimumab arm, the majority received an anti-PD-1 agent (42.0%) as compared to those treated with nivolumab (10.0%) or nivolumab plus ipilimumab (10.0%).[5] Furthermore, more patients treated with nivolumab received an anti-CTLA-4 therapy (26.0%) as compared to those treated with nivolumab plus ipilimumab (6.0%) or ipilimumab (4.0%).[5]

There were a total of seven (0.7%) protocol deviations in the CheckMate 067 Trial.[4] In the nivolumab plus ipilimumab arm, one protocol deviation occurred because the patient had a prior systemic anti-cancer treatment in the metastatic setting. In the ipilimumab arm, one protocol deviation occurred because the patient had received concurrent anti-cancer therapy. In contrast, there were five protocol deviations in the nivolumab group. One patient had a baseline ECOG performance status greater than 1 and four patients received concurrent anti-cancer therapy while on-treatment.[70]

CheckMate 069

Data on the patient disposition was obtained from the 29-Feb-2016 database lock.[7] In total, 179 patients were screened for enrollment and 142 patients were randomized in a 2:1 ratio to receive nivolumab plus ipilimumab (N = 95) or ipilimumab (N = 47). The median duration of follow-up from randomization at the database lock was 24.5 months (range: 9.5-25.7).[7]

At the database lock, 13.7% of patients on nivolumab plus ipilimumab and 12.8% on ipilimumab were still receiving their assigned therapies (Table 9).[7] The proportion of patients who discontinued treatment was similar across the two treatment groups (nivolumab with ipilimumab: 85.3% and ipilimumab: 85.1%).[7] The primary reasons for discontinuation of nivolumab plus ipilimumab were drug toxicity (48.4%) and disease progression (17.9%). In contrast, on the ipilimumab arm, the primary reasons for discontinuation were disease progression (40.4%) and drug toxicity (21.2%). Additionally, one patient (2.1%) on ipilimumab died. There were no major differences in patient disposition among the two treatment groups for *BRAF* wild-type and mutation positive carriers.[69] Sixty-three percent of all randomized patients on nivolumab plus ipilimumab and 48.0% on ipilimumab were still being followed up for secondary and exploratory outcomes (Table 9).[7]

Table 9: Summary of patient disposition in the CheckMate 069

	Nivolumab plus Ipilimumab (N=95)	Ipilimumab (N = 47)
Not treated	1 (1.1)	1 (2.1)
Patients in the treatment period, n (%)		
Continuing	13(13.7)	6(12.8)
Not continuing	81(85.3)	40(85.1)
Reason for not continuing the treatment, n (%)		
Study drug-related toxic effects	46(48.4)	10(21.3)
Disease progression	17(17.9)	19(40.4)
Patient request to discontinue treatment	7(7.4)	2(4.3)

	Nivolumab plus Ipilimumab (N=95)	Ipilimumab (N = 47)
AE unrelated to treatment	6(6.3)	3(6.4)
Other reason	3(3.2)	3(6.4)
Withdrew consent	1(1.1)	1(2.1)
Death	0	1(2.1)
Not reported	1(1.1)	1(2.1)
Patients in the follow-up period, n (%)		
Continuing	59 (63.0)	22 (48.0)

Data source: Hodi et al (2016)[7]

Among patients who had progressive disease on nivolumab plus ipilimumab, [redacted] were treated beyond progression; whereas, [redacted] of patients on ipilimumab were treated beyond progression.[69] (*Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by manufacturer that it can be publicly disclosed*.)

As stated in the protocol, patients randomized to the combination treatment group who progressed could receive a subsequent therapy while those randomized to the ipilimumab arm could cross over and receive a 3 mg/kg dose of nivolumab.[8] Fifty-five percent of patients who were treated with ipilimumab, and had disease progression, crossed-over and received nivolumab.[9] Additionally, three patients from this treatment group received either nivolumab or pembrolizumab off study.[9] However, in the combination arm, 85% of patients discontinued treatment.[7]

At the 29-Feb-2016 database lock, the median time to subsequent therapy was 6.1 months (range: 4.2 to 7.4) for those randomized to ipilimumab and it had not been reached for those on nivolumab plus ipilimumab.[9] A larger proportion of all randomized patients on ipilimumab received more than one subsequent therapy as compared to those on nivolumab plus ipilimumab (70% vs. 35%) (Table 10).[9] There were no notable differences between *BRAF* wild-type carriers and *BRAF* mutation positive carriers.

Table 10: Subsequent anticancer therapies after discontinuation

	All randomised patients, n (%)		***BRAF* wild-type carriers, n (%)**		***BRAF* mutation-positive carriers, n (%)**	
	Nivolumab and ipilimumab (N=95)	Ipilimumab (N=47)	Nivolumab and ipilimumab (N=72)	Ipilimumab (N=37)	Nivolumab and ipilimumab (N=23)	Ipilimumab (N=10)
Any subsequent therapy[a]	33 (35)	33 (70)	26 (36)	25 (68)	7 (30)	8 (80)
Systemic therapy	27 (28)	30 (64)	21 (29)	22 (60)	6 (26)	8 (80)
Anti-PD-1 agents	17 (18)	29 (62)[b]	13 (18)	22 (59)	4 (17)	7 (70)
BRAF inhibitor[c]	4 (4)	6 (13)	0	0	4 (17)	6 (60)
MEK inhibitor[c]	3 (3)	7 (15)	1 (1)	1 (3)	2 (9)	6 (60)
Investigational agent	4 (4)	2 (4)	3 (4)	2 (5)	1 (4)	0
Radiotherapy	17 (18)	17 (36)	12 (17)	13 (35)	5 (22)	4 (40)
Surgery	11 (12)	13 (28)	10 (14)	9 (24)	1 (4)	4 (40)

A: Patients may have received more than one subsequent therapy.
B: Including 26 (55%) patients who received nivolumab after progression on ipilimumab (per protocol); 3 patients received nivolumab or pembrolizumab off study.
C: Patients may have received *BRAF* and MEK inhibitors in combination.
Data source: Hodi et al 2016[7]

There were two (1.4%) protocol deviations in the CheckMate 069 Trial.[7] One patient on each arm of the study no longer met the study criteria. One patient had a pleural effusion unrelated to the study medication while the other patient pursued surgery.[7]

e) Limitations/Sources of Bias

Overall, CheckMate 067 and CheckMate 069 were well designed phase III and phase II, double blind RCTs. These trials used adequate random sequence generation and allocation concealment through an IVRS with a third-party. Furthermore, study personnel and patients were blinded to randomization status until patients progressed and discontinued treatment. Study personnel and patients were blinded to randomization status until patients progressed and discontinued treatment. However, there are a few limitations that should be taken into consideration:

- For the CheckMate 067 Trial, the Manufacturer provided pCODR with three database lock dates, which include: 17-Feb-2015, Nov-2015 and 13-Sept-2016. The 17-Feb-2015 and 13-Sept-2016 database locks were used to analyze PFS and overall survival as per protocol. However, the Nov-2015 database lock was an additional descriptive that represents 18 months of follow-up. By conducting this unplanned interim analysis, the Manufacturer may have increased the risk of a type 1 error in subsequent overall survival analyses because it is unclear whether they applied a penalty for the final analysis.

- Overall survival was immature at the time of the latest database cut off in CheckMate 069. 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 ipilimumab could cross over and received nivolumab. Furthermore, overall survival was an exploratory outcome and it may not be powered to detect an effect.

- CheckMate 067 was only designed to assess the effect of 1) nivolumab versus ipilimumab or 2) nivolumab plus ipilimumab versus ipilimumab on the effect of PFS and overall survival. The Manufacturer stated that ipilimumab was considered a standard of care for all patients with advanced melanoma and adding a third statistical comparison would have increased the risk of multiplicity and required a larger sample size.[3] Thus comparisons between nivolumab and the combination arm are descriptive only and should be interpreted with caution.

- CheckMate 069 was not designed to explore the effect of nivolumab plus ipilimumab as compared to ipilimumab in *BRAF* mutation-positive carriers. Moreover, the Manufacturer stated that all analyses performed in this subgroup were descriptive. Therefore it is difficult to truly assess whether *BRAF* mutation-positive carriers benefit from the drug combination.

- CheckMate 069 used ORR as a primary outcome; however, the adequacy of this measure as a primary outcome is unclear. Although ORR is correlated with overall survival, this statistical correlation does not necessarily imply that it is predictive of overall survival.

- Both trials included patients with an ECOG status of ≤ 2. Performance status is a well-established prognostic factor in advanced melanoma and the generalizability of these trials to a broader patient population may be limited.

- Although the CheckMate 067 and CheckMate 069 trials have demonstrated that nivolumab plus ipilimumab may be effective in the first-line setting, there is still a lack of evidence comparing this therapy to other *BRAF* inhibitors, such as dabrafenib and trametinib. The Manufacturer tried to address this concern in the indirect comparison; however, they were unable to do so because of methodological issues. Therefore, it is difficult to truly establish the clinical and economic impact of the combination in the Canadian context.

6.3.3 Detailed Outcome Data and Summary of Outcomes

Efficacy Outcomes

CheckMate 067

Progression free survival

The co-primary endpoints in CheckMate 067 were PFS and overall survival. PFS was defined as the time from randomization to the date of first documented progression, as determined by the investigator, or death due to any cause, whichever occurred first.[65] Subjects who died without reported progression were considered to have progressed at the date of their death. Patients who started any subsequent anti-cancer therapies prior to disease progression were censored at the time of their last tumor assessment.[3]

For PFS, the study was designed to have 83% power to reject the null hypothesis of an HR of 0.71 (489 progressive events) using a two-sided significance level of α=0.005 for the comparisons between nivolumab versus ipilimumab and nivolumab plus ipilimumab versus ipilimumab.[3] As stated in the protocol, PFS was assessed after all subjects had 9 months of follow-up based on the power calculation or after a minimum 6 month follow-up period.[3] This analysis used an intention-to-treat (ITT) approach and PFS distributions were estimated using Kaplan-Meier methods and a log-rank test stratified by PD-L1 status, *BRAF* mutation status and AJCC metastasis stage. The Manufacturers also used Cox regression models to estimate the HR of PFS and 99.5% confidence intervals (CI). The study was not designed to make statistical comparisons between nivolumab and nivolumab plus ipilimumab,[71] and thus the presented results are considered as descriptive.

The database lock date for the PFS analysis was on 17-Feb-2015.[2] At this time point, 55.1% (N = 174) of patients on nivolumab, 48.1% (N = 151) on nivolumab plus ipilimumab and 74.3% (N = 234) of patients on ipilimumab had disease progression or died.[2] Median PFS was 6.9 months (95% CI, 4.3 to 9.5) for patients treated with nivolumab, 11.5 months (95% CI, 8.9 to 16.7) for those treated with nivolumab plus ipilimumab and 2.9 months (95% CI, 2.8 to 3.4) for those treated with ipilimumab.[2] Treatment with nivolumab plus ipilimumab was associated with a prolonged PFS as compared to ipilimumab in patients with advanced melanoma (HR: 0.42; 99.5% CI, 0.31 to 0.57; P < 0.001).[2] The robustness of these results was confirmed using supportive and sensitivity analyses. On the other hand, the HR estimate comparing nivolumab plus ipilimumab to nivolumab was 0.74 (95% CI, 0.60 to 0.92).

Additionally, for this review, the CGP identified several subgroups of interest to explore the effect of the three treatment groups on PFS. These subgroups include: age, sex, ECOG status, smoking status, *BRAF* status, metastasis stage, lactase dehydrogenase and PD-L1 status. The clinical benefit of nivolumab plus ipilimumab was similar across all subgroups; however, in the Larkin et al (2015) publication, the median PFS had not been reached for many of the pre-planned subgroups.[2] For instance, there was consistent effect of nivolumab plus ipilimumab as compared to ipilimumab on the effect of PFS among *BRAF* mutation-positive (HR: 0.47 [95% CI, 0.32 to 0.68]) and wild-type-carriers (HR: 0.41 [95% CI, 0.32 to 0.53]) but the median PFS for both *BRAF* mutation-positive carriers and wild-type carriers had not been reached in the nivolumab plus ipilimumab group.[2]

Moreover, the Manufacturer observed a beneficial effect of nivolumab plus ipilimumab as compared to ipilimumab regardless of PD-L1 expression level (PD-L1 ≤5% [HR: 0.42, 95% CI, 0.32 to 0.64] vs. PD-L1 ≥5% [HR: 0.39, 95% CI, 0.25 to 0.62]).[2,61]

Overall survival

The other co-primary endpoint in CheckMate 067 was overall survival, which was defined as the time from randomization to the date of death due to any cause in all patients.[65] The trial had 99% power to reject the null hypothesis of a HR of 0.65 for overall survival (442 deaths events) using a two-sided significance level of α=0.02 for a 28 month follow-up period or a minimum follow-up of 22 month for all comparisons.[3] However, at the database lock of 13-Sept-2016, the Manufacturer reported that the actual number of observed events was 28% lower than anticipated, thus the analysis had 95% power to detect a HR of 0.65.[4]

The effect estimates for overall survival were obtained from the 13-Sept-2016 database lock, which represents 28 months of follow-up for all subjects. At this time point, 44.9% (N = 142) of patients on nivolumab, 40.8% (N = 128) of patients on nivolumab plus ipilimumab and 62.5% (N = 197) of patients on ipilimumab had died.[4] The median overall survival time was 20.0 months (95% CI, 17.1 to 24.6) in the ipilimumab group and it had not been reached for the nivolumab or in the nivolumab plus ipilimumab groups.[5] Treatment with nivolumab plus ipilimumab was associated with longer survival as compared to the ipilimumab group in patients with advanced melanoma (HR: 0.55, 98% CI: 0.42 to 0.72; P < 0.0001).[4] In contrast, there was no statistical difference between nivolumab plus ipilimumab and nivolumab on overall survival (HR: 0.88, 95% CI, 0.69 to 1.12).[5] These results should be interpreted with caution because median overall survival time had not been reached for nivolumab plus ipilimumab or nivolumab and the trial was not powered for a comparison between nivolumab and nivolumab plus ipilimumab.

The CGP identified several subgroups of interest for overall survival, such as: age, sex, ECOG status, *BRAF* status, metastasis stage, lactase dehydrogenase and PD-L1 status. The Manufacturer showed that there was a consistent beneficial effect of nivolumab plus ipilimumab as compared to ipilimumab for these subgroups.[4] As previously mentioned, these results should also be interpreted with caution due to small sample sizes and median overall survival had not been reached for the nivolumab plus ipilimumab group.

Objective Response Rate

ORR was the key secondary endpoint in the CheckMate 067 trial. It was defined as the proportion of patients with a best overall response, which is the sum of those with a complete response (CR) or partial response (PR).[65] Best response rates were determined by the investigator using RECIST 1.1 and it was classified prior to disease progression or subsequent anticancer therapy. For the analysis, a hierarchical testing approach was used to control for type 1 error.[3] In this hierarchy, ORR could only be assessed if PFS was statistically significant between treatment groups.

At the 13-Sept-2016 database lock, more patients in the nivolumab plus ipilimumab group demonstrated an ORR as compared to those in the ipilimumab group (58.9% [95% CI, 53.3 to 64.4] vs. 19.0% [95% CI, 14.9 to 23.8]) (Table 11).[5] The ORR in the nivolumab group was 58.9% (95% CI, 53.3 to 64.4).[5] The Manufacturer noted that there were differences in patients who had partial and complete responses at the two database locks. This occurred because patients who had a PR at the 17-Feb-2015 database lock had converted to a CR at the time of the later database lock.[69]

Table 11: Response to nivolumab plus ipilimumab or ipilimumab treatment in all patients with advanced melanoma in the CheckMate 067 Trial at the 13-Sept-2016 database lock

Outcome	Nivolumab N = 316	Nivolumab with ipilimumab N = 314	Ipilimumab N = 315
Best overall response			
Complete Response, n (%)	47 (14.9)	54 (17.2)	14 (4.4)
Partial Response, n (%)	49 (29.7)	131 (41.7)	46 (14.6)
Stable Disease, n (%)	31 (9.8)	36 (11.5)	67 (21.3)
Progressive Disease, n (%)	122 (38.6)	74 (23.6)	161 (51.1)
Not determined, n (%)	22 (7.0)	19 (6.1)	27 (8.6)
ORR, % (95% CI)[A]	44.6 (39.1, 50.3)	58.9 (53.3, 64.4)	19.0 (14.9, 23.8)
DOR, median in months (95% CI)[B]	31.1 (31.1, NR)	NR	18.2 (8.3, NR)
TTR, median in months (range)[C]	2.79 (2.3, 32.9)	2.76 (1.1, 28.8)	2.79 (2.5, 17.3)

ORR = overall response rate; DOR = duration of response; TTR = time to response, NR = Not reached.
A: Proportion of patients with the best overall response which is the sum of complete or partial responses.
B: Time from first documented response of either CR or PR, in patients with confirmed PR or CR, to the date of first documented disease progression or death due to any cause.
C: Time from the date of randomization to the date of the first documented CR or PR only in patients with confirmed CR or PR.
Data source: Larkin 2017[5] and CheckMate 067 CSR[4]

Duration of Response

DOR was defined as the time from the first documented response of either CR or PR, in patients with a confirmed PR or CR, to the date of first documented disease progression, as assessed by the investigator per RECIST 1.1, or death due to any cause.[3] The duration of response for nivolumab was 31.1 months (95% CI, 31.1 to not reached) and 18.2 months (95% CI, 8.3 to not reached) for ipilimumab.[5] The DOR was not reached for the nivolumab plus ipilimumab treatment group.[5]

Time to Objective Response (TTR)

TTR was defined as the time from randomization to the date of the first documented CR or PR only in patients with confirmed CR or PR.[3] At the database lock date of 13-Sept-2016, the TTR was 2.79 months (range: 2.3 to 32.9) in the nivolumab group, 2.76 months (range: 1.1 to 28.8) in the nivolumab plus ipilimumab group and 2.79 months (range: 2.5 to 17.3) in the ipilimumab group.[4]

CheckMate 069

Objective Response Rate

The primary endpoint in CheckMate 069 was ORR in *BRAF* wild-type carriers. It was assessed by the study investigator using RECIST 1.1 criteria and it was defined as the proportion of *BRAF* wild-type carriers with the best overall response.[8] In the trial, CR occurred when all target and non-target lesions had disappeared and when selected lymph nodes reduced to less than 10mm. PR occurred when there was at least a 30% decrease in the sum of the longest diameter of a target lesion from baseline.[64] ORR was measured at six months post-randomization or prior to subsequent therapy.[8] In order to have 87% power, 100 *BRAF* wild-type carriers were required to show a difference for an expected 40% ORR in nivolumab plus ipilimumab and 10% ORR in ipilimumab using a two-sided significance level of α= 0.05.[7]

ORR was tested at the 30-Jan-15 database lock (Table 12). The authors showed that *BRAF* wild-type carriers randomized to nivolumab plus ipilimumab had a higher ORR as compared to those treated with ipilimumab (61% [95% CI, 49 to 72] vs. 11% [95% CI, 3 to 25], respectively).[6] As a

secondary outcome in the hierarchical testing approach, ORR was assessed in all randomized patients. Similar results were reported, where there was a higher ORR in patients on nivolumab plus ipilimumab (59% [95% CI, 48 to 69]) as compared to ipilimumab (11% [95% CI, 3 to 23]).[6] In addition, *BRAF* mutation-positive carriers treated with nivolumab plus ipilimumab had a higher ORR (52% [95% CI, 31 to 73]) as compared to those treated with ipilimumab (10% [95% CI, 0 to 45]).[7] However, this was a descriptive analysis and these results should be interpreted with caution.

Table 12: Response to nivolumab plus ipilimumab or ipilimumab treatment in *BRAF* wild-type carriers with advanced melanoma in the CheckMate 069 Trial

Outcome	*BRAF* wild-type carriers		All randomized patients	
	Nivolumab with Ipilimumab (N = 72)	Ipilimumab (N = 37)	Nivolumab with Ipilimumab (N = 95)	Ipilimumab (N = 47)
Best overall response				
Complete Response, n (%)	16 (22)	0	21 (22%)	0
Partial Response, n (%)	28 (39)	4(11)	35 (37%)	5 (11%)
Stable Disease, n (%)	9 (13)	13 (35)	12 (13%)	14 (30%)
Progressive Disease, n (%)	10 (14)	15 (41)	15 (16%)	22 (47%)
Not determined, n (%)	9 (13)	5(14)	12 (13%)	6 (13%)
ORR, % (95% CI)[A]	61 (49-72)	11(3-25)	59 (48-69)	11 (3-23)
DOR, median in months (95% CI)[BC]	NR	NR	NR	NR
TTR, median in months (range)[D]	2.76 (2.3-5.3)	2.66(2.5-2.7)	2.8 (2.3-7.2)	2.7 (2.5-2.7)

ORR = overall response rate; **DOR** = duration of response; **TTR** = time to response, **NR** = Not reached.
A: ORR was defined as the proportion of patients with the best overall response which is the sum of complete or partial responses.
B: DOR was defined the time from first documented complete or partial response to the date of first documented tumour progression using RECIST 1.1 or death due to any cause.
C: Median duration of response was not reached at the 30-Jan-2015 or the 29-Feb-2016 database lock dates.
D: TTR was defined as the time from the date of randomization to the date of the first documented complete or partial response only in patients with confirmed complete or partial response.
Data sources: Postow et al (2015)[6] and Hodi et al (2016)[7]

DOR and TTR in months were also assessed as exploratory outcomes. DOR was defined as the time from first documented complete or partial response to the date of first documented tumour progression using RECIST 1.1 or death due to any cause.[8] The Manufacturer noted that at both database lock dates (30-Jan-15 and 29-Feb-16), the median DOR had not been reached for *BRAF* wild-type carriers or for all randomized patients.[6,7]

TTR was defined as the time from the date of randomization to the date of the first documented CR or PR only in patients with confirmed CR or PR. This outcome was assessed on 30-Jan-15.[8] The TTR among *BRAF* wild-type carriers in the nivolumab plus ipilimumab treatment group was 2.76 months (range: 2.3 to 5.3) and 2.66 months (range: 2.5 to 2.7) in the ipilimumab treatment group.[72]

Progression-Free Survival

PFS was a key secondary outcome in the CheckMate 069 trial. It was defined as the time from randomization to the date of the first documented progression as assessed by the investigator per RECIST 1.1 or death due to any cause.[8] Patients who started any subsequent anti-cancer therapies prior to disease progression were censored at the time of their last tumor assessment. For this

analysis, a hierarchical testing approach was utilized to control for type 1 error.[8] PFS in *BRAF* wild-type carriers could only be assessed if the ORR in all *BRAF* wild-type carriers was statistically significant. And if both of these analyses were statistically significant, then the PFS in all randomized subjects could be assessed. This analysis used an ITT approach, Kaplan-Meier methods and a stratified log-rank test. A Cox regression model was also used to estimate the HR of overall survival and 95% CI.

The PFS effect estimates were obtained from the 29-Feb-2016 database lock date, which represents two years of follow-up. At this time point, 43.1% of the *BRAF* wild-type carriers in the nivolumab plus ipilimumab group and 75.7% in the ipilimumab group had disease progression or died.[9] Median PFS had not been reached for those randomized to the combination group while it was 4.4 months (95% CI, 2.8 to 5.3) in the ipilimumab group.[9] Nivolumab plus ipilimumab was associated with a prolonged PFS as compared to ipilimumab among *BRAF* wild-type carriers (HR: 0.35; 95% CI, 0.21 to 0.59; P < 0.001).[9] However, since the median PFS survival had not been met in the nivolumab plus ipilimumab group these results should be interpreted with caution.

Similar findings were reported for PFS in all randomized patients. A consistent protective effect of nivolumab plus ipilimumab as compared to ipilimumab on PFS (HR: 0.36, 95% CI, 0.22 to 0.56; P <0.0001) yet the median PFS had not been reached in the nivolumab plus ipilimumab group.[9] Subgroup analyses of PFS were also performed in all randomized patients and showed that there were no significant differences across subgroups (Interaction P ≥ 0.05 for all).[7]

Overall survival

Overall survival was reported as an exploratory outcome and it was defined as the time between randomization to the date of death.[8] At the 29-Feb-2016 database lock, the median overall survival for *BRAF* wild-type carriers had not been reached for either treatment group. Furthermore, there was no statistical differences between nivolumab plus ipilimumab and ipilimumab on the effect of overall survival (P = 0.262).[7] Similar patterns were reported for all randomized patients. Notably, overall survival was exploratory and these results are most likely confounded, and thus, should be interpreted with caution.

Quality of Life

Patient related outcomes (PROs) were exploratory in the CheckMate 067 and the CheckMate 069 trials. The European Organization for Research and Treatment of Cancer core quality of life questionnaire (EORTC QLQ-C30) and the EuroQOL five dimensions questionnaire (EQ-5D) were used in both trials. The EORTC-QLQ-C30 measures nine multi-item scales, which includes: five functional scales (physical, role, cognitive, emotional, and social); three symptom scales (fatigue, pain, and nausea and vomiting); and a global health and quality-of-life scale. A lower score on the EORTC QLQ-C30 over time indicates better performance. In addition, the EQ-5D provides a standardized measure of health status for five dimensions of health. It also provides an assessment on a visual analog scale (VAS), which measures patients' health status using a vertical VAS scale that ranges from "Best imaginable health state" to "Worst imaginable health state".

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PROs were assessed at baseline and every six weeks.[3] For the final analysis, the PROs using 67 weeks follow-up period for all randomized patients was presented.[56,66]

The baseline completion rate of the EORTC QLQ-C30 for on-treatment patients was 89.9% for the nivolumab arm, 92.4% for the nivolumab plus ipilimumab arm and 88.6% for the ipilimumab arm.[56,66] It remained stable throughout the trial. Overall, there were no clinically meaningful differences in the EORTC QLQ-C30 global health, functional or symptom scales for patients in the

nivolumab, nivolumab plus ipilimumab and ipilimumab treatment groups using a minimally important difference (MID) of ≥10 points. Similar baseline completion rates were reported for EQ-5D (nivolumab with ipilimumab: 92.4% and ipilimumab: 88.3%). Likewise, there were no clinically meaningful differences using the EQ-5D instrument (MID ≥ 0.08) or the EQ-5D VAS instrument (MID ≥ 7 points).[56,66] However, at Week 67, fewer than 16 patients completed a PRO assessment in each arm.

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PROs were assessed at baseline and every six weeks for the first six months,[8] and a minimum of 25 weeks follow-up was reported.[58]

The adjusted baseline completion rate for the EORTC QLQ-C30 instrument was 65.3% in the nivolumab plus ipilimumab arm and 78.7% in the ipilimumab arm.[58] There was a reduction in the completion rate at week 13 for patients randomized to nivolumab plus ipilimumab arm as compared to ipilimumab arm (48.4% vs 75%). The Manufacturer noted that this change most likely coincides with patients switching from nivolumab plus ipilimumab to the nivolumab maintenance phase.[58] It was also reported that HRQoL worsened at Week 7 but improved and remained stable over time after Week 13 (to Week 25) for both the nivolumab plus ipilimumab and ipilimumab treatment arms.[58] Similar baseline completion rates (nivolumab with ipilimumab: 64.2% and ipilimumab: 76.6%) and HRQoL effect estimates were reported for the EQ-5D instrument (MID ≥ 0.08) and the EQ-5D VAS instrument (MID ≥ 7 points).

Harm Outcomes

CheckMate 067

Safety outcomes in the CheckMate 067 Trial were evaluated in 937 patients who received at least one dose of the study treatment (nivolumab: 313, nivolumab plus ipilimumab: 313 and ipilimumab: 311).[2] The reported safety data obtained from the 13-Sept-2016 database lock date will be presented in this section.

In the nivolumab plus ipilimumab arm, the median duration of study therapy was 2.83 months (95% CI, 2.40 to 3.91).[4] Patients in this treatment group received a median of four (range: 1.0 to 76.0) doses of nivolumab and a median of four (range: 1.0 to 4.0) doses of ipilimumab.[4] Forty-seven percent of patients received more than four doses of nivolumab and 56.9% received four doses of ipilimumab.[4] On the other hand, in the ipilimumab arm, the median duration of study therapy was 3.02 months (95% CI, 2.56 to 3.71).[4] Patients in this group received a median of four doses (range: 1 to 4) of ipilimumab and 69.5% had more than four doses.[4] In the nivolumab treatment group, the median duration of study therapy was 6.60 months (95% CI, 5.16 to 9.66).[4] Patients received a median of 15.0 (range: 1 - 77) doses of nivolumab and 85.3% received more than four doses.[4]

<u>Deaths</u>

At the time of the database lock, a higher proportion of patients on ipilimumab had died (62.7%) as compared to those on nivolumab (45.0%) or on nivolumab plus ipilimumab (40.6%).[4] The primary reason for death was disease progression in both groups (ipilimumab: 58.2%, nivolumab: 39.3% and nivolumab plus ipilimumab: 34.8%).[4] Furthermore, patients were more likely to die within 100 days of their last dose (ipilimumab: 19.0%, nivolumab: 16.6% and nivolumab plus ipilimumab: 14.7%) than within 30 days of their last dose (ipilimumab: 6.4%, nivolumab: 4.5% and nivolumab plus ipilimumab: 6.7%).[4] One death related to drug toxicity occurred in the nivolumab group (0.3%) while two deaths (0.6%) occurred in the nivolumab plus ipilimumab group and one death (0.3%) occurred in the ipilimumab arm. [4]

Serious Adverse Events

More serious treatment-related adverse events occurred in the nivolumab plus ipilimumab group (48.6%) than in the ipilimumab group (22.5%) or the nivolumab group (9.9%). Similar results were observed for Grade 3 to 4 treatment-related adverse events (combination: 36.7%, ipilimumab: 16.7% and nivolumab: 8.0%).[4]

All Grades and Grade 3 or 4 Adverse Events

There were more treatment-related adverse events in the nivolumab plus ipilimumab group (95.8%) as compared to the nivolumab group (86.3%) and the ipilimumab group (86.2%).[5] The most commonly reported treatment-related adverse events in at least 15% of patients were diarrhea (nivolumab: 21.4%, combination: 45.4% and ipilimumab: 33.8%), fatigue (nivolumab: 35.5%, combination: 37.7% and ipilimumab: 28.6%), pruritus (nivolumab: 21.4%, combination: 35.8% and ipilimumab: 36.3%), rash (nivolumab: 23.0%, combination: 29.1% and ipilimumab: 21.9%) and nausea (nivolumab: 13.1% combination: 28.1% and ipilimumab: 16.4%).[4] In addition, treatment-related Grade 3 to 4 events were higher in patients on nivolumab plus ipilimumab (58.5%) as compared to patients on ipilimumab or nivolumab (27.7% and 20.8%).[5] More treatment-related adverse events that led to a discontinuation occurred in the nivolumab plus ipilimumab arm (39.6%) than in the ipilimumab arm (16.1%) or the nivolumab arm (11.5%).[5] In order to manage treatment-related adverse events, patients in CheckMate 067 were given immune-modulating concomitant medications (IMMs). The Manufacturer provided the following statement: "IMMs, including topical agents, to manage adverse events were used in 47.0% of the patients in the nivolumab group, 83.4% of those in the nivolumab-plus-ipilimumab group, and 55.9% of those in the ipilimumab group, with secondary immunosuppressive agents (e.g., infliximab) used in 0.6%, 6.1%, and 5.1% of the patients, respectively."[69]

Table 13: Treatment-related adverse events in the CheckMate 067 Trial with most frequent treatment-related adverse events that occurred in ≥15% of any grade in any treatment group

Treatment-related adverse event	Nivolumab (N = 313)		Nivolumab and Ipilimumab (N = 313)		Ipilimumab (N = 311)	
	Any grade	Grade 3 to 4	Any grade	Grade 3 to 4	Any grade	Grade 3 to 4
AE*	270 (83.6)	65 (20.8)	300 (95.8)	183 (58.5)	268 (86.2)	86 (27.7)
AE that led to discontinuation*	36 (11.5)	24 (7.7)	124 (39.6)	97 (31.0)	50 (16.1)	44 (14.1)
SAE	31 (9.9)	25 (8.0)	152 (48.6)	115 (36.7)	70 (22.5)	52 (16.7)
Deaths*	1 (0.3)		2 (0.6)		1 (0.3)	
Diarrhea	67 (21.4)	9 (2.9)	142 (45.4)	30 (9.6)	105 (33.8)	18 (5.8)
Fatigue	111 (35.5)	3 (1.0)	118 (37.7)	13 (4.2)	89 (28.6)	3 (1.0)
Pruritus	67 (21.4)	1 (0.3)	112 (35.8)	6 (1.9)	113 (36.3)	1 (0.3)
Rash	72 (23.0)	1 (0.3)	91 (29.1)	10 (3.2)	68 (21.9)	5 (1.6)
Nausea	41 (13.1)	0	88 (28.1)	7 (2.2)	51 (16.4)	2 (0.6)
Pyrexia	21 (6.7)	0	60(19.2)	2 (0.6)	21 (6.8)	1 (0.3)
Decreased appetite	36 (11.5)	0	60 (19.2)	4 (1.3)	41 (13.2)	1 (0.3)
Increase in alanine aminotransferase level	12 (3.8)	3 (1.0)	59 (18.8)	27 (8.6)	12(3.9)	5 (1.6)
Vomiting	22 (7.0)	1 (0.3)	50 (16.0)	8 (2.6)	24 (7.7)	1 (0.3)
Increase in aspartate aminotransferase level	13 (4.2)	3 (1.0)	51 (16.3)	19 (6.1)	12 (3.9)	2 (0.6)

Hypothyroidism	32 (10.2)	0	51 (16.3)	1 (0.3)	14 (4.5)	0

AE = adverse events
Data source: CheckMate 067 CSR[4] and Larkin et al (2017)[5]

Adverse Events of Special Interest

The CGP requested additional information on select adverse events, such as: skin, gastrointestinal, hepatic and endocrine adverse events. The reported results were obtained from the 13-Sept-2016 database lock (Table 14). Patients treated with nivolumab plus ipilimumab were more likely to report skin, gastrointestinal, hepatic and endocrine treatment-related adverse events as compared to those treated with nivolumab or ipilimumab. This was similar for those reporting grade 3 to 4 adverse events.

Table 14: Summary of drug-related select adverse events reported up to 30 days after last dose

	Nivolumab (N = 313)		**Nivolumab + ipilimumab (N = 313)**		**Ipilimumab (N = 311)**	
	Total	Grade 3 or 4	Total	Grade 3 or 4	Total	Grade 3 or 4
Skin	143 (45.7)	7 (2.2)	192 (61.3)	19 (6.1)	172 (55.3)	9 (2.9)
Pruritus	67 (21.4)	1 (0.3)	112 (35.8)	6 (1.9)	113 (36.3)	1 (0.3)
Rash	72 (23.0)	1 (0.3)	91 (29.1)	10 (3.2)	68 (21.9)	5 (1.6)
Rash maculo-papular	14 (4.5)	2 (0.6)	38 (12.1)	6 (1.9)	38 (12.1)	1 (0.3)
Vitiligo	28 (8.9)	1 (0.3)	27 (8.6)	0	16 (5.1)	0
Gastrointestinal	70 (22.4)	11 (3.5)	150 (47.9)	48 (15.3)	117 (37.6)	36 (11.6)
Diarrhea	67 (21.4)	9 (2.9)	142 (45.4)	30 (9.6)	105 (33.8)	18 (5.8)
Colitis	7 (2.2)	3 (1.0)	40 (12.8)	26 (8.3)	35 (11.3)	24 (7.7)
Hepatic	24 (7.7)	8 (2.6)	102 (32.6)	62 (19.8)	23 (7.4)	5 (1.6)
Aspartate aminotransferase	13 (4.2)	3 (1.0)	51 (16.3)	19 (6.1)	12 (3.9)	2 (0.6)
Increase in alanine aminotransferase	12 (3.8)	3 (1.0)	59 (18.8)	27 (8.6)	12 (3.9)	5 (1.6)
Endocrine	54 (17.3)	5 (1.6)	104 (33.2)	20 (6.4)	36 (11.6)	8 (2.6)
Hypothyroidism	32 (10.2)	0	51 (16.3)	1 (0.3)	14 (4.5)	0
Hyperthyroidism	15 (4.8)	0	34 (10.9)	3 (1.0)	3 (1.0)	0

Data source: CheckMate 067 CSR[4]

CheckMate 069

In CheckMate 069, the safety set consisted of all patients enrolled in the trial who received at least one study dose (N =140). For this review, reported safety effect estimates were obtained from the database lock of 29-Feb-2016.[7]

In the nivolumab plus ipilimumab treatment group, patients received a median of four doses of nivolumab (range: 2 to 15) and four doses of ipilimumab (range: 1 to 4).[7] The Manufacturer reported that 57.4% of patients in the combination arm received four doses of both nivolumab and ipilimumab therapy while 40.4% of patients received more than four doses of nivolumab.[69] Only 40% of patients received nivolumab maintenance.[9] On the other hand, in the ipilimumab arm, the median number of doses was four (range: 3 to 4). In this group, 69.6% of all patients received all four doses of ipilimumab.[69]

Deaths

At the time of the database lock, 37% of patients on the nivolumab plus ipilimumab arm and 48% on the ipilimumab arm had died.[7] The Manufacturer stated that three deaths in combination group were treatment-related while no deaths occurred in the ipilimumab group.

Serious Adverse Events

A higher proportion of patients on nivolumab plus ipilimumab (36%) experienced a treatment-related serious grade 3 to 4 event as compared to those on ipilimumab (9%) (Table 15).[7] The most commonly serious adverse events for patients on nivolumab plus ipilimumab and on ipilimumab alone were colitis (11% and 2%) and diarrhea (5% and 4%), respectively.[7]

All Grades and Grade 3 or 4 Adverse Events

At the time of the 17-Feb-2016 database lock, patients in the nivolumab plus ipilimumab arm were more likely to experience a treatment-related grade 3 to 4 event as compared to those in the ipilimumab arm (54% vs. 20%) (Table 15).[7] Furthermore, treatment-related adverse events that led to discontinuation were higher in the nivolumab plus ipilimumab group as compared to the ipilimumab group (30% vs. 9%).[7]

In order to manage treatment-related adverse events in CheckMate 069, patients on nivolumab plus ipilimumab were treated with IMMs more often than those on ipilimumab (89.4% vs. 54.3%).[69] The Manufacturer provided a statement regarding the use of IMMs to the CGP, more specifically: "… The most commonly used systemic immunosuppressive agents across both treatment groups were glucocorticoids (82% of the patients in the combination group and 50% of the patients in the ipilimumab-monotherapy group). Infliximab was administered to 13% and 9% of the patients in the respective groups for adverse-event management. Hormone-replacement therapy was used to manage endocrine adverse events…".[69]

Table 15: Treatment-related adverse events in the CheckMate 069 Trial at the Feb-2016 database lock.

Treatment-related Adverse Events	**Nivolumab plus Ipilimumab N = 94**		**Ipilimumab N = 46**	
	Any grade	**Grade 3 to 4**	**Any grade**	**Grade 3 to 4**
AE	85 (92.0)	51 (54.0)	43 (93.0)	9 (20.0)
AE that led to discontinuation	35 (37.0)	28 (30.0)	4 (9.0)	4 (9.0)
SAE	NR	34 (36.0)	NR	4 (9.0)
Deaths	3 (3.0)		0 (0.0)	
	Grade 1–2	Grade 3-4	Grade 1–2	Grade 3-4
Diarrhea	33 (35.0)	9(10.0)	11 (24.0)	5(10.9)
Fatigue	29 (31.0)	5(5.2)	22 (48.0)	0 (0.0)
Pruritus	37 (39.0)	1(1.0)	15 (33.0)	0 (0.0)
Rash	36 (38.0)	4(4.0)	14 (30.0)	0 (0.0)
Nausea	19 (20.0)	1(1.0)	8 (17.0)	1(2.0)
Pyrexia	14 (15.0)	3(3.2)	6 (13.0)	0 (0.0)
Decreased appetite	11 (12.0)	0(0.0)	4 (9.0)	0(0.0)
Increase in alanine aminotransferase level	14 (15.0)	10(10.6)	4 (9.0)	0 (0.0)
Vomiting	11 (12.0)	1(1.0)	3 (7.0)	0 (0.0)
Increase in aspartate aminotransferase level	19 (20.0)	7(7)	4 (9.0)	0 (0.0)
Hypothyroidism	16 (17.0)	0(0.0)	6 (13.0)	0(0.0)

Treatment-related Adverse Events	Nivolumab plus Ipilimumab N = 94		Ipilimumab N = 46	
Colitis	5 (5.0)	12(13.0)	2 (4.0)	1(2.0)
Headache	11 (12.0)	2(2.0)	4 (9.0)	0 (0.0)
Dyspnea	7 (7.0)	2(2.0)	0 (0.0)	0 (0.0)

Data source: Hodi et al (2016)[7]

Adverse Events of Special Interest

The CGP requested additional information on select adverse events, such as: skin, immunological and endocrine adverse events. For all of these select adverse events, patients treated with the combination therapy were more likely to report any event or a grade 3 to 4 event as compared to those treated with ipilimumab (Table 16).

Table 16: Summary of drug-related select adverse events reported up to 30 days after last dose

	Nivolumab and Ipilimumab (N = 94)		Ipilimumab (N = 46)	
Adverse Events	Any grade	Grade 3 to 4	Any grade	Grade 3 to 4
Skin AEs	69 (73)	8 (9)	29 (63)	0
Rash	40 (43)	4 (4)	14 (30)	0
Pruritus	38 (40)	1 (1)	15 (33)	0
Gastrointestinal AEs	46 (49)	19 (20)	16 (35)	5 (11)
Diarrhea	42 (45)	9 (10)	16 (35)	5 (11)
Colitis	17 (18)	12 (13)	3 (7)	1 (2)
Hepatic AEs	30 (32)	12 (13)	4 (9)	0
Elevated ALT	24 (26)	10 (11)	4 (9)	0
Elevated AST	26 (28)	7 (7)	4 (9)	0
Endocrine AEs	29 (31)	5 (5)	7 (15)	2 (4)
Hypothyroidism	16 (17)	0	6 (13)	0
Hypophysitis	12 (13)	2 (2)	3 (7)	2 (4)

Data source: Hodi et al (2016)[7]

7 SUPPLEMENTAL QUESTIONS

7.1 Critical appraisal of the indirect treatment comparison between nivolumab plus ipilimumab and pembrolizumab

Background

The pCODR-conducted literature search only identified two RCTs that assessed the efficacy of nivolumab plus ipilimumab versus ipilimumab in patients with advanced melanoma.[2,6,7] Thus there is a lack of direct evidence comparing nivolumab plus ipilimumab to other PD-L1 inhibitors (i.e. pembrolizumab) or to other targeted therapies (i.e. dabrafenib with trametinib and/or vemurafenib). Given the absence of head-to-head trials, the Manufacturer conducted an indirect treatment comparison (ITC).

Other ITC comparisons have been conducted to compare nivolumab plus ipilimumab to other therapeutic agents. The Manufacturer provided an ITC for NICE[61] and PBAC.[62]

The objective of this section is to summarize and critically appraise the submitted ITC that provides evidence for the efficacy of nivolumab plus ipilimumab versus active therapies in treatment-naïve adult patients with advanced (unresectable or metastatic) melanoma.

Review of manufacturer's ITC

Objectives of manufacturer's ITC

The objectives of the Manufacturers' ITC were to compare nivolumab plus ipilimumab as a first-line treatment in patients with unresectable or metastatic melanoma to the following therapies:

- pembrolizumab 2 mg/kg q3w; and
- dabrafenib with trametinib and/or vemurafenib in *BRAF* mutation-positive carriers.

Study Eligibility and Selection Process

The Manufacturer conducted a systematic review to identify eligible studies (criteria in Table 17) for the ITC.[73]

Table 17: Population, interventions, and study design criteria for inclusion of studies[73]

Criteria	Description
Population	Adult patients with previously untreated unresectable stage III or IV melanoma
Interventions	The following treatments as monotherapy or as combination therapy were considered relevant competing interventions of interest: • Nivolumab • Ipilimumab • Pembrolizumab • Vemurafenib • Dabrafenib

Criteria	Description
	• Trametinib • Cobimetinib • Dacarbazine (DTIC) • Temozolomide • Fotemustine
Primary outcomes of interest	Each relevant study reported at least one of the following outcomes: • Progression-free survival (PFS) • Overall survival (OS)
Study design	Randomized controlled trials

The Manufacturer stated that they searched the following databases for their systematic review: MEDLINE and MEDLINE in Process (OVID SP), Embase (OVID SP) and Cochrane Central Register of Controlled Trials (CENTRAL). In addition, the Manufacturer also searched conference abstracts, including the American Society of Clinical Oncology (ASCO) annual meeting, European Society for Medical Oncology (ESMO) annual congress, Society for Melanoma Research (SMR) international congress, International Society for Pharmacoeconomics and Outcomes Research (ISPOR) annual international meeting and annual European congress and Society for Immunotherapy of Cancer (SITC) annual meeting. This search was originally performed on October 2014 and it has been periodically updated. The most recent updated was on June 2016.[73]

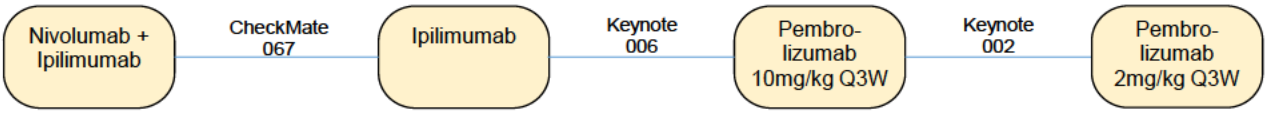
It was stated that two reviewers worked independently to screen titles and abstracts, as well as full text articles. If any discrepancies occurred, the investigators used a third party to provide consensus. Furthermore, if multiple publications were identified for a single trial then publications that provided the most recent data or relevant information were included.[73] However, it is unclear whether the following analyses were performed: screening calibration exercises, duplicate data extraction and risk of bias assessment for included studies.

Indirect treatment comparison methods

To determine whether an ITC was appropriate, the Manufacturer performed several steps. First, the Manufacturer identified common comparators across different trials. Second, they visually inspected the PFS and overall survival curves to verify the assumptions of proportional hazards. Lastly, they assessed the population, interventions, comparisons, outcomes and study design of the included trials to determine if they were comparable with regards to treatment-effect modifiers.

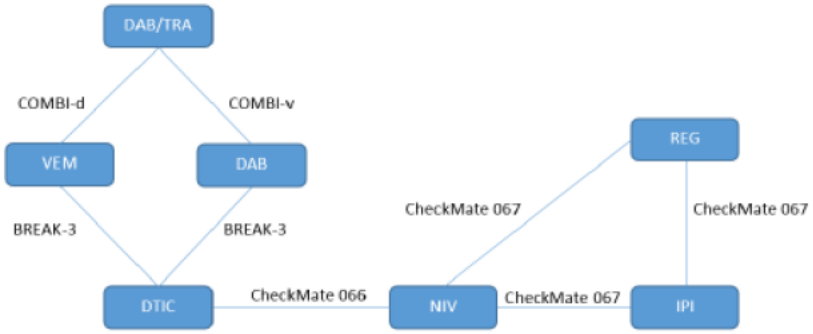
The Manufacturer reported that if the selected trials satisfied the assumptions of comparability, whereby the relative effects of a treatment should be the same in all trials included in the ITC, then they would conduct an ITC using the Bucher Method. Figure 2 represents the ITC. However, the Manufacturer did not report if they used any statistical methods to compare survival curves across trials, if they used a fixed or random effects model, if they tried to minimize bias of potential effect modifiers or if they attempted to assess heterogeneity within their final estimates.

Figure 2a. Network of Evidence Used for the Regimen and Pembrolizumab[73]



Abbreviations: mg/kg = milligrams per kilogram; Q3W = every three weeks

Figure 2b. Network diagram of trials relevant to indirect treatment comparison of targeted therapies[73]



Abbreviations: DAB = dabrafenib; DTIC = dacarbazine; DAB/TRA = dabrafanib + trametinib; IPI = ipilimumab; NIV = nivolumab monotherapy; REG = regimen; VEM = vemurafenib,

Results

Included studies

The systematic review identified a total of 464 citations. Among these articles, 361 articles were included for title and abstract screening and the Manufacturer performed full-text screening of 34 articles.[73] From the full-text screening, six publications were excluded because they did not include the intervention of interest, eight were excluded for a lack of appropriate comparators, one was excluded for outcomes, six were excluded for study design, and four were excluded for other reasons. In total, 12 publications were included, of which nine were published articles and three were conference abstracts.

To conduct the ITC between nivolumab plus ipilimumab and pembrolizumab 2 mg/kg q3w, the Manufacturer identified the following trials: CheckMate 067,[2,57] KEYNOTE 002[48,49] and KEYNOTE 006.[42,74] For the ITC between nivolumab plus ipilimumab and other targeted therapies, the following trials were selected: COMBI-v,[74] COMBI-D[37] and the BREAK-3.[75] Although the systematic review for the ITC was conducted using reference databases, there was also unpublished data available for the CheckMate 067 Trial.[4] The Manufacturer provided the following statement to explain why the most recent results were not used to inform the ITC: "The KM curves for overall survival (OS) and extrapolations from the latest data cut of CheckMate 067 (September 2016) were compared to the data cut from November 2015, which was used to inform the economic model. As shown in Figure 5, the KM curves from the 2016 data cut are the same as the curves from the November 2015 data cut."[68]

Based on the study eligibility criteria for the systematic review conducted by the Manufacturer, there may be a discrepancy between inclusion and exclusion criteria. One such example is the exclusion of CheckMate 069, which was a RCT that assessed the effect of nivolumab plus ipilimumab as compared to ipilimumab in 142 untreated patients with advanced melanoma.[6,7] The Manufacturer stated that they excluded this trial during article screening because "... of

substantial contamination of the OS data for the ipilimumab treatment group due to crossover to nivolumab (62% of patients in the ipilimumab arm had crossed over to receive anti-PD1 treatment)."[68] They also indicated that: "… the PFS HR of nivolumab plus ipilimumab vs ipilimumab is more favorable to [*nivolumab plus ipilimumab*] if the CheckMate 069 trial is considered. The HR for PFS of the Regimen relative to ipilimumab in CheckMate 069 is 0.36 (95% CI 0.22-0.56) while the HR for PFS of [*nivolumab plus ipilimumab*] in CheckMate 067 is 0.43 (95% CI 0.35-0.52). Using the PFS HR estimate from CheckMate 069 in the model as an alternative estimates, slightly improves the ICER".[41]

Trial characteristics

Details of the populations, interventions, comparators and outcomes used in CheckMate 067, KEYNOTE-006 and KEYNOTE-002 are reported in Table 18. The Manufacturer stated that there may be differences in potential effect modifiers, such as the line-of-therapy and brain metastases at baseline.[73] For instance, the patient populations in the KEYNOTE-002 trial had a mixture of first-line and second-line patients while all patients in CheckMate 067 and KEYNOTE-006 were given first line therapy. In order to explore if this effect modifier had an effect, the Manufacturer conducted a subgroup analysis of overall survival stratified by line of treatment in KEYNOTE-006 that did not show any difference between the groups; however, no P-value for difference was provided. Additionally, the Manufacturer also stated that there were differences in baseline brain metastasis across the studies, which varied from 3.5% to 10.1% in CheckMate 067 and KEYNOTE-006, respectively; however, the proportion of patients with brain metastasis at baseline was not reported in KEYNOTE-002. The Manufacturer concluded that they were unable to assess the treatment effect of brain metastasis across the different studies owing to a lack of data.

In addition to the previously mentioned effect modifiers, the CGP also identified other potential treatment effect modifiers, which include age, sex, *BRAF* carrier status, PD-L1 positive and ECOG status. It was noted that there were differences in the distribution of these effect modifiers across the included studies (Table 18).[73] For instance, more than a third of patients in CheckMate 067 and KEYNOTE-006 trials were *BRAF* mutation-positive carriers while greater than 20% carriers in the KEYNOTE-002 trial. Although there were differences across trials in the proportion of patients who were PD-L1 positive, the Manufacturer reported that different definitions of positivity were used in CheckMate-067 and KEYNOTE-006. Finally, the proportion of those who had an ECOG status of 1 at baseline was 26.6% in CheckMate 067, 31.3% in KEYNOTE 006 and 45% in KEYNOTE-002.[73] The CGP asked the Manufacturer to provide more details on their analysis of potential effect modifiers, such as ECOG status, and they stated: "Analysis of subgroups by ECOG status (0/1) in KEYNOTE-006 showed consistency of HRs of OS with the overall population. The HR of OS for pembrolizumab Q3W versus ipilimumab was 0.75 (95% CI, 0.52-1.07) in ECOG 0 and 0.60 (95% CI, 0.39-0.94) in ECOG 1, while in the overall population the HR of OS was 0.69 (95% CI, 0.52-0.90)."[68]

Table 18. PICOS results comparing CheckMate 067, KEYNOTE 006 and KEYNOTE 002[73]

PICOS Factor	Parameter	CheckMate-067 Larkin et al. 2015[2] Wolchok et al. 2016, ASCO (18-month)[57]		KEYNOTE-006 Robert et .al 2015[74] Schachter et al. 2016, ASCO[42]		KEYNOTE-002 Ribas et al. 2015[48] Hamid et al. 2016 ESMO[49]	
		Nivolumab + ipilimumab	Ipilimumab	Pembrolizumab 10mg Q3W	Ipilimumab	Pemborlizumab 10mg Q3W	Pembrolizumab 2mg Q3W
Population	Population	Previously untreated patients with unresectable stage III or IV melanoma		Patients with advanced melanoma		Confirmed progressive disease within 24 weeks after two or more ipilimumab doses and, if *BRAF*V600 mutant-positive, previous treatment with a *BRAF* or MEK inhibitor or both	
	% *BRAF* mutation-positive	32.2%	30.8%	35.0%	38.5%	22%	24%
	Median (range)	Mean:59 (18-88)	Mean: 61 (18-89)	63 (22-89)	62 (18-88)	60 (27-89)	62 (15-87)
	% Male	65.6%	64.1%	62.8%	58.3%	60%	58%
	% Brain metastasis	3.5%	4.8%	9.7%	10.1%	NR	NR
	% ECOG=1	26.4%	28.9%	31.8%	32.4%	46%	44%
	% PD-L1 positive [a]	21.7%	23.8%	79.8%	80.9%	NR	NR
Interventions and Comparators		Nivolumab 1mg/kg +ipilimumab 3mg/kg Q3W for 4 doses then nivolumab mg/kg Q2W	Nivolumab: nivolumab 3 mg/kg Q2W + matched placebo Ipilimumab: ipilimumab 3mg/kg Q3W for 4 doses + matched placebo	Pembrolizumab 10mg/kg Q3W (24 month)	Pembrolizumab: Pembrolizumab 2mg/kg Q2W (24 month) Ipilimumab: 4 doses of ipilimumab 3mg/kg Q2W	Pembrolizumab 10mg Q3W	Pembrolizumab 2mg Q3W
Outcomes	Median PFS	11.5 (8.9-16.7)	2.9 (2.8-3.4)	4.1	2.8	5.6 (4.2-7.7)	4.2 (3.1-6.2)
	ORR, % (95% CI)	57.5 (52.0-63.2)	19 (14.9-23.8)	36.1	13.3	25	21
	Median DOR, months (95% CI)	NR (20.5-NR)	14.4 (8.4 - NR)	NA	NA	NR (36 weeks - NR)	NR (25 weeks - NR)
	Median OS	NR	NR	NR	16.0	14.7*	13.4*
Study design	Sample size	314	315	277	278	181	180
	Design	RCT, phase III		RCT, phase III		RCT, phase II	

Abbreviations: NA = Not available

PICOS Factor	Parameter	CheckMate-067 Larkin et al. 2015[2] Wolchok et al. 2016, ASCO (18-month)[57]		KEYNOTE-006 Robert et .al 2015[74] Schachter et al. 2016, ASCO[42]		KEYNOTE-002 Ribas et al. 2015[48] Hamid et al. 2016 ESMO[49]	
		Nivolumab + ipilimumab	Ipilimumab	Pembrolizumab 10mg Q3W	Ipilimumab	Pemborlizumab 10mg Q3W	Pembrolizumab 2mg Q3W
A: Proportions of patients that are PD-L1 positive are reported in both trials, however different definitions of positivity used in CheckMate-067 and KEYNOTE-006. In CheckMate-067, positivity is defined as membranous PD-L1 staining in at least 5% of tumour cells, while in KEYNOTE-006 it is in at least 1% of tumour cells. Moreover, different assays were used.							

Indirect Treatment Comparison

Since the Manufacturer stated that the proportional hazards were not violated for PFS and overall survival after visual inspection, the Manufacturer performed a simple chained indirect comparison of nivolumab plus ipilimumab to pembrolizumab 2 mg/kg q3w using the Bucher method.[73,76] Here, ipilimumab acted as a common comparator for the CheckMate-067 and the KEYNOTE-006 Trials and the pembrolizumab 10mg/kg Q3W dose was used to link pembrolizumab 2mg/kg Q3W to ipilimumab. Estimates from CheckMate 067 were taken from the Nov-2015 database lock. The direct estimates of PFS and overall survival that were obtained from CheckMate 067, KEYNOTE-006 and KEYNOTE-002 are presented in Table 19.

Table 19: The direct effect estimates of PFS and overall survival from the CheckMate 067, KEYNOTE-006 and KEYNOTE-002 trials[73]

Outcomes	Study	Comparison	HR	Lower 95% CI	Upper 95% CI
OS	CheckMate 067[57]	Regimen vs Ipilimumab	0.61	0.48	0.77
	KEYNOTE-006[42]	Pembro 10 q3w vs Ipilimumab[b]	0.68	0.53	0.86
	KEYNOTE-002[49]	Pembro 10 q3w vs Pembro 2 q3w	0.87	0.67	1.12
PFS	CheckMate 067[57]	Regimen vs Ipilimumab	0.43	0.35	0.52
	KEYNOTE 006[42]	Pembro 10 q3w vs Ipilimumab[b]	0.61	0.50	0.75
	KEYNOTE 002[48]	Pembro 10 q3w vs Pembro 2 q3w	0.91	0.71	1.16
Abbreviations: **HR** = hazard ratio; **OS** = overall survival; **Pembro** = pembrolizumab; **q3w** = every three weeks; **Regimen** = Nivolumab plus ipilimumab					

Using an ITC, the Manufacturer showed that nivolumab plus ipilimumab was associated with a prolonged PFS as compared to pembrolizumab 2mg Q3W in patients with advanced melanoma (HR: 0.64, 95% CI, 0.44 to 0.93) (Table 20).[68] In contrast, the Manufacturer reported that there was no significant difference between nivolumab plus ipilimumab and pembrolizumab 2mg Q3W on overall survival (HR: 0.78, 95% CI, 0.51 to 1.19).[68] The Manufacturer also noted that KEYNOTE-002 may not have been powered to provide a significant result between the two treatment arms.[73]

Table 20. ITC results using Bucher method[68]

Effect Estimates	Outcome	HR	Lower 95% CI	Upper 95% CI
Nivolumab plus ipilimumab vs.	PFS	0.64	0.44	0.93
	OS	0.78	0.51	1.19

Effect Estimates	Outcome	HR	Lower 95% CI	Upper 95% CI
pembrolizumab 2mg Q3W				

Abbreviations: **HR** = hazard ratio; **PFS** = progression free survival; **OS** = overall survival; **q3w** = every three weeks

Critical Appraisal of the ITC

The quality of the ITC provided by the Submitter was assessed according to the recommendations made by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force on Indirect Treatment Comparisons.[77] Details of the critical appraisal are presented below.

Table 20: Adapted ISPOR Questionnaire to Assess the Credibility of an Indirect Treatment Comparison or Network Meta-Analysis†

ISPOR Questions	Details and Comments‡
1. Is the population relevant?	**Yes, in part.** The indication for this review was to assess the efficacy and safety of nivolumab, in combination with ipilimumab, in treatment-naïve adult patients with advanced (unresectable or metastatic) melanoma. The study population in CheckMate 067 consisted of untreated patients with unresectable stage III or IV melanoma. KEYNOTE-006 used a similar study population; however, patients enrolled in KEYNOTE-002 had confirmed progressive disease within 24 weeks after two or more ipilimumab doses and, if *BRAF*V600 mutant-positive, previous treatment with a *BRAF* or MEK inhibitor or both.
2. Are any critical interventions missing?	**No.** The Manufacturers included all relative interventions for this patient population in the systematic review.
3. Are any relevant outcomes missing?	**Yes.** In the ITC, the Manufacturer included OS and PFS but they did not consider other outcomes, such as overall response rate, safety outcomes and HRQoL.
4. Is the context (e.g., settings and circumstances) applicable to your population?	**Yes.** The settings of the three included trials were similar.
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 ITC.[73] In the summary, the Manufacturer described the information sources they used, their search strategy and their study selection criteria. However, it is unclear whether they performed screening calibration exercises, duplicate data extraction and risk of bias assessment.
6. Do the trials for the interventions of interest form one connected network of randomized controlled trials?	**Yes.** The Manufacturer used a simple chained indirect comparison with no closed loops.
7. Is it apparent that poor quality studies were included thereby leading to bias?	**Unclear.** The Manufacturer did not report if they assessed the quality of the included studies. In addition, they did not provide any information on the trial characteristics, such as method of randomization, treatment allocation concealment, blinding of outcome assessor and dropout rates.
8. Is it likely that bias was induced by selective reporting of outcomes in the studies?	**Unclear.** It is difficult to assess because it is unclear whether the Manufacturer assessed for selected outcomes.
9. Are there systematic differences in treatment effect modifiers (i.e. baseline patient or study characteristics that impact the treatment effects) across the	**Yes.** The Manufacturer provided a qualitative assessment of heterogeneity (Table 18); however, the Methods team felt that performing a subgroup analysis and a test for difference would have been more informative.

ISPOR Questions	Details and Comments‡
different treatment comparisons in the network?	The pCODR CGP also identified other potential effect modifiers, which include: *BRAF* mutation carrier status, brain metastasis, ECOG status, PD-L1 status and line-of-therapy. Among these potential modifiers, the Manufacturer only assessed the effect of line-of-therapy and brain metastasis at baseline. The Manufacturer also noted that the definition of PD-L1 positive status differed across the trials. Regardless, there was still an imbalances in the distribution of these effect modifiers across the studies.
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 the fact that patients in CheckMate-067 were untreated and that patients in KEYNOTE-002 were a mixture of untreated and previously treated. To address this potential bias, the Manufacturer stated that a subgroup analysis from KEYNOTE-002 suggested that prior treatment was not a treatment effect modifier. In addition, they were unable to assess the potential effect of brain metastases at baseline because it was not measured in KEYNOTE-002. The CGP also requested the Manufacturer assess the effect of ECOG status across the different trials. The Manufacturer reported that the HR of OS for pembrolizumab Q3W versus ipilimumab was 0.75 (95% CI, 0.52-1.07) in ECOG 0 and 0.60 (95% CI, 0.39-0.94) in ECOG 1, while in the overall population the HR of OS was 0.69 (95% CI, 0.52-0.90).
11. Were statistical methods used that preserve within-study randomization? (No naïve comparisons)	**Yes.** The Manufacturer used the Bucher Method.[76]
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?	**Not applicable.** There was no closed loop.
13. In the presence of consistency between direct and indirect comparisons, were both direct and indirect evidence included in the network meta-analysis?	**Not applicable.** There was no closed loop.
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?	**No.** According to the Methods Team, there appeared to be imbalances in the distribution of treatment effect modifiers across the different trials. It is unclear whether the Manufacturer attempted to minimize this bias.
15. Was a valid rationale provided for the use of random effects or fixed effect models?	**Unclear.** The Manufacturer did not indicate if they used a fixed or random effects model.
16. If a random effects model was used, were assumptions about heterogeneity explored or discussed?	**Unclear.**
17. If there are indications of heterogeneity, were subgroup analyses or meta-regression analysis with pre-specified covariates performed?	**Unclear.** Subgroup analysis or meta-regression analysis were not performed; however, the Methods Team does recognize that assessment of heterogeneity may have been difficult due to a limited number of studies included in the ITC.
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 Figure 2.
19. Are the individual study results reported?	**Yes.** The submitter provided the baseline characteristics of the trials used in the ITC as well as the effect estimates of PFS and overall survival.

ISPOR Questions	Details and Comments‡
20. Are results of direct comparisons reported separately from results of the indirect comparisons or network meta-analysis?	**Yes.** The Manufacturer has provided the direct comparisons of OS and PFS for CheckMate 067, KEYNOTE-006 and KEYNOTE-002.
21. Are all pairwise contrasts between interventions as obtained with the network meta-analysis reported along with measures of uncertainty?	**Yes.** The manufacturer provided the hazard ratio and 95% CI of PFS and overall survival that was obtained from the indirect comparison between nivolumab plus ipilimumab and pembrolizumab.
22. Is a ranking of interventions provided given the reported treatment effects and its uncertainty by outcome?	**No.**
23. Is the impact of important patient characteristics on treatment effects reported?	**No.**
24. Are the conclusions fair and balanced?	The ITC Report provided by the Manufacturer did not make any strong conclusions in their report. But the ITC performed by the Manufacturer showed that nivolumab plus ipilimumab was associated with a protective effect on PFS (HR: 0.78, 95% CI, 0.51 to 1.19) as compared to pembrolizumab while the effect estimate was attenuated for overall survival. However, these claims were weakened due to differences in patient inclusion criteria across the different trials and potential effect modifiers. Furthermore, the Manufacturer did not include any other patient important outcomes in their indirect comparison, and therefore, it is difficult to determine the overall benefit of this drug as compared to pembrolizumab.
25. Were there any potential conflicts of interest?	**Not reported.**
26. If yes, were steps taken to address these?	**Not applicable.**

HRQoL = health-related quality of life; ISPOR = International Society For Pharmacoeconomics and Outcomes Research; ITC = indirect treatment comparison; ORR = objective response rate; PFS = progression-free survival.
† Adapted from Jansen et al[77]
‡Bolded comments are considered a weakness of the ITC.

Conclusion

The Manufacturer submitted an ITC that compared nivolumab plus ipilimumab to pembrolizumab 2 mg Q3w in patients with advanced melanoma. The Manufacturer also sought to compare nivolumab plus ipilimumab to other targeted therapies in *BRAF* mutation positive carriers but they were unable to do so. The results of the ITC indicated that treatment with nivolumab plus ipilimumab was associated with a statistically significant beneficial effect on PFS (HR: 0.64, 95% CI, 0.44 to 0.93) as compared to pembrolizumab 2 mg Q3w. However, the results for overall survival were not statistically significant (HR: 0.78, 95% CI, 0.51 to 1.19). Furthermore, the Manufacturer was unable to assess the effect of nivolumab plus ipilimumab as compared to other relevant targeted therapies, such as dabrafenib plus trametinib and vemurafenib, because the proportional hazard assumptions were violated.

The overall conclusions of the ITC were limited because of substantial heterogeneity in the studies and patient characteristics among the included studies. Given these limitations, the comparative efficacy of nivolumab plus ipilimumab and pembrolizumab is uncertain. Additionally, the effect of nivolumab plus ipilimumab compared to other targeted agents in *BRAF* mutation-positive carriers is unknown.

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 the combination of nivolumab plus ipilimumab for 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. The manufacturer, as the primary data owner, did not agree to the disclosure of some clinical information which was provided to pERC for their deliberations, and this information has been redacted in this publicly posted Guidance Report.

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

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

APPENDIX A: LITERATURE SEARCH STRATEGY

See Appendix B for more details on literature search methods.

1. Literature search via OVID platform

Database(s): **EBM Reviews - Cochrane Central Register of Controlled Trials** November 2016, **Embase** 1974 to 2016 December 07, **Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)** 1946 to Present

Search Strategy:

#	Searches	Results
1	(Opdivo* or nivolumab* or 946414-94-4 or MDX 1106 or MDX1106 or BMS936558 or BMS 936558 or ONO4538 or ONO 4538 or 31YO63LBSN).ti,ab,ot,kf,kw,hw,rn,nm.	4020
2	(Yervoy* or ipilimumab* or strentarga* or Winglore* or 477202-00-9 or anti-CTLA4 or anti-CTLA-4 or MDX-CTLA 4 or MDX-CTLA4 or MDXCTLA-4 or MDXCTLA4 or MDX-010 or MDX010 or MDX101 or MDX 101 or BMS734016 or BMS 734016 or 6T8C155666).ti,ab,ot,kf,kw,hw,rn,nm.	10178
3	exp Melanoma/ or (melanoma* or melanocarcinoma* or melanomalignoma* or naevocarcinoma* or nevocarcinoma* or pigmentary cancer* or skin cancer*).ti,ab,kf,kw.	307788
4	1 and 2 and 3	1515
5	4 use pmez	229
6	4 use cctr	30
7	*Nivolumab/ or (Opdivo* or nivolumab* or MDX 1106 or MDX1106 or BMS936558 or BMS 936558 or ONO4538 or ONO 4538 or 31YO63LBSN).ti,ab,kw.	2305
8	*Ipilimumab/ or (Yervoy* or ipilimumab* or strentarga* or Winglore* or anti-CTLA4 or anti-CTLA-4 or MDX-CTLA 4 or MDX-CTLA4 or MDXCTLA-4 or MDXCTLA4 or MDX-010 or MDX010 or MDX101 or MDX 101 or BMS734016 or BMS 734016 or 6T8C155666).ti,ab,kw.	6676
9	exp Melanoma/ or (melanoma* or melanocarcinoma* or melanomalignoma* or naevocarcinoma* or nevocarcinoma* or pigmentary cancer* or skin cancer*).ti,ab,kw.	307654

10	7 and 8 and 9	714
11	10 use oemezd	493
12	11 and conference abstract.pt.	193
13	limit 12 to english language	193
14	limit 13 to yr="2011 -Current"	192
15	11 not 12	300
16	5 or 15	530
17	(Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial).pt.	1051374
18	Randomized Controlled Trial/	936764
19	exp Randomized Controlled Trials as Topic/	254680
20	"Randomized Controlled Trial (topic)"/	126315
21	Controlled Clinical Trial/	552727
22	exp Controlled Clinical Trials as Topic/	266189
23	"Controlled Clinical Trial (topic)"/	10615
24	Randomization/	199424
25	Random Allocation/	195558
26	Double-Blind Method/	379839
27	Double Blind Procedure/	138710
28	Double-Blind Studies/	245830

29	Single-Blind Method/	66320
30	Single Blind Procedure/	27839
31	Single-Blind Studies/	67770
32	Placebos/	326765
33	Placebo/	328311
34	Control Groups/	265775
35	Control Group/	265679
36	(random* or sham or placebo*).ti,ab,hw,kf,kw.	3468797
37	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.	686863
38	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.	2069
39	(control* adj3 (study or studies or trial*)).ti,ab,kf,kw.	1251310
40	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf,kw.	83723
41	allocated.ti,ab,hw.	146423
42	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf,kw.	88527
43	or/17-42	4476856
44	16 and 43	130
45	(Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or Clinical Study).pt.	1054051
46	(Clinical Trial or Clinical Trial, Phase II or Clinical Trial, Phase III or Clinical Trial, Phase IV).pt.	848585
47	Multicenter Study.pt.	305078

48	Randomized Controlled Trial/	936764
49	exp Randomized Controlled Trials as Topic/	254680
50	"Randomized Controlled Trial (topic)"/	126315
51	Controlled Clinical Trial/	552727
52	exp Controlled Clinical Trials as Topic/	266189
53	"Controlled Clinical Trial (topic)"/	10615
54	Clinical Studies as Topic/	259851
55	Clinical Trial/ or Phase 2 Clinical Trial/ or Phase 3 Clinical Trial/ or Phase 4 Clinical Trial/	1585029
56	Clinical Trials as Topic/ or Clinical Trials, Phase II as Topic/ or Clinical Trials, Phase III as Topic/ or Clinical Trials, Phase IV as Topic/	353294
57	"Clinical Trial (topic)"/ or "Phase 2 Clinical Trial (topic)"/ or "Phase 3 Clinical Trial (topic)"/ or "Phase 4 Clinical Trial (topic)"/	157591
58	Multicenter Study/ or Multicenter Study as Topic/ or "Multicenter Study (topic)"/	415243
59	Randomization/	199424
60	Random Allocation/	195558
61	Double-Blind Method/	379839
62	Double Blind Procedure/	138710
63	Double-Blind Studies/	245830
64	Single-Blind Method/	66320
65	Single Blind Procedure/	27839

66	Single-Blind Studies/	67770
67	Placebos/	326765
68	Placebo/	328311
69	Control Groups/	265775
70	Control Group/	265679
71	Cross-Over Studies/ or Crossover Procedure/	126742
72	(random* or sham or placebo*).ti,ab,hw,kf,kw.	3468797
73	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.	686863
74	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.	2069
75	(control* adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.	7186668
76	(clinical adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.	5430015
77	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf,kw.	83723
78	(phase adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.	385231
79	((crossover or cross-over) adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.	162121
80	((multicent* or multi-cent*) adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.	580913
81	allocated.ti,ab,hw.	146423
82	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf,kw.	88527
83	trial.ti,kf,kw.	669126
84	or/45-83	11990194

85	exp animals/	45352041
86	exp animal experimentation/	2076096
87	exp models animal/	1610850
88	exp animal experiment/	2076096
89	nonhuman/	5012150
90	exp vertebrate/	44101109
91	animal.po.	0
92	or/85-91	46770582
93	exp humans/	36206729
94	exp human experiment/	396151
95	human.po.	0
96	or/93-95	36208267
97	92 not 96	10563315
98	84 not 97	9770286
99	14 and 98	149
100	44 or 6	161
101	remove duplicates from 100	125
102	limit 101 to english language	120
103	102 or 99	269

2. **Literature search via PubMed**
   A limited PubMed search was performed to capture records not found in MEDLINE.

Search	Query	Items found
#7	Search **#6 AND publisher[sb]**	22
#6	Search **#5 AND** Filters: **English**	208
#5	Search **#2 AND #3 AND #4**	225
#4	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]**	121758
#3	Search **Ipilimumab[supplementary concept] OR ipilimumab*[tiab] OR Yervoy*[tiab] OR Winglore*[tiab] OR 477202-00-9[rn] OR anti-CTLA4[tiab] OR anti-CTLA-4[tiab] OR MDX-CTLA 4[tiab] OR MDX-CTLA4[tiab] OR MDXCTLA-4[tiab] OR MDXCTLA4[tiab] OR MDX-010[tiab] OR MDX010[tiab] OR MDX101[tiab] OR MDX 101[tiab] OR BMS734016[tiab] OR BMS 734016[tiab]**	2214
#2	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]**	839

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: nivolumab/ipilimumab, melanoma

Select international agencies including:

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

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

Search: nivolumab/ipilimumab, melanoma

Conference abstracts:

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

Search: nivolumab/ipilimumab, 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 (1946-2016 December 07) with Epub ahead of print, in-process records & daily updates via Ovid; Embase (1974-2016 December 7) via Ovid; The Cochrane Central Register of Controlled Trials (November 2016) 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, Yervoy/ipilimumab and melanoma.

Methodological filters were applied to limit retrieval to randomized controlled trials and controlled clinical trials. Where possible, retrieval was limited to the human population. The search was also limited to English-language documents, but not limited by publication year.

The search is considered up to date as of September 7, 2017.

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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