CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Pembrolizumab (Keytruda) for Melanoma Adjuvant Therapy

August 1, 2019

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LIST OF ABBREVIATIONS

AEs	Adverse events
AJCC	American Joint Committee on Cancer
BSC	Best supportive care
CGP	Clinical Guidance Panel
CI	Confidence intervals
CrIs	Credible intervals
DCR	Disease control rate
DIC	Deviance information criterion
DMFS	Distant metastases-free survival
DOR	Duration of response
EMA	European Medicines Agency
DRESS	Drug reaction with eosinophilia and systemic symptoms
ECOG	Eastern Cooperative Oncology Group
EMBASE	Excerpta Medica database
EORTC	European Organization for Research and Treatment of Cancer
EQ-5D-3L	European Quality of Life Five Dimensions Questionnaire
HR	Hazard ratio
HRQoL	Health-related quality of life
IFN α-2b	Interferon alfa-2b
IQR	Interquartile range
ITT	Intention-to-treat
MEDLINE	Medical Literature Analysis and Retrieval System Online
MID	Minimally important difference
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NR	Not reached
PD-L1	Programmed death-ligand 1
pCODR	pan-Canadian Oncology Drug Review
PEG-IFN α-2b	Peginterferon alfa-2b
pERC	pCODR Expert Review Committee
OR	Odds ratio
PROs	Patient-reported outcomes
ORR	Objective response rate
OS	Overall survival
PFS	Progression-free survival
PRFS2	Progression or recurrence-free survival 2
QLQ-C30	Quality of Life Questionnaire C30
QoL	Quality of life
Q3W	Every three weeks
RCT	Randomized controlled trial
RFS	Recurrence-free survival
SAE	Serious adverse event
TRAEs	Treatment-related adverse events

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 pembrolizumab as adjuvant treatment 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 pembrolizumab as adjuvant treatment for 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 pembrolizumab as adjuvant treatment for melanoma, a summary of submitted Provincial Advisory Group Input on pembrolizumab as adjuvant treatment for melanoma, and a summary of submitted Registered Clinician Input on pembrolizumab as adjuvant treatment for melanoma, and are provided in Sections 2, 3, 4, and 5 respectively.

1.1 Introduction

The objective of this review is to evaluate the efficacy and safety of pembrolizumab (Keytruda) as adjuvant treatment for patients with stage III melanoma with regional lymph node involvement who have undergone resection; and in the re-treatment of patients upon loco-regional or distant recurrence more than six months following a completed adjuvant course of pembrolizumab.

On April 2, 2019, a Notice of Compliance (NOC) was issued by Health Canada for the following indication: pembrolizumab for the adjuvant treatment of patients with stage III melanoma with lymph node involvement who have undergone complete resection. The requested reimbursement criteria are as follows: pembrolizumab for the adjuvant treatment of stage III melanoma following resection; and for retreatment of patients upon loco-regional or distant recurrence more than six months following a completed adjuvant course of pembrolizumab.

According to the Product Monograph, pembrolizumab (Keytruda) is a selective humanized monoclonal antibody designed to block the interaction between programmed cell death receptor-1 (PD-1) and its ligands, PD-L1 and PD-L2.

The recommended dose of pembrolizumab is a 200 mg fixed dose administered as an intravenous infusion over 30 minutes every three weeks for up to one year or until disease recurrence or unacceptable toxicity.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

The pCODR systematic review included one multicentre, placebo-controlled, double-blind phase III randomized controlled trial (RCT), KEYNOTE-054.[1] The RCT assessed the effect of adjuvant pembrolizumab as compared to placebo in patients with high-risk, resected stage III melanoma. In Part 1 of the trial, a total of 1,019 patients were randomly assigned to receive pembrolizumab at 200 mg every three weeks for 18 doses (Q3W, n = 514) or saline

placebo (n = 505). Patients who had documented disease recurrence in Part 1 were eligible to enter Part 2 of the trial. Here, patients who were randomized to receive pembrolizumab could be rechallenged with pembrolizumab while those randomized to placebo could cross-over and receive pembrolizumab.[2] The results of Part 2 are not expected until 31-Jul-2023.[3] Therefore, the focus of this review will be on Part 1.

Patients were included in the trial if they were at least 18 years of age; had histologically confirmed cutaneous melanoma with metastasis to regional lymph nodes; had either stage IIIA melanoma (i.e. patients with stage N1a melanoma had to have at least one micrometastasis measuring >1 mm in greatest diameter), stage IIIB or IIIC disease with no in-transit metastases as defined by the American Joint Committee on Cancer (AJCC) 2009 classification, 7th edition; and had a complete regional lymphadenectomy within 13 weeks before the start of treatment.[2]

Patients were assessed for recurrence every 12 weeks with computed tomography and/or magnetic resonance imaging for the first two years, then every six months through year five, and then every year thereafter. Withdrawal criteria for Part 1 were disease recurrence, completion of assigned regimen, adverse events (AEs), noncompliance, termination of the study, opinion of the Study Investigator, the patient or the legal representative. Patients who had documented disease recurrence in Part 1 of the trial were unblinded and could either continue receiving pembrolizumab or crossover from placebo and receive pembrolizumab in Part 2 of the trial.

The majority of patients enrolled in the trial were male (61.6%), stage IIIB (45.8%) and had positive programmed death-ligand 1 (PD-L1) expression (83.8%).[1]

Efficacy

The primary endpoints in the KEYNOTE-054 trial were recurrence-free survival (RFS) and RFS in a subgroup of patients with PD-L1 positive tumour expression.[2] Secondary outcomes were distant metastases-free survival (DMFS), DMFS in subgroup of patients with PD-L1-positive tumor expression, overall survival (OS) and OS in subgroup of patients with PD-L1-positive tumor expression. Exploratory outcomes were health-related quality of life (HRQoL), progression or recurrence-free survival 2 (PRFS2) and subgroup analyses for RFS. In addition, at the 02-October-2017 data cut-off, OS and DMFS were not available.

The KEYNOTE-054 trial was designed to provide adequate power for the assessment of RFS. The power calculation for RFS was based on a sample size of 900 patients. The trial protocol specified that 409 events (i.e. recurrence or death) were required to have 92% power to detect a hazard ratio (HR) of 0.70 using a one-sided alpha of 0.014.[1]

Initially, the trial was not designed to perform an interim analysis.[2] However, a protocol amendment on 02-October-2017 permitted an interim analysis to be performed when 330 RFS events had occurred.[2] The European Medicines Agency (EMA) requested that the Submitter perform an updated analysis of RFS at 02-May-2018, which represents seven additional months of follow-up after the 02-October-2017 data cut-off.[4]

At the 02-October-2017 data cut off, 135 patients in the pembrolizumab group had first recurrence of disease or died as compared to 216 patients in the placebo group. The median RFS in the pembrolizumab group was not reached (Not Reached [NR], 95% CI: NR to NR) and it was 20.4 months (95% CI: 16.2, NR) in the placebo group.[4] Eggermont et al (2018) reported that treatment with pembrolizumab was associated with a prolonged RFS as compared to placebo (HR: 0.57, 98.4% CI: 0.43 to 0.74; p=0.0001).[1]

At the updated 02-May-2018 data cut-off, 404 events had occurred in the trial, with 30.7% in the pembrolizumab group and 48.7% in the placebo group.[4] Treatment with pembrolizumab was associated with a prolonged RFS as compared to placebo (HR: 0.56, 98.4% CI: 0.44 to 0.72; p<0.0001).[4]

The authors also performed a pre-specified subgroup analysis that assessed the effect of PD-L1 status on RFS.[1] Among patients with a positive PD-L1 tumour, Eggermont et al (2018) reported that treatment with pembrolizumab was associated with a prolonged RFS as compared to placebo (HR: 0.54, 95% CI: 0.42 to 0.69; p<0.001).[1] Similar results were reported for those with a negative PD-L1 tumour (HR: 0.47, 95% CI: 0.26 to 0.85; p=0.01) but there was no significant difference among those with an indeterminate PD-L1 tumour (HR: 0.88, 95% CI: 0.29 to 2.72, p=0.7709).[1] It should be noted that the subgroup analysis was not pre-specified in the PD-L1 negative population.[4]

Quality of Life

HRQoL was measured using the European Organization for Research and Treatment of Cancer (EORTC) QoL Questionnaire C30 (QLQ-C30) and European Quality of Life Five Dimensions Questionnaire (EQ-5D-3L).[2] HRQoL was measured at baseline, every 12 weeks after randomization for two years and then every six months thereafter.[2] The data cut-off for the analysis was 02-October-2017.[5] For the purpose of this review, data up to Week 48 was reported because of decreased compliance rates due to patients crossing over to receive pembrolizumab in Part 2 of the trial.

HRQoL was measured as the change from baseline to week 48 using the EORTC QLQ-C30 global health status/QoL score (defined as a ≥10-point decrease).[5] At the 02-October-2017 data cut-off, the baseline global health status was similar for patients in both the pembrolizumab and placebo groups and remained stable over time. There were no significant differences between the two treatment groups at Week 48 and the minimally important difference (MID) was not reached.[5]

The baseline EQ-5D was similar for patients in both the pembrolizumab and placebo groups and remained stable over time. There were no significant differences between the two treatment groups at Week 48 and the MID was not reached.[5] Similar results were observed for the EQ-5D VAS.[5]

Harms Outcomes

The safety set in the KEYNOTE-054 trial consisted of patients who had received at least one dose of the study treatment. There was a total of 1,011 patients in the safety set, with 509 patients in the pembrolizumab group and 502 patients in the placebo group.[1]

More patients in the pembrolizumab group (13.8 %) had one or more AEs that led to a dose discontinuation as compared to those in the placebo group (3.6%).[4] Moreover, 12.2% of patients in the pembrolizumab group discontinued due to a drug-related AEs relative to 1.6% of patients in the placebo group.[6]

More grade 3 or greater AEs were reported in the pembrolizumab group as compared to the placebo group (31.6% versus 18.5%).[1] More treatment-related AEs (TRAEs) of any grade occurred in the pembrolizumab group as compared to the placebo group (77.8% versus 66.1%).[1] Likewise, more grade 3 or greater TRAEs were reported in the pembrolizumab group as compared to the placebo group (14.7% versus 3.4%).[1]

The National Institute for Health and Care Excellence (NICE) Report stated that 25.1% of patients in the pembrolizumab arm and 16.3% of patients in the placebo arm had a serious

adverse event (SAE).[6] Similarly, more treatment-related SAEs occurred in the pembrolizumab group (13.0%) as compared to the placebo group (1.2%).[6]

More immune-related AEs of any grade occurred in the pembrolizumab group as compared to the placebo group (37.3% vs. 9.0%).[1] More endocrine immune-related AEs occurred in the pembrolizumab group as compared to the placebo group (23.4% vs. 5%).[1] As compared to placebo, more grade 3 or 4 immune-related AEs occurred in the pembrolizumab group (0.6% vs 7.1%).[1]

In the pembrolizumab group, one patient died from treatment-related autoimmune myositis involving respiratory muscles while one death was attributed to a drug reaction with eosinophilia and systemic symptoms (DRESS) from the initiation of vemurafenib and cobimetinib.[6] No deaths occurred in the placebo group.[1]

Table 1: Highlights of the key outcomes in the KEYNOTE-054 trial.

Outcomes	KEYNOTE-054	
Efficacy[1]	**Pembrolizumab (N=514)**	**Placebo (N= 505)**
RFS in all patients, median (95% CI)	NR (NR to NR)	20.4 months (16.2, NR)
HR (98.4% CI)[2]	0.57(0.43 to 0.74)	
p-value	0.0001	
RFS in patients with a positive PD-L1 tumour[3], median (95% CI)	NR (NR to NR)	NR (17.1 to NR)
HR (95%CI)	0.54 (0.42 to 0.69)	
p-value	<0.001	
Harms, n (%)[1]	**Pembrolizumab (N=509)**	**Placebo (N= 502)**
AE (any grade)	475 (93.3)	453 (90.2)
Grade ≥3	161 (31.6)	93 (18.5)
TRAE AE (any grade)	396 (77.8)	332 (66.1)
TRAE AE (Grade ≥3)	75 (14.7)	17 (3.4)
WDAE	70 (13.8)	18 (3.6)

Abbreviations: AE = adverse events, CI = confidence interval; NR = not reached; TRAE = treatment-related adverse events; WDAE = withdraws due to adverse events.

[1]02-October-2017 data cut off
[2]Eggermont et al (2018) reported that treatment with pembrolizumab was associated with a prolonged RFS as compared to placebo in patients with a negative PD-L1 tumour (HR: 0.47, 95% CI: 0.26 to 0.85; p=0.01) but there was no significant difference among those with an indeterminate PD-L1 tumour (HR: 0.88, 95% CI: 0.29 to 2.72, p=0.7709).[1]
[3]It should be noted that the subgroup analysis was not pre-specified in the PD-L1 negative population.[4]

1.2.2 Additional Evidence

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

Patient Advocacy Group Input

Two patient advocacy groups, the Melanoma Network of Canada (MNC) and the Save Your Skin Foundation (SYSF), provided input on pembrolizumab in the adjuvant setting for melanoma patients. For a summary of this input, refer to Section 3.

Provincial Advisory Group (PAG) Input

Input was obtained from all nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified clinical and economic factors that could impact the implementation of pembrolizumab as adjuvant treatment for stage III melanoma. For a summary of this input, refer to Section 4.

Registered Clinician Input

Two inputs from registered clinicians were received by pCODR: one submission on behalf of a single oncologist in Ontario, and a joint submission from clinicians from Cancer Care Ontario capturing the perspectives of four oncologists. In total, input was provided by five oncologists. For a summary of this input, please refer to Section 5.

Summary of Supplemental Questions

- Critical appraisal of the Manufacturer's submitted network meta-analysis (NMA) comparing the efficacy and safety of adjuvant anti-cancer therapies in the treatment of melanoma. See section 7.1 for more information.

Comparison with Other Literature

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

1.2.3 Factors Related to Generalizability of the Evidence

Table 2 addresses the generalizability of the evidence from the KEYNOTE-054 trial;[1] 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 Factors that May Affect Generalizability.

<table>
<tr><th>Domain</th><th>Factor</th><th>Evidence
(KEYNOTE-054 trial)[1]</th><th>Generalizability Question</th><th>CGP Assessment of Generalizability</th></tr>
<tr><td rowspan="2">Population</td><td>Histologic type of disease</td><td>The KEYNOTE-054 trial limited its inclusion criteria to patients with cutaneous melanoma.</td><td>Are the trial results generalizable to other types of melanoma (i.e., mucosal, ocular)?</td><td>Patients with non-cutaneous melanoma subtypes such as mucosal or ocular melanoma were ineligible for the trial. The CGP believes there is no reason to expect pembrolizumab to behave differently in these subtypes than nivolumab, based on data from the Checkmate 238 trial, however, in the absence of evidence, the use of pembrolizumab as adjuvant treatment to surgical resection should be limited to those patients presenting with cutaneous melanoma, which includes acral melanoma.</td></tr>
<tr><td>Stage of disease</td><td>Patients were enrolled in the trial if they had stage IIIA melanoma (patients with stage N1a melanoma had to have at least one micrometastasis measuring >1 mm in greatest diameter) or stage IIIB or IIIC disease with no in-transit metastases using the AJCC 2009 criteria, 7th edition. Although the AJCC has been updated (8th edition), patients who were enrolled in the trial would have been classified as stage III. Thus, the updated AJCC classification does not impact the trial results.

Table 1: Baseline characteristics of patients enrolled in the KEYNOTE-054 trial according to AJCC 7th edition.
<table>
<tr><th>Stage of Disease</th><th>Pembrolizumab
N = 514</th><th>Placebo
N= 505</th></tr>
<tr><td>Stage IIIA</td><td>77 (15.0)</td><td>76 (15.0)</td></tr>
<tr><td>Stage IIIB</td><td>240 (46.7)</td><td>232 (45.9)</td></tr>
</table>
</td><td>Are the trial results also generalizable to patients with completely resected stage IIB/C with T4 lesions (high-risk node negative) and completely resected stage IV disease, since these patients are also offered adjuvant treatment?</td><td>The trial excluded patients with resected stage IV melanoma. Although the CGP does not expect pembrolizumab to behave differently than nivolumab with respect to resected stage IV disease, there currently is no direct evidence upon which to base the use of the pembrolizumab in these patients. Stage IIC patients were also excluded from the trial; the results of ongoing adjuvant clinical trials in these patients are awaited, and they</td></tr>
</table>

<table>
<tr><th>Domain</th><th>Factor</th><th>Evidence
(KEYNOTE-054 trial)[1]</th><th>Generalizability Question</th><th>CGP Assessment of Generalizability</th></tr>
<tr><td></td><td></td><td>
<table>
<tr><td>Stage IIIC with 1-3 positive lymph nodes</td><td>87 (16.9)</td><td>95 (18.8)</td></tr>
<tr><td>Stage IIIC with ≥4 positive lymph nodes</td><td>110 (21.4)</td><td>102 (20.2)</td></tr>
</table>

Table 2: The effect of pembrolizumab as compared to placebo on RFS stratified by stage of disease among patients from the KEYNOTE-054 trial.
<table>
<tr><td>Stage of Disease</td><td>Pembrolizumab N = 514</td><td>Placebo N= 505</td><td>HR (95% CI)</td></tr>
<tr><td>Stage IIIA</td><td>6/77</td><td>15/76</td><td>0.38(0.11-1.31)</td></tr>
<tr><td>Stage IIIB</td><td>62/240</td><td>97/232</td><td>0.58(0.38-0.88)</td></tr>
<tr><td>Stage IIIC</td><td>67/197</td><td>104/197</td><td>0.58(0.38-0.86)</td></tr>
<tr><td colspan="4">P-value for interaction: 0.69</td></tr>
</table>
</td><td></td><td>should be used to inform the use adjuvant pembrolizumab in stage IIC disease.</td></tr>
<tr><td></td><td>Performance Status</td><td>Patients were enrolled in the trial if they had an ECOG status of 0 or 1.

Table 3: Baseline characteristics of patients enrolled in the KEYNOTE-054 trial
<table>
<tr><td>ECOG Status</td><td>Pembrolizumab N = 514</td><td>Placebo N= 505</td></tr>
<tr><td>0</td><td>485 (94.4)</td><td>475 (94.1)</td></tr>
<tr><td>1</td><td>29 (5.6)</td><td>30 (5.9)</td></tr>
<tr><td colspan="3">Data Source: EMA Report[4]</td></tr>
</table>
</td><td>Do the trial results apply to patients with an ECOG status >1?</td><td>In clinical practice both patients and clinicians will want to consider adjuvant pembrolizumab in patients with an EGOG status greater than 1. As the disease has been completely resected it is anticipated that an EGOG status of 2 reflects comorbidities as opposed to a reflection of disease activity. Occasionally a complication of a complete lymphadenectomy may render a patient ECOG 2. The toxicity profile of pembrolizumab is favourable enough to offer it to patients who have comorbidity but are felt to still be suitable candidates for adjuvant treatment of their resected melanoma.</td></tr>
</table>

<table>
<tr><th>Domain</th><th>Factor</th><th>Evidence
(KEYNOTE-054 trial)[1]</th><th>Generalizability Question</th><th>CGP Assessment of Generalizability</th></tr>
<tr><td></td><td>Age</td><td>Patients were enrolled in the trial if they were ≥ 18 years of age.

Table 4: Baseline characteristics of patients enrolled in the KEYNOTE-054 trial
<table>
<tr><th>Age</th><th>Pembrolizumab
N = 514</th><th>Placebo
N= 505</th></tr>
<tr><td>Median (range) — yr</td><td>54 (19-88)</td><td>54 (19-83)</td></tr>
<tr><td><50yr—no.(%)</td><td>193 (37.5)</td><td>186 (36.8)</td></tr>
<tr><td>50 to <65 yr—no. (%)</td><td>196 (38.1)</td><td>193 (38.2)</td></tr>
<tr><td>≥65yr—no.(%)</td><td>125 (24.3)</td><td>126 (25.0)</td></tr>
</table>
Table 5: The effect of pembrolizumab as compared to placebo on RFS stratified by age among patients from the KEYNOTE-054 trial
<table>
<tr><th>Age</th><th>Pembrolizumab
N = 514</th><th>Placebo
N= 505</th><th>HR (95% CI)</th></tr>
<tr><td>18 to <65yr</td><td>96/389</td><td>154/379</td><td>0.57(0.41-0.80)</td></tr>
<tr><td>≥65yr</td><td>39/125</td><td>62/129</td><td>0.55(0.32-0.93)</td></tr>
<tr><td colspan="4">P-value for interaction: 0.86</td></tr>
</table></td><td>Are the results of the trial applicable to younger patients, e.g. pediatric and adolescent patients?</td><td>Melanoma can rarely occur in younger patient populations. There is currently no evidence to suggest that pembrolizumab would not be safe in treating pediatric patients based on early data (KEYNOTE-051 trial) in pediatric advanced melanoma patients.</td></tr>
<tr><td></td><td>Type of lymph node involvement</td><td>Patients were enrolled in the trial if they had a complete regional lymphadenectomy performed within 13 weeks of starting their assigned therapy.

Table 6: Baseline characteristics of patients enrolled in the KEYNOTE-054 trial
<table>
<tr><th>Type of lymph node involvement — no. (%)</th><th>Pembrolizumab
N = 514</th><th>Placebo
N= 505</th></tr>
<tr><td>Microscopic</td><td>187 (36.4)</td><td>161 (31.9)</td></tr>
<tr><td>Macroscopic</td><td>327 (63.6)</td><td>344 (68.1)</td></tr>
</table>
Table 7: The effect of pembrolizumab as compared to placebo on RFS stratified by type of lymph node involvement among patients from the KEYNOTE-054 trial
<table>
<tr><th>Type of lymph node involvement</th><th>Pembrolizumab
N = 514</th><th>Placebo
N= 505</th><th>HR (95% CI)</th></tr>
<tr><td>Microscopic</td><td>35/187</td><td>50/161</td><td>0.56(0.32-0.99)</td></tr>
<tr><td>Macroscopic</td><td>100/327</td><td>166/344</td><td>0.59(0.42-0.81)</td></tr>
<tr><td colspan="4">P-value for interaction: 0.86</td></tr>
</table></td><td>In practice, completion lymphadenectomy may not be considered the standard of care for all the melanoma patients.

Does the type of surgery impact the interpretation of the trial results (efficacy or toxicity) with respect to the target population (e.g., Canadian clinical practice, patients</td><td>Since the adjuvant trials were commenced there has been a change in practice (based on evidence from the MSL-2 trial) where completion lymph node dissection is not a requirement to receive adjuvant therapy to surgery. Patients and clinicians therefore may wish to defer completion lymph node dissection following a positive sentinel lymph node biopsy.

As a consequence of this change, clinicians do not have as much information with respect to true nodal involvement. The KEYNOTE-054 eligibility criteria specified that patients with completely resected stage IIIA disease were required to have lymph</td></tr>
</table>

Domain	Factor	Evidence (KEYNOTE-054 trial)[1]	Generalizability Question	CGP Assessment of Generalizability
			undergoing other surgeries)?	node metastasis measuring >1 mm. However, the CGP was in agreement that they would not want to apply a requirement with respect to degree of involvement in one solitary lymph node. This aligns with Health Canada's Notice of Compliances for adjuvant pembrolizumab, nivolumab and dabrafenib-trametinib, which do not exclude patients with nodal metastases measuring < 1mm. Therefore, the CGP recommends all stage III patients be considered eligible for treatment with adjuvant pembrolizumab.
	Autoimmune disorders	Patients were excluded from the trial if they had an autoimmune disorder.	Does the exclusion of patients with autoimmune disorders limit the interpretation of the trial results with respect to the target population?	Patients that required systemic steroid therapy treatment in the past two years or any other form of immunosuppressive therapy within seven days prior to the first dose of study medications were excluded from the trial. In clinical practice with increasing clinical competence of management of the immune related events, these agents are often presented to patients with a pre-existing immune-related illness with a pro-con discussion of risks and benefits. This is undertaken in close collaboration with the managing consultant of their known autoimmune disease. Therefore, it is expected that clinicians/patients with pre-existing immune mediated

<table>
<tr><th>Domain</th><th>Factor</th><th>Evidence
(KEYNOTE-054 trial)[1]</th><th>Generalizability Question</th><th>CGP Assessment of Generalizability</th></tr>
<tr><td></td><td></td><td></td><td></td><td>illness may consider using pembrolizumab as an adjuvant to surgical treatment.</td></tr>
<tr><td></td><td>Biomarkers</td><td>The effect of PD-L1 expression on treatment efficacy was explored in the trial. Patients were required to provide a tumor sample from melanoma-positive lymph nodes. PD-L1 expression was assessed using immunohistochemistry assay (22C3 antibody) and expression levels were scored on a scale of 0 to 5. PD-L1 positivity was defined as a score of 2 or higher (i.e., staining on >1% of cells).

Table 8: Baseline characteristics of patients enrolled in the KEYNOTE-054 trial
<table>
<tr><td>PD-L1 expression — no. (%)</td><td>Pembrolizumab N = 514</td><td>Placebo N= 505</td></tr>
<tr><td>Positive</td><td>428 (83.3)</td><td>425 (84.2)</td></tr>
<tr><td>Negative</td><td>59 (11.5)</td><td>57 (11.3)</td></tr>
<tr><td>Intermediate</td><td>27 (5.3)</td><td>23 (4.6)</td></tr>
</table>
Table 9: The effect of pembrolizumab as compared to placebo on RFS stratified by PD-L1 expression among patients from the KEYNOTE-054 trial
<table>
<tr><td>PD-L1 expression</td><td>Pembrolizumab N = 514</td><td>Placebo N= 505</td><td>HR (95% CI)</td></tr>
<tr><td>Positive</td><td>102/428</td><td>176/425</td><td>0.54(0.39-0.74)</td></tr>
<tr><td>Negative</td><td>20/59</td><td>27/57</td><td>0.60(0.28-1.28)</td></tr>
<tr><td>Intermediate</td><td>13/27</td><td>13/23</td><td>0.80(0.29-2.19)</td></tr>
<tr><td colspan="4">P-value for interaction: 0.60</td></tr>
</table></td><td>Is the biomarker an effect modifier (i.e., differences in effect based on biomarker status)? Are the results of the trial applicable to all subgroups equally? Is there a substantial group of patients excluded from the trial to whom the results could be generalized?</td><td>In clinical practice PD-L1 is not performed on melanoma specimens; and therefore, degree of PD-L1 positivity would not change clinicians' recommendations with respect to treatment for melanoma.</td></tr>
<tr><td>Intervention</td><td>Administration of intervention</td><td>Pembrolizumab intravenously every 3 weeks for a total of 18 doses (approximately one year) or until disease recurrence or unacceptable toxic effects occurred.</td><td>Are the results of the trial generalizable to a different dose or administration schedule?</td><td>This dose schedule requires less chemotherapy suite chair time in comparison to nivolumab in the Checkmate 238 trial where dosing was weight-based (3 mg per kilogram) every two weeks. Currently there are no data from the adjuvant setting to inform dosing pembrolizumab every six weeks versus three weeks. In Canada, the average</td></tr>
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Domain	Factor	Evidence (KEYNOTE-054 trial)[1]	Generalizability Question	CGP Assessment of Generalizability
				weight of individuals is increasing, therefore, in order to capitalize on weight-based dosing, centres would require infrastructure to cohort patients receiving the drug in order to avoid wastage.
Comparator	Standard of Care	KEYNOTE-054 trial compared pembrolizumab to placebo.	Are the results of the trial applicable given other adjuvant treatment regimens (i.e., IFN) are available in the Canadian setting?	The comparator used in the trial was placebo (observation). The CGP felt this choice of comparator was completely appropriate considering the minimal use of IFN in Canadian clinical practice.

1.2.4 Interpretation

Melanoma is the most commonly diagnosed cancer in individuals between the ages of 20 and 29 years. It often hits patients at the peak of their life with respect to family, career and social interactions and thus is a stress not only to the patient but to their family and care providers. Although treatment options have improved over the years for recurrent and metastatic melanoma and the survival rates at 1, 3, 5, and 10 years have continuously improved with the introduction of CTLA-4 and PD-1 inhibitors, the results are still not ideal with respect to efficacy and/or toxicity. There is therefore a great clinical need to move treatment into the adjuvant setting. Ipilimumab was the first drug to enter the adjuvant setting. Unfortunately, toxicity was prohibitive and Health Canada approval for the indication of adjuvant treatment was not advanced.

The KEYNOTE-054 trial[1] enrolled patients who were 18 years of age or older and had histologically confirmed cutaneous melanoma with metastasis to regional lymph nodes. Ocular and mucosal melanoma patients were excluded from the trial. Eligible patients had to have either stage IIIA (patients with stage NA1 had to have at least 1 micrometastasis measuring >1mm in greatest diameter), IIIB or IIIC melanoma with no in-transit metastases as defined by the AJCC 7th edition. A complete regional lymphadenectomy was required to have been performed within 13 weeks before the start of treatment. Exclusion criteria included an ECOG performance status score >1, autoimmune disease, uncontrolled infections, use of systemic glucocorticoids and previous systemic therapy for melanoma. Patients were randomly assigned in a 1:1 ratio to receive either an intravenous infusion of a standard dose of pembrolizumab 200 mg (n=514) or placebo (n=505) every three weeks for a total of 18 doses, or until disease recurrence, unacceptable toxic effects, a major protocol violation, or withdrawal of consent occurred. The primary endpoint of the study was RFS in the overall ITT population and in the subgroup of patients with PD-L1 positive tumours. Tumour samples from melanoma positive lymph nodes were required to be sent for central pathologic review of PD-L1 expression; and membranous expression of PD-L1 tumour and tumour associated immune cells were considered positive if the immunohistochemistry assay (22C3 antibody) stained >1% of cells. The choice of RFS as a primary endpoint was pragmatic as access to treatment for relapsed patients has improved the survival of patients with metastatic melanoma from months to years. RFS is now recognized as a surrogate for OS in the adjuvant treatment of stage II and III melanoma based on trials evaluating INF and ipilimumab;[7] confirmation of this correlation based on more current trial data (pembrolizumab, nivolumab, dabrafenib-trametinib) is awaited. The secondary end points of the trial included DMFS, OS, safety, and HRQoL.

After a minimum follow-up of 15 months, a RFS benefit was observed in the KEYNOTE-054 trial in patients treated with pembrolizumab compared with placebo; the HR for recurrence or death was 0.57 (98.4% CI, 0.43-0.74; p=0.0001) and the 12-month rate of RFS in resected stage III A-C patients was 75.4% in the pembrolizumab group and 61% in the placebo group. In the subgroup of patients with PD-L1 positive tumours (n=853) the 12-month RFS rate was 77.1% in the pembrolizumab group and 62.6% in the placebo group (HR for recurrence or death was 0.54). The benefit in RFS was seen in patients with both BRAF-mutated and -wildtype disease, and while all subgroup analyses indicated a trend that favoured treatment with pembrolizumab, a clear benefit from treatment was observed in patients with stage IIIB and C disease, patients with PD-L1 positive tumours and patients with ulcerated primary lesions. In terms of safety, the rate of grade 3 or greater toxicities was roughly doubled in pembrolizumab-treated patients (31.6% versus 18.5%), and grade ≥ 3 treatment-related AEs were also higher at 14.7% versus 3.4% respectively. The overall toxicity profile of pembrolizumab observed in the adjuvant setting is similar to that seen in patients with metastatic disease with no new safety signals and is certainly improved compared to published toxicities of ipilimumab. The incidence of diarrhea, one of the most

common side effects, was 19% in the pembrolizumab group for all grades and 8% for grades ≥ 3. There was one treatment-related death in the pembrolizumab group attributed to myositis.

There were 13.8% of patients in the pembrolizumab group who required a dose discontinuation compared to 3.6% in the placebo group;[4] and 12.2% of patients in the pembrolizumab group discontinued due to a drug-related AE relative to 1.6% of patients in the placebo group.[6] There were 55.4% of patients in the pembrolizumab group and 58.6% in the placebo group who completed one year of adjuvant treatment. The most common reason for treatment discontinuation in both groups was disease recurrence (52% and 89% for the pembrolizumab and placebo groups, respectively). Quality of life was measured using the EORTC QLQ-C30 and the EQ-5D-3L instruments and demonstrated that baseline global health status was similar for patients in both the pembrolizumab and placebo groups and remained stable over time. Prior to treatment crossover, no significant differences between the two treatment groups were observed at Week 48 and the MCID was not reached. Similar results were seen for the EQ-5D-3L.

Since crossover from placebo to active treatment was permitted in the trial it will be more difficult to analyze the effect of pembrolizumab on OS, as well as to make cross trial comparisons with the two other adjuvant trials (Checkmate 238 and COMBI-AD). The Submitter provided an unpublished NMA as part of the submission but its usefulness in providing indirect estimates of treatment effect was limited as IFN was the only active comparator included in the analysis.[8] Cross trial comparisons specifically with the Checkmate 238 trial is somewhat difficult as resected stage IV patients with no other evidence of disease were included in that trial but excluded from KEYNOTE-054. In these trials the RFS rates reported at one year for stage IIIB and IIIC patients were 72.2% with pembrolizumab (KEYNOTE-054), 72.3% with nivolumab (Checkmate 238), and 61.6% with ipilimumab (Checkmate 238).

Part 2 of the KEYNOTE-054 trial enrolled patients with documented recurrence to retreatment with pembrolizumab or crossover from placebo to active treatment. Patients originally assigned to the pembrolizumab group who experienced recurrence more than six months after completing one year of adjuvant therapy could be retreated with pembrolizumab. Patients originally assigned to the placebo group could receive pembrolizumab provided they had no evidence of brain metastasis or CNS disease, had an ECOG performance status of 0 to 2 and no evidence of a second occurrence or progression before enrollment in Part 2. Upon recurrence (local, regional or distant) patients could also receive surgery as indicated. Part 2 of the trial is ongoing, and as of the primary analysis data cut-off date (02-October-2017), 109 (21.6%) of the 505 patients initially assigned to placebo have crossed over into Part 2 and received pembrolizumab;[4] and one patient (0.2%) of the 514 patients initially assigned to pembrolizumab has been rechallenged with pembrolizumab.[4] The total number of patients who were eligible for Part 2 of the trial has not been reported.

Prior to the initiation and publication of data from trials evaluating targeted agents and immunotherapies, the only Health Canada approved systemic treatment for use as adjuvant therapy to surgery was IFN. This treatment was not well tolerated, and its benefit was marginal at best. Health Canada has now approved the BRAF MEK inhibitor combinations, nivolumab and pembrolizumab for adjuvant treatment in stage III resected melanoma patients. The introduction of pembrolizumab as adjuvant treatment to surgery for patients with resected melanoma offers a clinically meaningful benefit in RFS and fills a greatly unmet need in clinical practice. This is supported by clinicians as well as the commentary of the patient advocacy groups. A melanoma diagnosis, both in the adjuvant and metastatic setting, conveys great uncertainty to patients and families at the peak of their lives.

The PAG raised a number of points to be considered if pembrolizumab were to be recommended for reimbursement, specifically with respect to generalizability of evidence and treatment sequencing with other adjuvant regimens including BRAF MEK inhibitors dabrafenib and trametinib, and nivolumab. The CGP has addressed these points below.

Stage of disease
The KEYNOTE-054 trial was restricted to patients with stage IIIA to IIIC disease according to the AJCC 7th edition. Therefore, there are no data on the efficacy of pembrolizumab in the setting of stage IV disease, where the disease is resected to no evidence of disease. Although clinicians would not expect pembrolizumab to behave differently than nivolumab in this setting, there is no direct evidence upon which to base the use of the drug in stage IV patients. Stage IIC patients were also not included in the KEYNOTE-054 trial and based on the most recent AJCC 8th edition, data suggest these patients fair less well than stage IIIA. Clinicians are awaiting the results of ongoing adjuvant clinical trials that include these patients to inform on the use of pembrolizumab in stage IIC disease.

Patients with past or current in-transit metastases or satellites were not permitted in the KEYNOTE-054 trial. The presence of microsatellites, satellites or in-transit metastases is categorized based on number of tumour involved regional lymph nodes. It should be noted in the AJCC 8th edition presence of microsatellites, satellites, or in-transit metastases are classified as N1C (no regional lymph nodes), N2C (one clinically occult or clinically detected), or N3C (2 or more clinically occult or clinically detected). The CGP acknowledges there will be clinicians who will want to have a discussion with patients about the pros and cons of adjuvant treatment where there are satellite or in-transit metastases (who may or may not have been resected to no evidence of disease); in these patients, treatment with adjuvant pembrolizumab should be made on a case by case basis.

Degree of metastatic lymph node involvement
The KEYNOTE-054 eligibility criteria specified that patients with completely resected stage IIIA (AJCC 7th edition) disease were required to have lymph node metastasis measuring >1 mm to be enrolled in the trial. There was a lot of discussion among the CGP with respect to a minimum requirement for nodal metastasis. The CGP was in agreement that since only sentinel lymph node biopsy is currently being done in clinical practice (versus completion lymphadenectomy), clinicians do not have as much information with respect to true nodal involvement and therefore would not want to apply a requirement with respect to degree of involvement in one solitary lymph node. This aligns with Health Canada's Notice of Compliances for adjuvant pembrolizumab, nivolumab and dabrafenib-trametinib, which do not exclude patients with nodal metastases measuring < 1mm. Therefore, the CCP feels all stage III patients (A through D, AJCC 8th edition) should be eligible for adjuvant pembrolizumab.

Intention of treatment
Patients registered on KEYNOTE-054 had a completely resected primary melanoma. There is great clinical interest, however, in the role of giving these agents in a neoadjuvant setting in the clinical situation of borderline resectable lymphadenopathy. Neoadjuvant treatment implies that the treatment plan is to resect tumours once they are down staged by systemic therapy. To date there are no data based on phase 3 trials on the use of neoadjuvant pembrolizumab in this clinical scenario. In clinical practice locally advanced melanomas that are not amenable to curative intent due to morbidity of the surgery are treated as advanced disease. Should there be a dramatic response of the primary lesion rendering them surgically resectable then surgery is certainly a treatment option that would be discussed with the patient.

Performance status
Patients enrolled in the KEYNOTE-054 trial were required to have an ECOG performance status 0 to 1, which is certainly reasonable in the adjuvant setting since disease has been completely resected. Few patients in the adjuvant setting will present with an ECOG of 2 based on melanoma status, however, an ECOG of 2 in the adjuvant setting would likely be an indication of either complications from completion lymphadenectomy or due to comorbidities. The CGP felt that if these scenarios were not felt to be the cause of life threating complications in the future or contraindications to treatment then patients with an ECOG of 2 would be suitable for treatment with pembrolizumab.

PD-L1 status as a predictive marker
In KEYNOTE-054, PD-L1 status was tested on lymph node biopsies and positivity was certainly higher in this trial (83.7%) compared to the Checkmate 238 trial of nivolumab (PD-L1 < 5% was 60.7%). Although studies have used different cut-offs, PD-L1 positivity is usually in the range of 30%-40%. That being said, in clinical practice PD-L1 is not performed on melanoma specimens and degree of positivity would not change clinicians' recommendations with respect to treatment for this particular disease site (as it was not predictive of a differential response to therapy).

Dose scheduling
The dose schedule of pembrolizumab in the KEYNOTE-054 trial was 200 mg over 30 minutes every three weeks up to a total of 18 administrations, unacceptable toxicity, or disease recurrence. This schedule requires less chemotherapy suite chair time in comparison to nivolumab (Checkmate trial) where dosing was weight based (3 mg per kilogram) every two weeks. Currently there are no data from the adjuvant setting to inform dosing pembrolizumab every six weeks versus three weeks. In Canada, the average weight of individuals is increasing, therefore, in order to capitalize on weight-based dosing, centres would require infrastructure to cohort patients receiving the drug in order to avoid wastage.

In response to the pERC initial recommendation, clinicians, the Submitter, and PAG provided feedback related to pERC's conclusion that dosing of pembrolizumab could either follow the flat dose used in the KEYNOTE-054 trial or be weight-based (2 mg/kg) up to a cap of 200 mg as used in other patient populations. Clinicians and the Submitter felt the dosing of pembrolizumab should follow the KEYNOTE-054 trial since its use is for curative intent and the efficacy of weight-based dosing with a cap has not been established in the adjuvant setting. PAG commented on the inconsistency between the adjuvant pembrolizumab and nivolumab recommendations regarding dosing; for nivolumab, the recommendation states dosing should follow the clinical trial evidence but for pembrolizumab the recommendation states both flat- and weight-based dosing are reasonable. In reviewing the stakeholder feedback on dosing, the CGP noted that since the efficacy of a flat dose of 200 mg has been established with pembrolizumab in the KEYNOTE-054 trial and considering previous studies (in the metastatic setting) have shown therapeutic equivalence of the two dosing approaches (flat- versus weight-based)[9] and various doses per kg (2-10/kg),[10] in their opinion, under-treatment with weight-based dosing is not of appreciable concern. The CGP agreed that either dosing approach is reasonable and provincial jurisdictions will have to choose between implementing flat- versus weight-based dosing.

Finally, clinicians providing feedback on the initial recommendation also indicated that clarification is needed regarding the definition of disease recurrence (resectable versus non-resectable). They cited that since most patients will not receive radiation or completion lymph node dissection in the adjuvant setting (as was done in the trial), there may be more local versus distant recurrences. As such, patients with local recurrence may have surgical resection and qualify for further adjuvant systemic therapy versus patients

with distant recurrence who qualify for metastatic treatment options. The CGP agreed with the clinician feedback that clarification in the definition of recurrence is needed to distinguish the different management approaches required. In their opinion, the CGP suggests pembrolizumab be administered up to a total of 18 administrations, unacceptable toxicity, or until disease recurrence, at which point the intent of further therapy (adjuvant or metastatic) should be re-evaluated based on the extent of recurrence.

Placebo as a comparator
The comparator used in the KEYNOTE-054 trial was placebo (observation), a choice the CGP felt was completely appropriate considering the minimal use of IFN in clinical practice. It is unlikely that pembrolizumab will be directly compared to nivolumab in a future phase 3 trial. Further, the submitted NMA did not include pembrolizumab as a comparator, so no indirect comparative estimates of efficacy were provided.

Options for treatment
With respect to advising the PAG on preferred treatment options in the adjuvant setting, the CGP noted that pembrolizumab, nivolumab, and dabrafenib-trametinib are all currently Health Canada approved for the adjuvant treatment of stage III melanoma, and therefore, the clinician will potentially have three treatment options to present to patients. Dabrafenib-trametinib would only be available to those patients with BRAF-mutated melanomas, which is a significant but minority of patients with melanoma.

In considering a choice between immunotherapy with either pembrolizumab or nivolumab it's important to highlight that these agents were not evaluated in exactly the same population of melanoma patients, and therefore one has to be careful with respect to cross trial comparisons and generalizations of the evidence. The CGP identified the following important differences between the KEYNOTE-054 and Checkmate 238 trials:

- pembrolizumab was compared to placebo, whereas nivolumab was compared to ipilimumab;
- stage IV patients with metastatic disease who were resected to no evidence of disease were allowed in the nivolumab trial but were excluded from the pembrolizumab trial;
- dosing frequency was different between the two trials, with pembrolizumab administered every three weeks versus every two weeks for nivolumab;
- dosing was different between the two trials (capped versus weight-based) with pembrolizumab administered as one standard dose and nivolumab administered using weight-based dosing.

In the absence of direct comparative evidence that can guide treatment decision-making, choice of immunotherapy should follow an informed discussion amongst the clinical team and patients/caregivers of the pros and cons of each agent that takes into consideration such factors as mode of administration (oral versus IV), tolerance of medications, expected side effects, lifestyle issues, and distance from treatment centres. The toxicity profiles between pembrolizumab and nivolumab appear to be quite comparable both in melanoma and other tumour sites.

Selection of optimal systemic therapy as adjuvant treatment for patients with BRAF mutated melanoma.
At present there are no data to guide treatment with respect to optimal systemic therapy for patients with completely resected BRAF-mutated melanoma other than the treatment and patient characteristics noted above. It should be noted that patients with both BRAF-wild type and BRAF-mutated stage III melanoma benefited from adjuvant pembrolizumab. For patients who start dabrafenib-trametinib as first selected adjuvant treatment and develop toxicity/intolerance, there are no data to guide treatment recommendations in

this clinical situation. Based on oncologic principles, however, the CGP felt that up to one year of adjuvant treatment with a PD-1 inhibitor would be appropriate for high-risk patients. Starting a novel adjuvant therapy after intolerance would involve a discussion between the clinician and the patient that takes into consideration the duration of dabrafenib-trametinib that was received.

Sequencing currently available adjuvant therapy
Patients previously treated with INF as adjuvant to surgery were permitted enrolment into the KEYNOTE-054 trial; specifically, eligible patients who had been previously treated with IFN for thick primary melanomas without evidence of lymph node involvement. As there are very few to any patients receiving adjuvant IFN in Canada the number of individuals that would be potentially eligible to switch to a PD-1 inhibitor would be minimal. For patients who have previously completed an adjuvant course of ipilimumab and have not progressed, the CGP felt there would be no indication for a second adjuvant treatment. For patients who are already on ipilimumab with a planned duration of three years, it is unclear in the absence of evidence what the best duration of ipilimumab would be with respect to positive outcomes. In patients who have been on ipilimumab for less than one year and who wish to stop the regimen due to toxicity, clinicians on a case by case basis may wish to discuss the use of pembrolizumab to complete a total of one year of adjuvant treatment.

Reinitiating of pembrolizumab as adjuvant treatment after interruption for toxicity
Dose modifications for treatment-related AEs were permitted in the KEYNOTE-054 trial and were managed according to a dose adjustment scheme specified in the trial protocol. Accordingly, the CGP felt a similar adjustment scheme to manage toxicity and clinical judgement should be used in clinical practice when deciding to reinitiate adjuvant treatment with pembrolizumab. In the KEYNOTE-054 trial patients received 18 doses of pembrolizumab over approximately one year or until disease recurrence or unacceptable toxic effects. After interruption for toxicity, patients were required to be placed back on therapy within three weeks of the scheduled interruption unless otherwise specified by the treating investigator.

Impact of the utilization of pembrolizumab as adjuvant treatment to surgery on subsequent treatment decision making in the metastatic relapse setting
There are no data to inform optimal sequencing of treatments; however, patients in the KEYNOTE-054 trial received a variety of post-study treatments that included anti-CTLA4, anti-PD-1/PD-L1, and targeted agents. As previously noted, Part 2 of the trial, which is evaluating the efficacy of retreatment with pembrolizumab at recurrence, will provide some information with respect sequencing; however, data from Part 2 are not yet available. The criterion used for retreatment was greater than six months post completion of adjuvant pembrolizumab. This timeframe is in keeping with clinical practice in other tumour sites. In patients who relapse quickly, in less than six months off of adjuvant pembrolizumab, treatment choice in discussion with the patient will be based on factors that include bulk of disease and comorbidities. This group of patients would be offered dual immunotherapy with an anti-CTLA-4 and PD-1 inhibitor.

In patients with BRAF mutated melanoma who have completed one year of adjuvant dabrafenib-trametinib and have recurred, whether their disease has been resected to no evidence of disease, they would be eligible for retreatment with BRAF MEK inhibitors, PD-1 inhibitors or dual immunotherapy. The regimen chosen for each patient would be dependent upon a discussion between the clinician and the patient with respect to bulk of disease, tolerance of treatment, time interval before recurrence (time-to-progression or disease-free interval), and comorbidities.

Current NCCN guidelines recommend a switch to either ipilimumab or to add ipilimumab in patients who relapse after single agent PD-1 immunotherapy. If there has been a sufficient length of time (greater than six months) from completion of adjuvant PD-1 inhibitor treatment, re-challenge with the same agent would be feasible. As previously noted, data on retreatment will be forthcoming from Part 2 of the KEYNOTE-054 trial.

In response to the pERC initial recommendation, the Submitter provided feedback related to the lack of guidance on retreatment with pembrolizumab in the adjuvant setting and on optimal sequencing of treatments in the metastatic relapse setting specifically for patients with BRAF-wild-type melanoma. In reviewing this feedback, the CGP reiterated that in the absence of evidence for retreatment and optimal sequencing, the choice of subsequent treatment (including rechallenge) will be at the discretion of the treating oncologist and will be made on an individual basis that considers a patient's tumour mutation status as well as other factors that include time-to-relapse, location of relapse, and comorbidities.

1.3 Conclusions

The CGP was unanimous in their opinion that the adoption of pembrolizumab as adjuvant therapy to surgery represents a net clinical benefit to patients with completely resected stage III melanoma (AJCC 8th edition) based on data from the KEYNOTE-054 trial, which demonstrated a clinically and statistically significant benefit in RFS compared to placebo. In the absence of OS data, RFS has become an accepted surrogate for this outcome, and the comparator used in the trial (placebo/observation) certainly reflects current Canadian practice. The toxicity profile of pembrolizumab is readily managed in the community and is certainly acceptable to patients and their care providers, as evidenced by input received from patients with experience with the drug. The KEYNOTE-054 trial represents a high quality of evidence to guide treatment decision making, and pembrolizumab would provide another option to the two other adjuvant drugs (nivolumab, dabrafenib-trametinib) thus fulfilling one of the identified gaps in the management of melanoma patients.

2 BACKGROUND CLINICAL INFORMATION

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

2.1 Description of the Condition

Malignant melanoma is a relatively uncommon but aggressive skin cancer with an estimated incidence in Canada of 7200 cases per year.[11] Approximately 1 in 50 Canadians will be diagnosed with a malignant melanoma in their lifetime. While the disease may be uncommon melanoma is the most commonly diagnosed cancer in individuals between the ages 20 and 29, creating a disproportionate societal impact. Unfortunately, the incidence of melanoma in Canada continues to rise despite the efforts of patient advocacy groups, public awareness campaigns to educate the public regarding risk factor modification, specifically avoidance of ultraviolet radiation. Most diagnoses of melanoma represent early stage disease and are cured with surgery alone. However, a proportion of patients will present with locally advanced cancers which, while also amendable to surgery, portend a high risk of relapse and death. Prognosis varies within the subset of patients presenting with nodal involvement, but for those at highest risk for relapse (stage IIID AJCC 8th edition) the five- and ten-year disease-specific survival rate is 32% and 24%, respectfully.[12]

The patient eligibility criteria of the adjuvant trials referenced herein, in regards to stage, have used the AJCC 7th edition classification system. More recently an 8th edition has been released. Changes to the 8th edition include modifications to T category with respect to thickness, omission of mitotic rate, and the division of stage III disease into four sub-categories, A, B, C and a new category D (T4B N 3A/B/C/M0), which are based on both T and N category involving tumour thickness, ulceration, number of lymph nodes involved and micro satellite and in-transit metastasis. Based on the 8th edition classification, the melanoma survival probabilities at ten years for stage IIIA is 88%, IIIB 77%, IIIC 60%, and IIID 24%;[12] versus the AJCC 7th edition where ten-year survival is approximately 68% for stage IIIA, 44% for IIIB, and 22% for IIIC.[13]

For patients with metastatic melanoma, effective systemic treatment strategies prior to the era of targeted and immunotherapies did not exist. More recently, targeted inhibition of the mitogen-activated protein kinase (MAPK) signalling pathway has emerged as an extremely effective palliative therapy that has also improved the survival of patients with melanoma that harbors a mutation in the BRAF gene. Mutations at the BRAF V600 codon in approximately 40% of the total patient population results in constitutive activation of the signalling cascade leading to dysregulated cellular proliferation and metastatic spread of disease. For those patients with BRAF-mutant melanoma, agents such as dabrafenib and vemurafenib represent highly effective palliative therapy.[14,15]

As an alternative to targeted therapy (or for the majority of melanoma patients with non-mutated or wild-type BRAF disease) immune checkpoint inhibitors have similarly impacted patient survival. Ipilimumab, an inhibitor of cytotoxic T-Lymphocyte antigen-4 (CTLA-4) was the first immunotherapy to improve the survival of patients with metastatic melanoma,[16] followed by similar successes with agents such as nivolumab and pembrolizumab.[14,17] The latter study demonstrated targeting the Programmed Death-1 (PD-1) checkpoint molecule was superior to CTLA-4 inhibition, however more recent data suggests there may be further gain from dual blockade of CTLA-4 and PD-1, extending the three-year survival for patients with metastatic melanoma to nearly 60%.[18] Immunotherapy is also active in BRAF-mutated melanoma, and offers another option for these patients before or after the targeted therapies mentioned above. With these improvements in patient survival in the metastatic setting, it should not be surprising that attempts have

been made to reduce the risk of relapse and death in patients with locally advanced, non-metastatic melanoma. Both targeted and immunotherapies have been tested in the adjuvant setting, and both strategies have yielded improved patient outcomes.

2.2 Accepted Clinical Practice

For patients presenting with resected stage III or IV melanoma current adjuvant treatment options are limited, particularly with respect to systemic therapy. In Canada, high-dose IFN is indicated as adjuvant to surgical treatment in patients 18 years of age or older with malignant melanoma who are free of disease but at high risk for systemic recurrence, within 56 days of surgery (product monograph). In practice however, IFN is infrequently prescribed. The approval for the use of adjuvant high-dose IFN came at a time when no efficacious treatments were available for patients with recurrent disease, a clinical scenario which fortunately has changed for the better with the introduction of targeted and immunotherapies. Furthermore, IFN as adjuvant to surgical treatment for patients with melanoma has been well studied, and meta-analyses support the use of the treatment in a relatively small proportion of patients. As an example, a recent Cochrane meta-analysis examining 10,499 patients across 18 RCTs identified a benefit from the use of adjuvant IFN with respect to DFS and OS, reporting a HR for the latter of 0.91.[19] The same meta-analysis reported a number needed to treat (NNT) of 35 to prevent one death from melanoma recurrence, and when the significant toxicity of the treatment regimen is considered the actual benefit to the patient population is further diminished, particularly when one recognizes the data utilized within the meta-analysis predates the use of checkpoint inhibitor therapy. In addition, IFN use is generally limited to younger patients with no or few comorbidities, as the toxicity to older patients is significant. Finally, although unproven, it seems plausible that the durable immunotherapy responses observed in patients with metastatic disease could further diminish the small gains seen with the use of IFN. Attempts have been made to identify a subset of patients for whom the use of adjuvant IFN may confer a greater benefit; although not supported by the previously referenced Cochrane meta-analysis, more recent studies suggest patients with ulcerated primary melanomas may derive greater benefit versus the unselected patient population.[20] If confirmed, the use of ulceration as a predictive biomarker could in theory reduce the NNT to confer a benefit from IFN, although it is worth noting the aforementioned clinical trial utilized pegylated IFN-alpha, a treatment not currently approved in Canada as an adjuvant to surgery.[21]

Given the relatively modest clinical benefit observed after treatment with adjuvant IFN, in practice most patients decline this treatment option, instead choosing observation alone. Although not rooted in evidence, the option of active surveillance is routinely offered to patients with resected melanoma. This is a relevant point, as active surveillance is not without an associated cost. Practice will differ between Canadian cancer centres, but most will offer a variant of a schedule of assessments that includes clinical assessments performed on a 3-6-month basis as well as periodic re-staging imaging, although the benefit from diagnostic imaging has not yet been conclusively proven. In a subset of patients with resected nodal disease (or in patients with resected in-transit metastatic disease) radiation therapy may be considered as an adjuvant to surgical resection, although neither relapse-free nor OS are improved with this strategy.[21]

2.3 Evidence-Based Considerations for a Funding Population

High quality randomized clinical trials support the use of targeted or immunotherapy as adjuvant treatment following surgical resection of stage III malignant melanoma.

In the COMBI-AD trial,[22] patients were randomized to receive the combination of dabrafenib with trametinib versus treatment with matched placebos, with RFS as the primary endpoint and OS and safety included as secondary endpoints. To be eligible, adult patients (≥18 years of age) must have undergone complete resection of histologically confirmed stage IIIA (limited to lymph-node metastasis of >1 mm), IIIB, or IIIC cutaneous melanoma (according to the criteria of the AJCC, 7th edition) with BRAF V600E or V600K mutations. None of the patients had undergone previous systemic anticancer treatment or radiotherapy for melanoma. All the patients had undergone completion lymphadenectomy with no clinical or radiographic evidence of residual regional node disease within 12 weeks before randomization, had recovered from definitive surgery, and had an ECOG performance status of 0 or 1. As reported in 2017, with a median follow-up of 2.8 years, the estimated 3-year rate of RFS was 58% in the combination-therapy group and 39% in the placebo group (HR for relapse or death was0.47; 95% CI, 0.39 to 0.58; p<0.001). The three-year OS rate was 86% in the combination-therapy group and 77% in the placebo group (HR for death was 0.57; 95% CI, 0.42 to 0.79; p=0.0006). While the OS data were not statistically significant according to a pre-specified interim analysis threshold, a strong trend towards improvement with treatment with dabrafenib-trametinib was demonstrated. A benefit with respect to relapse or death across all subgroups studied was seen with the exception of the 10% of patients included with V600K BRAF mutations, although a strong trend favoring the active treatment group was observed even in this small subset of patients. Importantly, the HR for relapse or death was 0.50 or less in each of stage IIIA, IIIB and IIIC disease. In addition to demonstrating improvement in RFS, the tolerability of treatment in this patient population was similar to that seen in the metastatic setting, with 41% of patients experiencing a grade 3 or 4 toxicity (versus 14% of placebo-treated patients), and 26% of patients experiencing an AE leading to treatment discontinuation. The most commonly reported toxicities stemmed from the so-called pyrexic syndrome, including fever, chills, headache, fatigue and nausea.

CTLA-4 directed therapy has been compared against placebo in patients with resected stage III melanoma.[23] After patients had undergone complete resection of stage III cutaneous melanoma, they were randomly assigned to receive ipilimumab at a dose of 10 mg per kilogram (475 patients) or placebo (476) every 3 weeks for four doses, then every 3 months for up to 3 years or until disease recurrence or an unacceptable level of toxic effects occurred RFS was the primary end point. Secondary end points included OS, DMFS, and safety. At a median follow-up of 5.3 years, the five-year rate of RFS was 40.8% in the ipilimumab group, as compared with 30.3% in the placebo group (HR for recurrence or death was 0.76). The rate of OS at five years was 65.4% in the ipilimumab group, as compared with 54.4% in the placebo group (HR for death was 0.72). Despite the fact that more patients in the placebo group received post-protocol treatment with both CTLA-4, PD-1 and BRAF-directed therapies at the time of relapse, the survival advantage to adjuvant ipilimumab was preserved, suggesting this treatment strategy is unlikely to be negated by a potential salvage effect of reserving the use of immune checkpoint inhibitors for the time of relapse. Subgroup analyses demonstrated the benefit to treatment with ipilimumab as adjuvant to surgery was greatest in those patients at highest risk for disease relapse (stage IIIC patients, specifically those with four or more lymph nodes positive for metastatic melanoma) and again, patients with ulcerated primary melanomas seemed to derive proportionally greater benefit (HR for death was 0.64). Treatment with ipilimumab at a dose of 10 mg/kg resulted in nearly half of patients experiencing a grade 3-5 immune-related AE (42.7% versus 2.7% in the placebo group). In the ipilimumab group of treated patients, five patients died from a drug-related cause: three patients died of intestinal perforation (colitis), while one patient each died from myocarditis and multi-organ failure secondary to Guillain Barré syndrome. An approval from Health Canada for the use of

ipilimumab as adjuvant therapy to surgery was not sought. Upon funding of other adjuvant systemic treatments, there would be no demand for ipilimumab.

The CheckMate 238 RCT compared adjuvant CTLA-4 -directed therapy against inhibition of PD-L1.[24] In this double-blind, phase 3 trial 906 patients who had undergone complete resection of stage IIIB, IIIC, or IV melanoma received an intravenous infusion of either nivolumab at a dose of 3 mg per kilogram of body weight every 2 weeks or ipilimumab at a dose of 10 mg per kilogram every three weeks for four doses and then every 12 weeks. The patients were treated for a period of up to one year or until disease recurrence, a report of unacceptable toxic effects, or withdrawal of consent. The primary end point was RFS in the ITT population. With a minimum follow-up of 18 months, the 12-month rate of RFS was 70.5% in the nivolumab group and 60.8% in the ipilimumab group (HR for disease recurrence or death was 0.65). Treatment-related grade 3 or 4 AEs were reported in 14.4% of the patients in the nivolumab group compared to the 45.9% of those in the ipilimumab group; treatment discontinuation because of any AEs was 9.7% and 42.6% of the patients, respectively. There were two treatment-related deaths in the ipilimumab group. Nivolumab was superior to ipilimumab in both patients with PD-L1 expression greater than as well as less than 5%. CheckMate 238 is a unique trial as it studied patients in the adjuvant setting as well as including patients who had completely resected stage IV disease (including CNS metastases) rendered no evidence of disease. It also included patients with mucosal and acral-lentiginous melanoma patients although it did exclude ocular melanoma. The HR for relapse or death was statistically non-significant within each of these subgroups, due to the small numbers of patients enrolled.

Pembrolizumab has been studied in the adjuvant setting and is the focus of the current pCODR review; the KEYNOTE-054 trial compared pembrolizumab to placebo in patients with stage III melanoma.[1] Refer to section 6 of this report for a summary and critical appraisal of the evidence from this trial.

The evidence seems clear that cutaneous melanoma patients surgically rendered free of macroscopic disease stage III draw significant clinical benefits when using either targeted or immune checkpoint treatment as adjuvant treatment to surgery. In most trials available evidence reveals a benefit with respect to RFS although the study comparing ipilimumab against placebo as adjuvant treatment to surgery supports an advantage in terms of overall patient survival. This trial has the longest duration of follow-up. There exists inter trial heterogeneity with respect to patient populations in the three adjuvant trials. One trial did not allow patients with resected stage IV disease and two of the three trials that allowed stage IIIA disease required a minimal focus of nodal disease of 1mm in the setting of completion lymphadenectomy. None of the trials of CTLA-4 checkpoint inhibitors identified a preferential benefit to treatment in BRAF-mutated or wild type melanoma.

2.4 Other Patient Populations in Whom the Drug May Be Used

The use of systemic therapy, targeted or immune checkpoint inhibitors, as adjuvant treatment to surgery demonstrates a clinical benefit to patients with completely resected malignant melanoma with lymph node involvement. When specifically considering pembrolizumab as an adjuvant treatment option, the patient population in whom treatment may be considered will in large be defined by the inclusion criteria used in the KEYNOTE-054 trial.[1] Exceptions to this statement may include considerations related to the following factors:

- **Patient age -** In the KEYNOTE-054 trial patients had to be 18 years of age or older. Melanoma can rarely occur in younger patient populations. There is currently no evidence to suggest that pembrolizumab would not be safe in treating pediatric patients based on early data (KEYNOTE-051 trial) in pediatric advanced melanoma patients.[25]

- **Performance status -** An ECOG performance status of 0 to 1 was a criterion for enrolment into the KEYNOTE-054 trial. In clinical practice both patients and clinicians will want to consider adjuvant pembrolizumab in patients with an EGOG status greater than 1. As the disease has been completely resected it is anticipated that an EGOG status of 2 reflects comorbidities as opposed to a reflection of disease activity. Occasionally a complication of complete lymphadenectomy may render a patient ECOG 2. The toxicity profile of pembrolizumab is favourable enough to offer it to patients who have comorbidity but are felt to still be suitable candidates for adjuvant treatment of their resected melanoma.
- **Site of primary** – The KEYNOTE-054 trial restricted enrolment to patients with cutaneous melanoma. Patients with non-cutaneous melanoma subtypes such as mucosal or ocular melanoma were ineligible for the trial. The CGP believes there is no reason to expect pembrolizumab to behave differently than nivolumab in these sub-types based on data from the Checkmate 238 trial; however, in the absence of evidence, the use of pembrolizumab as adjuvant treatment to surgical resection should be limited to those patients presenting with cutaneous melanoma.

  In response to the pERC initial recommendation, clinician feedback was received to specify acral melanoma as a type of cutaneous melanoma that should be eligible for treatment with adjuvant pembrolizumab. The CGP noted that the KEYNOTE-054 trial did not include patients with acral melanoma; however, they consider the evidence from the trial generalizable to patients with this subtype of cutaneous melanoma.
- **Stage of disease -** The KEYNOTE-054 trial was restricted to patients with stage IIIA to IIIC melanoma according to the AJCC 7th edition and excluded patients with resected stage IV melanoma. Although the CGP does not expect pembrolizumab to behave differently than nivolumab with respect to resected stage IV disease, there currently is no direct evidence upon which to base the use of the pembrolizumab in these patients. Stage IIC patients were also excluded from the KEYNOTE-054 trial but results of ongoing adjuvant clinical trials are awaited; these results should be used to inform the use adjuvant pembrolizumab in stage IIC disease.
- **Patients who wish to defer completion lymph node dissection following positive biopsy** Since the adjuvant trials (Checkmate 238, KEYNOTE-054, COMBI-AD) were commenced there has been a change in practice where completion lymph node dissection is not a requirement to receive adjuvant therapy to surgery. The second multi-center selective lymphadenectomy trial (MSL-2) compared observation against completion lymph node dissection for patients with melanoma positive sentinel lymph node biopsy.[26] The results of this clinical trial have established observation within this patient population as a viable treatment strategy as melanoma specific-survival was not improved with reflexive completion lymph node dissection. Patients and clinicians therefore may wish to defer completion lymph node dissection following a positive sentinel lymph node biopsy.
- **Retreatment -** In Part 2 of the KEYNOTE-054 trial patients who recurred at least six months after treatment with pembrolizumab were recommenced on pembrolizumab or initiated on pembrolizumab if they were on placebo. The results of Part 2 are not currently available (expected in 2023) yet the Submitter has included retreatment as part of the criteria for reimbursement. The Submitter provided evidence for retreatment (as proof of concept) from a separate trial in advanced melanoma patients; [27] however, the CGP considered these data not applicable to the target patient population of this review, and was of the opinion that guidance regarding retreatment should await the results of Part 2 of the trial.
- **Adjuvant radiotherapy** - Patients treated with radiation adjuvant to surgery were not entered into the KEYNOTE-054 trial. Radiation as adjuvant therapy to surgical resection of

melanoma confers an advantage in terms of loco-regional control, however, this benefit does not translate to improvement in patient survival.[21] Nonetheless, the situation may arise where clinicians may wish to consider radiation and systemic therapy as adjuvant treatment to surgery.

- **Patients with active autoimmune disease** - Patients that required systemic steroid therapy treatment in the past two years or any other form of immunosuppressive therapy within seven days prior to the first dose of study medication were excluded from the KEYNOTE-054 trial. In clinical practice with increasing clinical competence of management of immune related events, these agents are often presented to patients with a pre-existing immune-related illness with a pro-con discussion of risks and benefits. This is undertaken in close collaboration with the managing consultant of their known auto-immune disease. Therefore, it is expected that patients with pre-existing immune mediated illness as well as their families and care providers may consider using pembrolizumab as an adjuvant to surgical treatment following complete resection of the disease.

3 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

Two patient advocacy groups, the Melanoma Network of Canada (MNC) and the Save Your Skin Foundation (SYSF), provided input on pembrolizumab in the adjuvant setting for melanoma patients with lymph node involvement who had undergone complete resection. Their input is summarized below.

Information was obtained by MNC through an online survey, which was emailed via a link to a list of patients in MNC's database. The survey was also made available through social media using Facebook and Twitter. The survey was made available to Canadian patients and caregivers, regardless of stage, between November 29, 2018 and December 31, 2018. A total of 164 patients and 127 caregivers responded to the survey. The demographic characteristics of patients are summarized in Table 3.

Table 3: Demographic characteristics of Patients of MNC's survey.

Demographic variable	N (%)
Patients	164
Sex	
Male	76
Female	88
Metastatic disease	16
Adjuvant disease	13
Age of respondents	
18 to 30 years	4 (2.44)
31 to 40 years	17 (10.37)
41 to 50 years	24 (14.63)
51 to 60 years	44 (26.83)
61 to 70 years	45 (27.44)
Greater than 70 years	30 (18.29)
Stage of disease	
Stage 0	26
Stage 1	7
Stage 2	14
Stage 3	43
Stage 4	38
Unknown	36
Geographical location	
Ontario	110
Alberta	20
British Columbia	10
Quebec	12
Other provinces	12

SYSF obtained information through a survey, one-on-one conversations and through personal experience. SYSF were able to provide input from 63 respondents. A total of 48 patients were interviewed, 39 (81%) of whom were female. Of the 48 patients interviewed, 2% (n=1) were between 18 years and 29 years of age, 19% (n=9) were between 30 and 39 years of age, 27% (n=13) were between 40 and 49 years of age, 27% (n=13) were between 50 and 59 years of age, and 25% (n=12) were 60 years or older. Approximately half of interviewees were employed (52%, n=25), while others were employed working part time (13%, n=6), not working or looking for work (10%, n=5), retired (17%, n=8), or disabled or not able to work (10%, n=5). SYSF indicated interviewing patients from all Canadian provinces, in addition to interviewing nine patients who were not living in Canada, residing in the USA and Australia.

Fear and anxiety, scarring and disfigurement, fatigue, pain and depression are the symptoms patients feel most strongly about being controlled related to their disease. Scarring and

disfigurement related to melanoma was stated to have caused patients great stress. Not only does this side effect cause embarrassment to patients, it was also reported to have caused some patients to lose their jobs. One patient was unable to continue working because they had reduced depth perception related to losing an eye due to their melanoma. While not frequently used in Canada, some patients, in both the MNC and SYSF surveys, reported receiving treatment with interferon. Side effects were reported to be very difficult to manage, and with one patient stating that their *"oncologist said at the time that I was close to, or at the point of permanent damage"* due to interferon. Interferon treatment was not efficacious for these patients, which further made side effects unbearable.

Six patients in the SYSF sample were reported to have experience with pembrolizumab in the adjuvant setting; while in the MNC survey, 13 and 16 patients reported having experience with pembrolizumab in the adjuvant and metastatic setting, respectively. Compared to interferon, patients reported side effects as being less severe, easily manageable, and allowing them to maintain quality of life. Fatigue was the most commonly reported side effect from patients according to both SYSF and MNC. Both patients and caregivers expressed gratefulness for having the option of pembrolizumab. However, there was distress expressed regarding the cost of pembrolizumab and the lack of access if patients were unable to get into a trial. One caregiver stated that their physician stated they could either *"pay $100,000 or wait until the cancer gets to Stage IV. We all feel helpless and powerless because we do not have that money."*

Quotes are reproduced as they appeared in the surveys, 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. Please see below for a summary of specific input received from the patient advocacy groups.

3.1 Condition and Current Therapy Information

3.1.1 Experiences Patients have with Melanoma

It should be prefaced that for section 3.1 of this summary, all information provided by SYSF reflect all melanoma patients regardless of stage of disease. SYSF asked patients to rate aspects of melanoma from least to most important; results are available in Table 4.

Table 4: Aspects of melanoma patients want controlled (SYSF).

Aspect of melanoma	N (%)
Fear and/or anxiety	55 (88)
Scarring and disfigurement	45 (71)
Fatigue	41 (65)
Pain	32 (50)
Depression	32 (50)
Weight loss or weight gain	30 (48)
Disrupted sleep	30 (48)
Negative impact to family or social life	25 (39)
Financial loss or job loss	20 (31)
Nausea or vomiting	20 (31)
Headaches	20 (31)
Loss of/gain of appetite	18 (29)
Lymphedema	17 (27)
PTSD	14 (23)
Cognitive impairment	14 (23)
Damage to organ	13 (21)
Mobility issues	12 (19)
Breathing problems	4 (6)
No side effects	4 (6)

SYSF surveyed patients about the symptoms that they felt were the most important to control. The most important symptom patients felt they wanted to control was mental health (i.e., fear, anxiety, depression and outlook) (n=46, 73%). Other important symptoms included: fatigue (n=30, 48%), pain (n=25, 40%), lymphedema (n=14, 23%), and scarring and disfiguration (n=13, 21%).

MNC indicated that currently there are no adjuvant therapies covered by provincial health plans, other than interferon. However, interferon was stated not to be prescribed in most hospitals due to its ineffectiveness and side effects. Surgery is offered to patients with high risk of recurrence (Stage IIIA/B/C/D) and has physical impacts on patients, such as mobility issues for some, scarring and lymphedema. Patients also experience high stress when they are told there is a high risk of recurrence after surgery, with no optimal systemic treatment options available to them afterwards. The impact of both the physical and emotional stress related to surgery was stated to impact patients' daily lives, including the ability to work and to engage in daily activities.

MNC stated that while interferon may have previously been provided to patients in the adjuvant setting, most hospitals no longer prescribe it due to the ineffectiveness and side effects. Table 5 provides a list of side effects reported by 137 patients responding to MNC's survey. The most common side effects reported by patients included scarring and disfigurement and fear and anxiety.

Table 5: Side effects experienced by patients interviewed by MCN.

Side effect	N (%)
Scarring and disfigurement	94 (68.61)
Pain	43 (31.39)
Edema or fluid retention	26 (18.98)
Lymphedema	41 (29.93)
Mobility issues (unable to walk or impaired movement)	20 (14.60)
Gastrointestinal issues	16 (11.68)
Breathing problems	9 (6.57)
Headaches	18 (13.14)
Peripheral neuropathy (nerve pain or damage)	21 (15.33)
Disrupted sleep	56 (40.88)
Appetite loss or weight gain	30 (21.90)
Fear or anxiety	83 (60.58)
Fatigue	54 (39.42)
Depression	46 (33.58)
Post-traumatic stress	20 (14.60)
Cognitive impairment	8 (5.84)
Nausea or vomiting	8 (5.84)
Damage to organs, such as lungs, liver brain	17 (12.41)
Negative impact to family or social life	39 (28.47)
Financial loss or job loss	30 (21.90)
Impact on sexuality	24 (17.52)
None - there has been no impact	6 (4.38
Other	25

MNC provided a series of statements from patients regarding their experiences with melanoma. Many of the comments expressed concern on physical disfigurement related to melanoma. For example, patients indicated experiencing *"scarring and nerve damage,"* the *"loss of [an] eye"* which resulted in this patient losing their depth perception, and another patient had *"one ear removed making wearing glasses difficult."* As a result of the

physical disfigurement caused by melanoma, many comments were related to job loss and its financial impact. *"Financial loss was experienced from inability to work at the time of the post-op recovery."* A patient who lost an eye was unable to work at their job which also resulted in financial and emotional stress.

The comments provided by MNC also indicated that patients experienced an inability to engage in daily activities, where one patient stated experiencing *"general exhaustion limiting daily activities"* while another stated experiencing *"effects on work and daily routine's; limits on activities."* Many also commented on the mental toll their condition took on themselves and their families. *"The depression and emotional toll is draining." One patient stated feeling "severe depression [and] anxiety."*

Quotes from MNC also indicated high levels of stress anxiety related to the recurrence of disease. *"I worry about a recurrence a great deal of the time. I have had several recurrences and it has left me with physical and emotional scars." "I live with constant fear and anxiety my cancer will return/progress." "The fear of the disease progressing is always at the back of my mind. The mental stress is always there." "Anxiety over recurrence and cancer paranoia.; Anxiety when you have to go for regular visits and scans."*

SYSF provided a series of quotes commenting on symptoms affecting the day-to-day lives of patients. Similar to quotes provided by MNC, patients commented on fear and anxiety of disease recurrence. *"Fear of return of the disease is frequent. Which results in anxiety." "I am 5 years post diagnosis of Stage 2c melanoma and I still worry it will come back." "Most affected by PTSD especially after treatment during ongoing follow up."* Patients also commented on fatigue, as one patient stated the fatigue had forced them to slow *"down at work and with [their] kids."* The impact from mental stress was not only reported among patients but also from loved ones. One patient stated, *"My work suffers as do relationships since not sleeping well, scared and depressed."* Physical impacts, such as *"nerve damage from surgery" and "lymphedema",* were also stated as symptoms affecting daily living for patients.

SYSF reported that only 10% of patients interviewed found that they were limited due to disease or treatment and were unable to work. The majority of patients (90%) were able to manage ongoing symptoms.

3.1.2 Patients' Experiences with Current Therapy for Melanoma

The treatment experience of patients (as reported to SYSF) is summarized in Table 6. Patients who received interferon reported experiencing fatigue (100%), flu like symptoms (100%), weight loss (95%), nausea and vomiting (90%), hair loss or thinning (90%), and some form of depression (90%). All patients who received interferon stated that side effects could not be managed. Most patients (95%) also said that the side effects of interferon were not worth the result as they all had re-occurrence of disease in stage IV. SYSF indicated that interferon was not recommended by the physician of patients who received it. MNC, who indicated that interferon is not commonly prescribed to patients due to its lack of effectiveness, also reported that patients responding to their survey also elected to take interferon. The following quotes were provided by patients who had experience with interferon treatment; they comment on the numerous and severe side effects, depression, financial impact and impacts on family as a result of interferon.

"Financial impact from inability to work, cognitive impairments, fatigue, sense of self, confidence decline, unable to meet family commitments due to fatigue and risk of infection" "I struggle daily with all of the issues I clicked on previously. Interferon

triggered Sarcoidosis in my lungs and has not gone into remission. I also have fibromyalgia too. All diagnosed right after I finished my yearlong treatment of Interferon"

"I experienced a severe toxic reaction to Interferon Alpha affecting the nervous system, being unable eat, read or write, with speech becoming difficult and profound depression. The oncologist said at the time that I was close to, or at the point of permanent damage"

"I had Interferon Treatments for a year 12 years ago. It was unbearable. My Drs. this time around would not recommend it as they felt it was outdated and would not help me"

"Erratic heart relate; fevers, chills, nausea, diarrhea -serious burning diarrhea, collapsed veins, 24/7 headaches, enormous weight loss and loss of appetite, depression beyond belief, extreme fatigue, low blood counts and liver issues, financial loss of income, sleeplessness, hair loss, loss of sense of smell, muscle cramps and aches. It was the most horrible thing I ever was on."

"Financial, could not work due to tiredness and body aches moodiness as that also effects the mental health because your just the same and it takes a toll on the family and the house. And with a small child they don't understand why or what's going on."

Table 6: Treatments reported by patients interviewed by SYSF.

Treatment	N (%)
Interferon	24 (38)
"Wait and watch for progression"	24 (38)
Other clinical trials	9 (15)

SYSF provided a series of quotes from patients who had experience being treated with observation also called the "watch and wait" method. All of the quotes indicate that patients would have appreciated a treatment option, not only for their condition, but to also relieve the stress and anxiety of being without any available options.

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

"We did not receive any treatment. If we would have gotten something, maybe we would not have gone to stage 4"

"It would have meant the world to me to be offered treatment. It would have been a game changer!"

'Having a treatment option would have given me Peace of Mind."

"It would have meant to not have to worry as much"

"I could feel like I was getting treatment and I might have a chance to stop it before it comes back"

"Less fear that we'd miss something between appointment with dermatologist and I would be less likely to end up terminal or massive spreading before it is found again"

"The possibility of not having to have another surgical procedure and the fear that the next diagnosis wouldn't be caught early enough."

"I would have tried anything"

MNC asked patients which symptoms they wanted controlled. Patients reported reduced pain, scarring, disfigurement, lymphedema, emotional issues and the ability to work as important side effects they wanted controlled by their treatments. In regards to unmet need, most patients reported wanting therapies with fewer side effects than interferon, with improved outcomes to reduce recurrence rates and spread of disease. The following quotes provided by MNC mirror sentiments provided by patients in SYSF's submission commenting on the lack of available options. The quotes also express the frustration patients feel about having availably treatment options that they may not be able to access at the moment.

"I would hope new therapies would offer better disease management outcomes. I would hope it would prevent recurrences or spread of disease and I hope there would be less side effects so I could have a somewhat normal life and continue to work."

"Frustration due to the lack of options. Feeling of despair due to being denied a lifesaving treatment because of inability to pay out of pocket. Anger due to feeling that my health care provider is not advocating on my behalf."

"I was told that my chance of survival is low and that there is drug therapy's out there that has proven to help but it's not covered so I can't have it. This caused a great deal of stress and anger. This has caused a high amount of stress and leading to depression"

MNC provided statements from patients' and caregivers' on their expectations regarding new treatments. MNC indicated there is a need for a greater variety and more effective treatment options. The lack of relevancy of interferon compared to immunotherapies was indicated for melanoma in the adjuvant setting, as interferon does not provide patients with an efficacious treatment, nor are the side effects tolerable.
SYSF indicated that patient's expectations for future treatments include: longer survivorship, possibly a cure, fewer side effects, better quality of life, and access to better treatments. Some of the quotes provided by SYSF include the following:

"Longer overall survivorship."

"Maybe a cure."

"Lessening spread of minimizing I so I can have as much time as possible with my toddler. Getting ahead of the fight before I get sick."

"Treatments that work, work quickly, that have minimal side effects and are cost manageable."

"Promise, evidence based data for decision making, safety (limited risk of adverse events)."

"Hopefully if treated in stage 3 disease will not progress."

"Stage 3C is a "chance" at saving your future and Keytruda was a life line. We don't know if it 's worked yet… and it only works on 30% of patients, so more options are needed to help prevent moving to Stage IV"

"Immediate access to immunotherapy instead of surgery and radiation"

3.1.3 Impact of Melanoma and Current Therapy on Caregivers

MNC indicated that 23 patients reported having no caregiver, and had to deal with the diagnosis and treatments on their own. Stress and anxiety due to lack of available treatment options in the adjuvant setting was expressed by caregivers as well. Caregivers also experienced fatigue due to increased caregiving responsibilities, and reduced income

from taking time off work for appointments and home care. Impacts on the households of patients and caregivers were reported due to the lost income, and cost of treatments. Caregivers also face uncertainty about the future and fear of losing their loved ones.

Quotes from caregivers regarding their experiences taking care of their loved ones were provided by both the MNC and SYSF. These quotes express the significant time commitment involved in caregiving, stress about watching their loved ones suffer, and the financial toll involved in caregiving. The quotes also indicate the strain the condition has on family dynamics, as some comments discussed challenges with relationships as a result of the disease.

"It is a significant time commitment to attend appointments and it is taxing emotionally because you are constantly witness to your loved ones suffering, but you don't feel like you can put your troubles on them."

"Incredibly stressful and frustrating, side effects range and are a day to day evolution of symptoms at times, financial hardship, more time commitment, patient cannot help with much at home so somewhat a burden managing the household and decreased ability to work while caring for patient."

"Changing the responsibilities to just one parent and becoming a caregiver to the other is an emotional rollercoaster and then the financial stress of going to one income with all the Bills is insane"

"Had to assist my daughter financially when she was off work under going interferon. Had to take her to her medical appointments. It has been very hard to watch her struggle with life at times. I would switch places with her in a heartbeat. Have suffered depression myself."

" My family continues to have fear of recurrence".

"In 2013 first diagnosed with stage 2, removed with little follow up. 2017 stage 4, whole lot of issues, lots of appointments. Trying to work and take care of my spouse and manage all the appointments. As a caregiver I am physically and emotionally exhausted."

"Had to move provinces, leave school, find a job, and ultimately our new marriage ended in divorce."
"My spouse had to deal with my anxiety and fears, difficult to talk about."

"Financially drained because my husband misses work to take care of me and I have to travel 4 hours each way to my melanoma specialist."

"Lost time at work, arguing over the disease, just not knowing enough about treatment options or disease in general."

"The entire family is still in shock! We do not know what to do and where to seek help. The doctor told us that the only drug that would help the cancer not advance to stage IV is not approved. She offered that we could pay $100,000 or wait until the cancer gets to Stage IV. We all feel helpless and powerless because we do not have that money. We were told there is a 60% chance that it will go to stage IV."

"Just knowing how much time I have left, planning for my stage 4, hard on relationship and financial worry!"

3.2 Information about the Drug Being Reviewed

3.2.1 Patient Expectations for and Experiences To Date with Pembrolizumab

A total of 29 patients were reported to have experience with pembrolizumab from MNC, 13 received the drug in the adjuvant setting and 16 in the metastatic setting. SYSF indicated six patients having experience with pembrolizumab in the adjuvant setting; half of whom (n=3) received it through a clinical trial, while the other three patients received through compassionate access. Since most patients were on observation following surgery, they did not have anything to compare treatment with pembrolizumab to. However, prior surveys conducted by MNC for pCODR for patients with metastatic melanoma indicated that pembrolizumab was well tolerated by most patients. Furthermore, MNC stated that compared to interferon, there were significantly less side effects with pembrolizumab. Comments included by MNC indicate that the side effects of pembrolizumab were very limited, and manageable with over the counter medications, such as Advil, Tylenol or Gravol.

"Keytrua has been a 'walk in the park" for me with no symptoms except for a loonie-sized irritation in the palm of my hand. Interferon rendered me extremely tired and unable to function normally. Keytruda eliminated all that."
"No fatigue, no problems as with interferon while on Keytruda"
"Treatment allowed to maintain quality of life without major issues, I stayed working and active throughout"
"Yes, I could manage them, lots of Advil and Tylenol and Gravol and now that I am a year and a half post treatment I am very happy I did take the preventative route"

MNC included a list of side effects reported by 29 metastatic patients on a trial (Table 7). The most common side effects included fatigue or weakness (62%), and skin rash (55%). Of the six patients reporting experience with pembrolizumab on behalf of SYSF, the following side effects were experienced: fatigue (n=3), gastro issues (n=3), headaches (n=2), loss/gain of appetite (n=1), and rash, fever and rapid heartbeat (n=1). Three patients experienced no side effects. All six patients interviewed by SYSF stated that the side effects of pembrolizumab were mild in nature, closely monitored and immediately managed. All of the patients who experienced side effects stated that the benefits of pembrolizumab outweighed the experience of the side effects. Of the 29 patients who received pembrolizumab from MNC's survey, 24 stated that benefits of treatment outweighed side effects.

Table 7: Side effects reported by metastatic patients (MNC survey).

Side effect	N (%)
Fatigue or weakness	18 (62.07)
Skin rash	16 (55.17)
Shortness of breath, cough or chest pain (pneumonitis)	8 (27.59)
Muscle or joint pain	8 (27.59)
Hormone or thyroid problems	6 (20.69)
Fever or flu like symptoms	5 (17.24)
Headaches	5 (17.24)
Pain	4 (13.79)
Diarrhea or colitis	4 (13.79)
Weight gain	4 (13.79)
Cognitive impairment	3 (10.34)
Sexual impairment	3 (10.34)
Constipation	3 (10.34)
Weight loss or loss of appetite	3 (10.34)
Bleeding or bruising more easily	2 (6.90)
Liver problems	2 (6.90)
Kidney problems	0

Side effect	N (%)
None	4 (13.79)
Other	14

According to MNC, caregivers felt relief, and very grateful for their loved ones who had been given pembrolizumab. MNC stated that caregivers felt as though they had won a lottery to have gotten into a clinical trial and not to have to worry about out-of-pocket expenses. Issues of frequent travel, cost of parking, and being unable to work were indicated as hardships caregivers faced with accessing treatment.

"Had to scramble to get on the clinical trial as it was closing. Don't know what I would have done otherwise."
"Travelling long distance, leaving work, financial."
"Due to the issue I had, I had to travel to the hospital few times a week and I was unable to work."

MNC stated that patients and caregivers would appreciate access to therapies with improved survival and reasonable quality of life. For survival and/or prevention of disease, patients and caregivers are willing to accept some side effects related to treatment.

3.3 Additional Information

While 38 patients interviewed by SYSF were not able to receive pembrolizumab, all of them wished that they could have. Twenty-eight patients could not obtain pembrolizumab as they had a progression of disease, and 44 patients stated that if they were offered pembrolizumab in early stages of melanoma, they would have taken it. According to SYSF, patients were told about pembrolizumab by their physicians, but they were then told they would have to pay for it to access it. One patient stated that having no treatment options offered felt *"terrifying"* and described the *"mental anguish"* as a result of this on their family. Another patient stated, *"My entire family has been looking to find a way to pay for the treatment or find a clinical trial. We can't afford it and that's painful."* Moreover, one patient stated that with treatment they could continue to *"take care of [their] children and grandchildren and [their] husband and work, pay taxes and be a contributing member of society instead of being a burden to the system. It would mean saving a human life."* SYSF also provided a letter a letter indicating the collaborative efforts of SYSF and the Canadian Skin Patient Alliance, and their support of SYSF's submission for this review.

MNC highlighted the difficulty patients in the adjuvant setting experience in trying to access therapy for their condition, and that lack of treatments available for melanoma patients compared to other types of cancers. According to MNC, patients in both the adjuvant and metastatic settings often rely on compassionate access programs, waiting for government reviews and negotiations to complete.

4 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

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

Overall Summary

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

Clinical factors:

- Eligible patient subpopulations

Economic factors:

- Additional resources to administer, monitor and treat immune-mediated side effects

Please see below for more details.

4.1 Currently Funded Treatments

PAG identified that currently in all provinces high-dose interferon-alfa (IFN) is used for adjuvant treatment of high-risk melanoma, or observation for those intolerant to or unwilling to undergo IFN therapy. PAG also noted that immunotherapies (e.g., pembrolizumab, nivolumab) may also be available for advanced melanoma irrespective of BRAF status. Nivolumab and dabrafenib-trametinib are currently under review at pCODR for the adjuvant treatment of patients with melanoma.

PAG noted that the comparator in the KEYNOTE-054 trial was placebo. PAG is seeking information on data comparing pembrolizumab with IFN.

4.2 Eligible Patient Population

The KEYNOTE-054 trial excluded patients with ECOG PS of 2 as well as patients with mucosal or ocular melanoma. PAG is seeking guidance on whether pembrolizumab would be limited to patients with ECOG PS of 0-1 and cutaneous melanoma (e.g., not mucosal or ocular melanoma).

PAG is seeking guidance on whether the following patients would be eligible for adjuvant pembrolizumab:

- patients with completely resected stage IV disease as well as resected stage IIB/C disease with T4 lesions (high risk node negative) who are fit and motivated for treatment
- those currently being treated with interferon-alfa or on observation
- patients who have received adjuvant ipilimumab and have not progressed
- patients who are BRAF mutation positive and received one year of dabrafenib-trametinib therapy and have not progressed, whether they should be eligible upon relapse if their disease was completely resectable
- neoadjuvant treatment for patients with borderline resectable lymphadenopathy
- patients disease free following treatment of in-transit metastases, and are node negative

4.3 Implementation Factors

The recommended dose of pembrolizumab for adjuvant melanoma is 200 mg over 30 minutes every 3 weeks for a total of 18 administrations or until disease recurrence or unacceptable toxicity; as well as re-treatment for patients whose disease recurred more than 6 months after completing one year of adjuvant pembrolizumab treatment.

The dose is 200 mg for adjuvant melanoma in the reimbursement request and the KEYNOTE-054 trial. PAG noted trials suggest that weight-based dose of 2 mg/kg and 200 mg fixed dose are similar. Although fixed dose would minimize drug wastage, PAG is seeking guidance on weight-based dosing up to a cap of 200 mg for adjuvant melanoma; given the use of this dosing schedule in the metastatic melanoma setting and the high cost of fixed dose compared to weight-based dose for patients weighing less than 100 kg. PAG is also seeking clarification on a dosing schedule of every 6 weeks with pembrolizumab.

PAG noted some patients may interrupt treatment with pembrolizumab due to toxicity or other reasons. PAG is seeking guidance on the appropriateness of re-initiation with pembrolizumab after toxicity resolution or treatment interruption for other reasons and if this occurs, clarification on the total duration of therapy (i.e., one year of treatment or a total of 18 administrations).

Pembrolizumab requires increased chair time and resources for drug administration as patients would alternatively be observed or receive subcutaneous IFN after completing intravenous induction therapy. PAG noted that additional clinic visits and bloodwork throughout the 1 year may be required in this patient population to deliver adjuvant pembrolizumab therapy, as IFN is not well tolerated, and based on experience, many patients do not complete 1 year of IFN therapy and some patients decline IFN therapy. PAG identified that additional nursing and pharmacy resources are required for monitoring and treating side effects (e.g., immune-mediated side effects of pneumonitis, ulcerative colitis, and Crohn's).

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

4.4 Sequencing and Priority of Treatments

PAG is seeking guidance on the appropriate treatment options in the metastatic setting as well as treatment-free interval following adjuvant therapy.

For patients who have received pembrolizumab in the adjuvant setting and then develop metastatic disease,

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

- Patients in the trial were BRAF mutation positive or negative. PAG noted that adjuvant treatment with dabrafenib and trametinib may be available. What would be the best treatment for BRAF mutation positive patients in the adjuvant setting?

PAG is also seeking information for patients who have received the total of 18 administrations of pembrolizumab and do not have disease recurrence, what appropriate treatment options are available. PAG is also seeking guidance on whether there is a preference for PD-1 inhibitor (i.e., nivolumab or pembrolizumab) in the adjuvant setting.

4.5 Companion Diagnostic Testing

PAG is seeking clarity on whether PD-L1 testing would be required in this setting.

4.6 Additional Information

None provided.

5 SUMMARY OF REGISTERED CLINICIAN INPUT

Two inputs from registered clinicians were received by pCODR: one submission on behalf of a single oncologist in Ontario, and a joint submission from clinicians from Cancer Care Ontario capturing the perspectives of four oncologists. In total, input was provided by five oncologists.

The single clinician input received considered nivolumab the main adjuvant treatment option for patients with resected melanoma. Other therapies mentioned included targeted therapy with BRAF and MEK inhibitors. All clinicians providing input highlighted there is an unmet need for additional adjuvant treatment options, as the evidence for adjuvant nivolumab is limited to patients with stage IIIB or higher melanoma. Patients with stage IIIA melanoma were not included in the randomized control trial evaluating nivolumab to ipilimumab. Both clinician inputs indicated a preference for pembrolizumab over nivolumab among BRAF-wild type patients in the adjuvant setting, citing pembrolizumab was very tolerable and safe. For patients who are BRAF-positive, the clinicians providing input stated that treatment preference in the adjuvant setting will likely be based on individual patient factors. While the preferred initial adjuvant treatment may not be the same for all patients who are BRAF-positive, clinicians stated that having the option of switching patients from BRAF and MEK inhibitor targeted treatments to pembrolizumab, and vice versa, would be beneficial for BRAF-positive patients who become resistant.

While some clinicians may consider nivolumab and pembrolizumab therapeutically equivalent, some input suggested that clinicians may prefer to use pembrolizumab over nivolumab for its less frequent administration schedule (every three weeks versus every two weeks, respectively). Administering adjuvant pembrolizumab at a weight-based dosing schedule up to a cap was supported by the clinicians. Use of pembrolizumab for adjuvant treatment for greater than a year was stated to potentially benefit some patients; however, it was suggested that eligibility criteria for reimbursement specify treatment by number of doses and not by time period. There were also sentiments that eligibility criteria for reimbursement for melanoma treatment in the adjuvant setting should be kept consistent with those in the metastatic setting.

5.1 Current Treatment(s) for Resected Stage III Melanoma

According to one of the clinician inputs, nivolumab was stated to be the most relevant comparator as the primary treatment option for adjuvant therapy in melanoma. BRAF and MEK inhibitors in combination were also mentioned as adjuvant therapy for patients who are BRAF-positive. For mucosal melanomas, the joint clinician input stated that peg-IFN or chemotherapy, such as carbo-taxel or temozolomide, were the main therapies.

5.2 Eligible Patient Population

The single clinician input stated that there is an unmet need for additional adjuvant treatment options, as currently nivolumab, which is the only adjuvant therapy approved for reimbursement, can only be given to patients with stage IIIB and higher melanoma based on evidence from a randomized control trial comparing nivolumab to ipilimumab. The input stated that the trial comparing pembrolizumab to placebo included stage IIIA patients and above, which increases access to an immunotherapy for all stage III patients considered to be high risk. In addition to showing benefit in the adjuvant setting, the input suggested there is a benefit of pembrolizumab in the neoadjuvant setting for bulky stage III disease for the purpose of shrinking down a tumour for an easier and more successful operation. Both of the clinician inputs referred to an ongoing randomized controlled trial for high risk stage IIC patients for pembrolizumab for adjuvant melanoma, as stage IIC patients were indicated to often do much worse than Stage 3A

patients. However, the data for this trial are not yet mature.

The joint clinician input indicated that they would like to see the inclusion of resected stage IV patients in the funding request, similar to the pCODR review for adjuvant nivolumab in melanoma. The rationale for this inclusion was based on potential discrepancies in eligibility criteria for immunotherapy in the adjuvant setting.

5.3 Relevance to Clinical Practice

Input from the single clinician stated that use of pembrolizumab would occur after surgery in the adjuvant setting for all stage III patients. Once again, it was highlighted that this current indication under review includes stage IIIA patients, who currently are not eligible for adjuvant nivolumab according to reimbursement criteria. Contraindications to pembrolizumab, as to most cancer therapies and which represent a minority of patients, include active auto-immune diseases and poor ECOG status; overall, pembrolizumab was stated to benefit the majority of patients. The option for clinicians to have access to both nivolumab and pembrolizumab was stated as a benefit, though there are no contraindications differing from nivolumab, sometimes a patient who does not respond to nivolumab may respond to pembrolizumab.

Both inputs agreed that pembrolizumab is a very safe and tolerable single agent PD-1 inhibitor; a randomized control trial was referred to as showing significant benefit and reasonable toxicity. The joint clinician input stated that there are data supporting the use of relapsed free survival as a surrogate endpoint for overall survival in melanoma.

5.4 Sequencing and Priority of Treatments with Pembrolizumab

The joint clinician input stated that pembrolizumab would most likely replace interferon or observation and could be used for high and low risk patients regardless of BRAF status. The individual clinician input stated that pembrolizumab may serve as an additional option instead of a replacement. For BRAF-positive patients, the clinician stated potentially starting with a combination of BRAF and MEK inhibitors and switching to pembrolizumab if patients become resistant (or vice versa).

5.5 Companion Diagnostic Testing

Both clinician inputs agreed that testing should not be a consideration in treatment algorithms, and that diagnostic testing is not required for pembrolizumab. The single clinician input stated that it may be useful to determine BRAF status before beginning treatment and the turnaround time for the BRAF testing is approximately two weeks at their centre.

5.6 Implementation Factors

5.6.1 In regards to question 3.4 above, please include considerations for use of BRAF/MEK inhibitors, single agent PD-1 immunotherapy (nivolumab or pembrolizumab), and combination immunotherapy (nivolumab + ipilimumab) for both clinical scenarios of relapse during or after adjuvant pembrolizumab.

5.6.1.1 Please comment on recommended treatment options in the first-line metastatic setting as well as treatment-free interval after completing adjuvant therapy.

In regards to the metastatic setting, the single clinician input indicated that being able to switch to an immunotherapy following treatment with a BRAF and MEK inhibitor combination in the adjuvant setting would be beneficial for durability of response among patients who are rapidly progressing and who are BRAF-positive. The option of switching to

an immunotherapy following treatment with BRAF and MEK inhibitor combination is currently not available in Ontario. In addition, immunotherapy is unavailable for use in the second-line for patients who do not respond to an initial BRAF and MEK inhibitor treatment.

Both inputs agreed that six months or greater was a reasonable treatment free interval after completion of adjuvant treatment. However, it was noted by the joint clinician input that the timeframe would be dependent on a number of factors, including location of relapse, aggressiveness of disease, time to relapse, BRAF status, etc. For patients who relapse later, clinicians would like the option of retreat with pembrolizumab. Patients with visceral metastasis were also stated as another patient group that should be eligible for pembrolizumab retreatment, either as a single agent or in combination with ipilimumab.

5.6.1.2 In what clinical scenarios would nivolumab or pembrolizumab be the preferred treatment option in the adjuvant melanoma setting? Please comment on the preference considering patient preference, efficacy, safety, and administration.

The individual clinician input stated that nivolumab and pembrolizumab are therapeutically equivalent. However, nivolumab may only be given to patients with Stage IIIB disease and above, while pembrolizumab may be given to patients who are Stage IIIA and above. Both clinician inputs agreed that administration of pembrolizumab may be preferential for BRAF wild type patients. It should be noted that BRAF-positive patients can still benefit from either nivolumab or pembrolizumab, as both treatments are safe, efficacious and tolerated; however, the joint clinician input indicated that pembrolizumab may be preferred over nivolumab as the treatment schedule is less frequent at every three weeks compared to every two weeks, respectively.

5.6.1.3 Patients in the KEYNOTE-054 trial were BRAF mutation positive or negative. What would be the preferred treatment for BRAF mutation positive patients in the adjuvant setting (e.g., dabrafenib-trametinib, pembrolizumab, or nivolumab)? Please comment on the preference considering patient preference, efficacy, safety, and administration.

The two clinician inputs had differing opinions about preferred treatment for BRAF-positive patients in the adjuvant setting. The individual clinician input stated that a combination BRAF and MEK inhibitor treatment would be preferred based on a benefit in overall survival. In addition, side effects from a BRAF and MEK inhibitor combination may be reversible, whereas side effects due to immunotherapy may be permanent. The single clinician input also noted that an immunotherapy would then still be an available option for patients who then recur after being treated with a BRAF and MEK inhibitor therapy. The joint clinician input stated that the choice of treatment would be dependent on clinician and patient preferences with consideration of comorbidities. The toxicity of dabrafenib-trametinib was stated to be quite bad by the joint clinician input, making pembrolizumab or nivolumab a preferential option even for BRAF-positive patients. While the clinicians highlighted the lack of direct evidence comparing dabrafenib-trametinib to either pembrolizumab or nivolumab, the joint input suggested that it would be optimal for clinicians to complete treatment with the opposite agent, either pembrolizumab or nivolumab, should treatment with the first agent require stopping due to toxicity in under a year.

5.6.2 The recommended dosing for adjuvant pembrolizumab is 200mg over 30 minutes every 3 weeks for a total of 18 administrations. In the metastatic melanoma setting, a weight-based dose of 2mg/kg up to a cap of 200mg is used.

5.6.2.1 Would it be reasonable for adjuvant pembrolizumab to be administered at a weight-based dosing schedule up to a cap?

5.6.2.2 Administration every 6 weeks rather than 3 weeks?

The joint clinician input stated that it would be reasonable for adjuvant pembrolizumab to be administered at a weight-based dosing schedule up to a cap. They also suggested that an administration schedule every six weeks versus every three weeks may be reasonable if evidence was available to demonstrate the same efficacy and toxicity. The individual clinician input stated they could not reliably answer this question and deferred to the recommendations from studies and the drug company.

5.6.3 Pembrolizumab is recommended for re-treatment of patients whose disease recurred more than 6 months after completing one year of adjuvant pembrolizumab treatment. If adjuvant pembrolizumab was available, in clinical practice:

5.6.3.1 Is this time frame reasonable?

5.6.3.2 Are there instances where these patients should be treated beyond 1 year of treatment?

All clinicians agreed that the timeframe for retreatment with pembrolizumab after six months of completing one year of adjuvant pembrolizumab was reasonable. The joint input highlighted that these patients should still be able to receive a PD-1 inhibitor at a later time. Abridgment with radiation therapy until patients reach the six-month mark (such as with lymphoma) was another option stated by the clinicians.

The input noted that the trial treated patients in the adjuvant setting for one year, and that evidence for treatment beyond this point is not available. Extended treatment may prove to be beneficial; however, it would need to be studied. The joint input stated that eligibility for reimbursement should be specified by number of doses and not by time period. For example, patients who stop treatment due to adverse events should still be able to receive the full course of their treatment regardless of time frame but by number of doses received. The input suggested that criteria in the adjuvant setting should be kept consistent with the metastatic setting

5.6.4 In clinical practice, is there evidence to extend the use of adjuvant pembrolizumab to patients that are disease free following treatment of in-transit metastases, and are node negative?

Both inputs stated that there was available evidence; the joint clinician input noted that these patients were included in the trial.

Input form the individual clinician stated that in-transit metastases are considered Stage III disease, very high risk, and should be offered adjuvant treatment. Patients who are node negative were stated to be potentially even more high risk than node only disease.

Both patients with Stage IIB and Stage IIC disease were stated to be at extremely high risk for metastatic recurrence despite the lack of nodal positivity. A clinical trial currently underway was highlighted by the individual clinician as evaluating whether node negative patients may benefit from adjuvant immunotherapy. The clinician suspected that patients, especially with Stage IIC disease, would benefit.

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the safety and efficacy of adjuvant pembrolizumab in stage III melanoma patients following resection; and in the re-treatment of patients upon loco-regional or distant recurrence more than six months following a completed adjuvant course of pembrolizumab.

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

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

Table 8: 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 pembrolizumab should be included.	Stage III melanoma patients following resection and in the re-treatment of patients upon loco-regional or distant recurrence more than 6 months following a completed adjuvant course of pembrolizumab Subgroups: • Stage of disease • ECOG performance status • Recurrence (distant vs local) • *BRAF* mutation status • Brain metastases[$]	Pembrolizumab monotherapy, 200 mg every 3 weeks for a total of 18 administrations (~1 year)	PD-1 inhibitor: • Nivolumab BRAF and MEK inhibitors: • Dabrafenib and trametinib Other: • Interferon alfa • Observation	Primary • OS • RFS • HRQoL Secondary • ORR** • DOR** • DCR** • PFS** • DMFS Safety • AEs • SAEs • WDAEs • Immune-related AEs • Dose adjustment, interruption and/or discontinuation • Time to discontinuation • Percent who completed treatment

Abbreviations: AE=adverse events; DCR=disease control rate; DMFS = distant metastasis-free survival; DOR=duration of response; HRQoL=Health-related quality of life; ORR=objective response rate; OS = overall survival; PFS=progression-free survival; RCT=randomized controlled trial; RFS = recurrent-free survival; SAE=serious adverse events; WDAE=withdrawals due to adverse events

Notes:

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

[$] This subgroup applies to treatment only

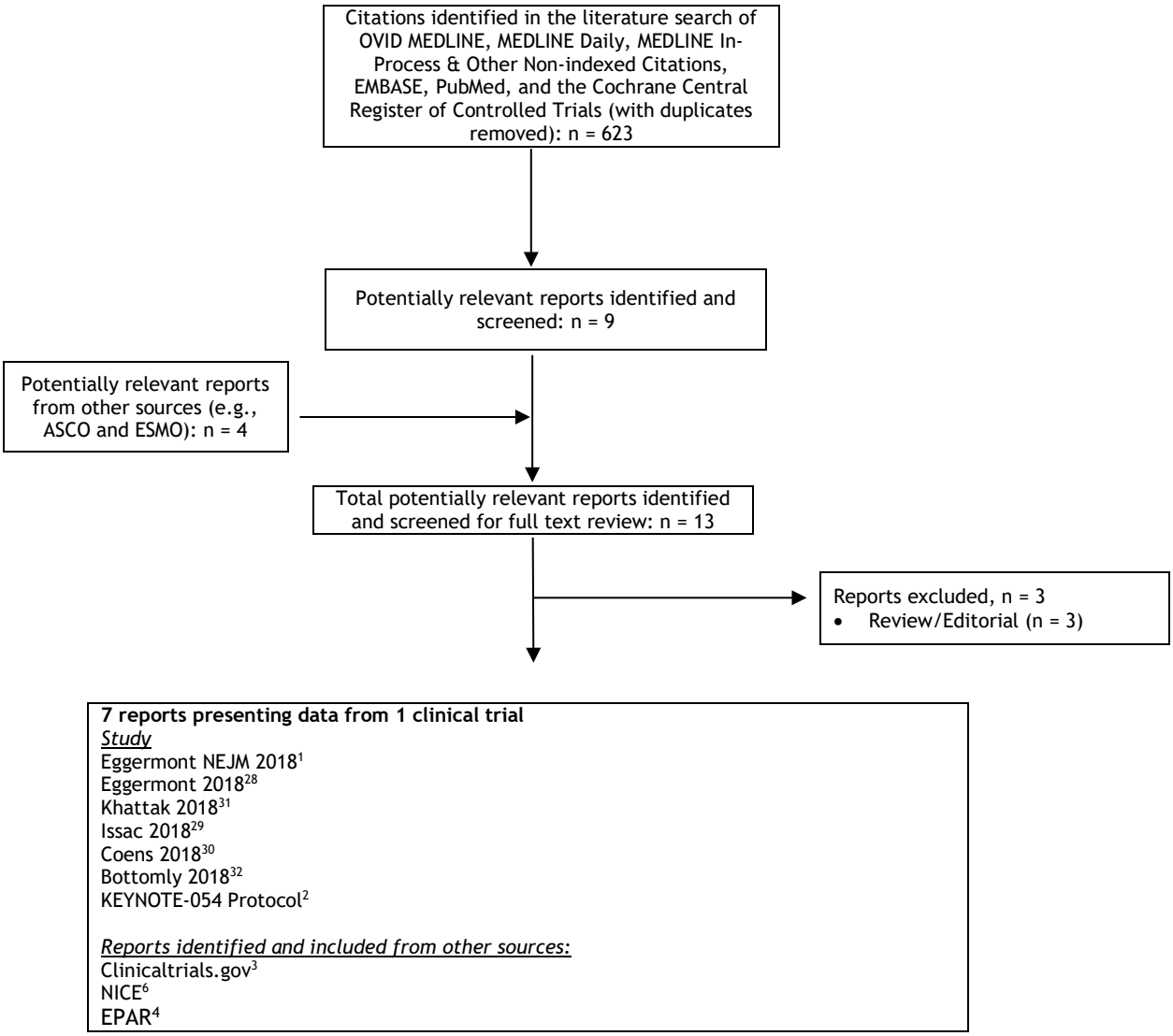
** These outcomes apply to retreatment only.

6.3 Results

6.3.1 Literature Search Results

Of the 633 potentially relevant reports identified, one study (KEYNOTE-054) reported in 10 citations, was included in the pCODR systematic review (Figure 1).[1-4,6,28-32] Three reports were excluded because they were reviews. Additional reports related to the KEYNOTE-054 trial were obtained from the Submitter.[5,8,33,34]

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



Note: Additional data related to the KEYNOTE-054 trial were also obtained through requests to the Submitter by pCODR [Checkpoint Responses[34], Clinical Rationale[33], Indirect Treatment Comparison[8], Health-Related Quality Analysis[5] and the Clinical Summary Report[35]]

6.3.2 Summary of Included Studies

The pCODR systematic review included one randomized controlled trial (RCT), the European Organization for Research and Treatment of Cancer (EORTC) 1325-KEYNOTE-054 trial (referred to as KEYNOTE-054 in this report), which assessed the safety and efficacy of pembrolizumab as an adjuvant therapy in patients with resected, high-risk stage III melanoma.[1] In Part 1 of the trial, a total of 1,019 patients were randomly assigned to receive pembrolizumab at 200 mg every 3 weeks for 18 doses (Q3W, n = 514) or placebo (n = 505). Patients who had documented disease recurrence in Part 1 were eligible to enter Part 2 of the trial. Here, patients who were randomized to receive pembrolizumab could be rechallenged with pembrolizumab while those randomized to placebo could cross-over and receive pembrolizumab.[2] The results of Part 2 are not expected until 31-Jul-2023.[3] Therefore, the focus of this review will be on Part 1 of the trial.

6.3.2.1 Detailed Trial Characteristics

a) Trials

Trial Design

The trial characteristics and select quality characteristics of the KEYNOTE-054 Trial are presented in Tables 9 and 10, respectively.

Table 9: Characteristics of the KEYNOTE-054 trial.

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes

Trial
EORTC-1325/KEYNOTE-054
 	
Other identifiers
NCT02362594
2014-004944-37
 	
Characteristics
Double-blind, placebo-controlled, phase 3 RCT
 	
Sample Size
N= 1019
 	
Number of centres and number of countries
123 centres in 23 countries
 	
Patient Enrolment Dates
August 2015 to November 2016
 	
Data cut-off
October 2, 2017
 	
Final Analysis Date
Trial is ongoing
 	
Funding
Merck
	Key Inclusion Criteria:
	• Complete resection of stage III melanoma (AJCC R0) with histologically confirmed cutaneous melanoma metastatic to lymph node, classified as (AJCC, 2010): stage IIIA with metastasis > 1 mm; any stage IIIB or IIIC. No past or current in-transit metastases or satellitosis. Patient population stage IIIA (> 1 mm metastasis) was capped at a maximum of 20% of the total patient population
	• Tumour tissue available for evaluation of PD-L1 expression
	• ECOG performance status of 0 or 1
	• Adequate organ function
	• The resection of stage III lymph nodes must have been performed in complete compliance with the Criteria for adequate surgical procedures for CLND.[2] This was required documentation in the medical file; patients without documentation of adequate resection were not eligible
	• To be considered as adequate, the surgical and pathological procedures had to include at least the following:
	  ○ Head and neck;
	  ○ Upper extremity
	  ○ Lower extremity
		Part 1 of the trial
		Intervention (Blind)
		Pembrolizumab (200 mg IV Q3W for a total of 18 doses [approximately 1 year])
		
		Versus
		
		Comparator (Blind)
		Saline placebo (IV 0 mg every 3 weeks for a total of 18 doses [approximately 1 year])
		
		Part 2 of the trial
		Intervention (Unblind)
		Pembrolizumab (200 mg IV Q3W for 2 years)
			Primary:
			• RFS
			• RFS in subgroup of patients with PD-L1-positive tumour expression
			
			Secondary:
			• DMFS
			• DMFS in subgroup of patients with PD-L1-positive tumour expression
			• OS
			• OS in subgroup of patients with PD-L1-positive tumour expression
			• Toxicity profile according to CTCAE v. 4.0
			• To evaluate the PK of pembrolizumab
			• To assess for development of ADA
			
			Tertiary:
			• HRQoL
			• Health outcomes evaluation

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
	○ Lymph node dissection for nodal recurrence • The maximum duration from surgery to first study drug treatment was 13 weeks. Treatment started only after complete wound healing from surgery. • Disease status for the post-surgery baseline assessment had to be documented by full Chest/Abdomen/Pelvis CT and/or MRI with Neck CT and/or MRI (for Head and Neck primaries) and complete clinical examination after informed consent and prior to enrollment • Disease-free (no loco-regional relapse or distant metastasis); no clinical evidence for brain metastases • BRAF mutation status (known or not done) • No prior therapy for melanoma except surgery for primary melanoma lesions (or previously treated with interferon for thick primary melanomas without evidence of lymph node involvement were eligible). **Key Exclusion Criteria:** • Mucosal or ocular melanoma • History of (non-infectious) pneumonitis that required steroids or current pneumonitis • History of or current interstitial lung disease • History of hematologic or primary solid tumour malignancy, unless no evidence of that disease for 5 years • Active autoimmune disease that has required systemic treatment in the past 2 years • Active infection requiring therapy • Unstable hyperthyroidism or hypothyroidism • Diagnosis of immunodeficiency • Systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of study medication • Known history of HIV, active Hepatitis B or C • Treatment with live vaccine within 30 days prior to the first dose of study medication are not eligible • Prior treatment with any CTLA4 monoclonal antibody or PD-1, PD-L1, or PD-L2 agent, or prior participation		• To evaluate predictive biomarkers for treatment difference in outcome • PRFS2

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
	in any Merck pembrolizumab clinical trial • Was participating or had participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks of the first dose of study medication		

Abbreviations: ADA = anti-drug antibodies; AJCC = American Joint Committee on Cancer; CLND = complete lymph node dissection; CT = computed tomography; CTLA4 = anti-cytotoxic T-lymphocyte-associated protein 4; CTCAE = Common Terminology Criteria for Adverse Events; DMFS = distant metastases-free survival; ECOG = Eastern Cooperative Oncology Group; HIV = human immunodeficiency virus; HRQoL = health-related quality of life; IV = intravenous; MRI = magnetic resonance imaging; PD-1 = anti-programmed cell death receptor 1; PD-L1 = anti-programmed cell death receptor ligand 1; PD-L2 = anti-programmed cell death receptor ligand 2; PRFS2 = progression/recurrence-free survival 2; PK = pharmacokinetics; OS = overall survival; Q3W = every 3 weeks; RCT = randomized controlled trial; RFS = recurrence free survival.

Table 10: Selected quality characteristics of the KEYNOTE-054 trial.

Study	Treatment vs. Comparator	Primary outcome	Required and final sample size	Randomization method and allocation concealment	Blinding	ITT Analysis	Final analysis	Early termination	Ethics Approval
KEYNOTE-054 Trial	Pembrolizumab versus Placebo [A]	RFS	900[B] 1019	Yes[C]	Yes[D,E]	Yes	No[F]	No	Yes

Abbreviations: ITT - intent-to-treat; **RCT** - randomized controlled trial; **RFS** = recurrence free survival.

[A] In Part 1, patients were randomized to receive (1:1) pembrolizumab or placebo. In Part 2, patients treated with placebo who had documented disease recurrence could cross-over to receive pembrolizumab, and patients treated with pembrolizumab who had documented disease recurrence could continue to receive pembrolizumab.

[B] The power calculation for RFS was based on a sample size of 900 patients. The trial required that 409 events (i.e. recurrence or death) were needed to have 92% power to detect a HR of 0.70 using a one-sided alpha of 0.014.[1]

[C] A centralized interactive voice-response system based on the minimization technique was used to randomize patients. Randomization was stratified by stage of disease (i.e. stage IIIA, stage IIIB, stage IIIC with one to three positive nodes, or stage IIIC with four or more positive nodes) and geographic location (i.e. North America, European countries, Australia and other countries as designated).

[D] KEYNOTE-054 was a double-blind, placebo-controlled, phase 3 RCT. In Part 1, patients, study personal and clinical investigators were blinded to treatment status. However, local pharmacists were aware of treatment assignment. An independent data and safety monitoring committee assessed safety data and the interim analysis of RFS using a random sample of patients in December 2017. The RFS analysis was performed by an independent statistician. Treatment status was unblinded in Part 2.

[E] Patients who had documented disease recurrence in Part 1 of the trial were unblinded and could either continue receiving pembrolizumab or cross-over from placebo and receive pembrolizumab in Part 2 of the trial.

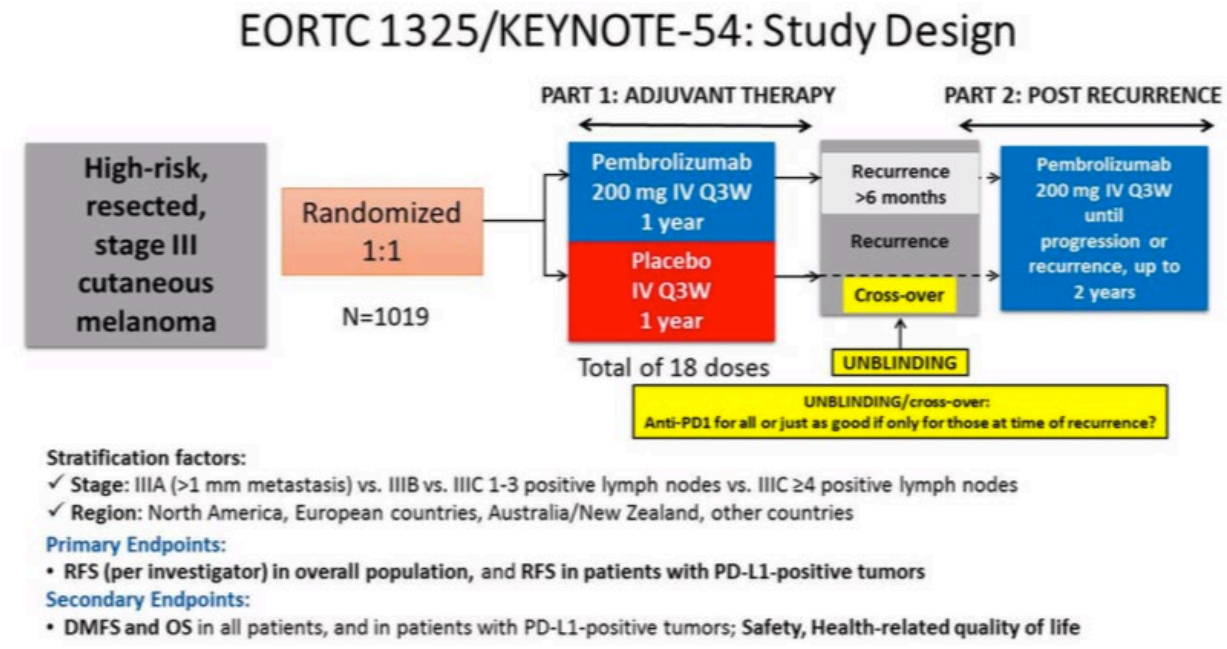
[F] The trial is ongoing and it is expected to be completed on 19-July-2023.[3]

KEYNOTE-054 is an international, placebo-controlled, phase III RCT that assessed the efficacy and safety of adjuvant pembrolizumab as compared to placebo in patients with high-risk, recurrent stage III melanoma. The trial was sponsored by Merck. The trial was conducted in 23 counties at 123 centres, which included: Australia, Austria, Belgium, Canada, Denmark, Finland, France, Germany, Israel, Italy, Japan, Netherlands, New Zealand, Norway, Poland, Portugal, Russia, Serbia, Spain, Sweden, Switzerland, United Kingdom and United States.[6] [redacted] Canadian patients were enrolled in the trial.[33] (*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.*)

Patients were enrolled in the trial if they were at least 18 years of age; had histologically confirmed cutaneous melanoma with metastasis to regional lymph nodes; had either stage IIIA melanoma (i.e. patients with stage N1a melanoma had to have at least one micrometastasis measuring >1 mm in greatest diameter), stage IIIB or IIIC disease with no in-transit metastases as defined by the American Joint Committee on Cancer (AJCC) 2009 classification, 7th edition; and had a complete regional lymphadenectomy within 13 weeks before the start of treatment. Patients were excluded from the trial if they had an Eastern Cooperative Oncology Group (ECOG) performance status score of more than 1; autoimmune disease; uncontrolled infections; use of systemic glucocorticoids; and previous systemic therapy for melanoma.[2] Further details are reported in Table 9.

Although melanoma is currently staged using the 8th edition of the AJCC classification (2017), patients were classified using the 7th edition of the AJCC (2009) in the KEYNOTE-054 trial.[1] One of the changes made in the 8th edition of the AJCC classification was to include an additional subgroup, stage IIID, to the stage III grouping. However, the addition of the fourth subgroup should not impact the results of the KEYNOTE-054 trial because only patients with stage IIIA, stage IIIB or IIIC melanoma with no in-transit metastases were enrolled in the trial.[33]

Figure 2: Study Design of the KEYNOTE-054 Trial.



Data Source: Eggermont 2018[1] From The New England Journal of Medicine, Eggermont et al., Adjuvant Pembrolizumab versus Placebo in Resected Stage III Melanoma, 378:1789-1801. © 2018 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

Figure 2 represents the study design of the KEYNOTE-054 trial. Prior to enrollment, patients were required to provide a sample of resected tumour material in order to evaluate PD-L1 expression. Patients were randomized using a central computerized interactive voice and web response system in a 1:1 ratio to receive either pembrolizumab or placebo. Randomization was stratified by stage (IIIA [>1 mm metastasis] vs. IIIB vs. IIIC 1-3 positive lymph nodes vs. IIIC ≥ 4 positive lymph nodes) and region (North America, European countries, Australia and other countries as designated). Patients, study personnel and clinical investigators were blinded to treatment status; whereas, local pharmacists were aware of treatment assignment. Patients in Part 1 were unblinded upon disease recurrence or if any safety issues developed.[2]

Patients were assessed for recurrence every 12 weeks with computed tomography and/or magnetic imaging for the first two years, then every six months through year five, and then every year thereafter. Withdrawal criteria for Part 1 were disease recurrence, completion of assigned regimen, adverse events (AEs), noncompliance, termination of the study, opinion of the Study Investigator, the patient or the legal representative.

Statistical Analysis

Endpoints: The primary endpoints in the KEYNOTE-054 trial were recurrence-free survival (RFS) and RFS in the subgroup of trial patients with PD-L1 positive tumour expression.[2] Secondary outcomes were distant metastases-free survival (DMFS), DMFS in the PD-L1-positive subgroup, overall survival (OS), OS in the PD-L1-positive subgroup and the pharmacokinetics of pembrolizumab. Exploratory outcomes were health-related quality of life (HRQoL), health outcomes evaluation, predictive biomarkers and progression or recurrence-free survival 2 (PRFS2).

Analysis Populations: The trial was composed of two analysis populations, which includes the intention-to-treat (ITT) population and the safety set population.[2] The ITT population was composed of all randomized patients regardless of the actual treatment they received and all efficacy analyses were performed in this patient population. The second analysis population was the safety set population and it was composed of all patients that received at least one dose of the study drug.[2]

Power: The power calculation for RFS was based on a sample size of 900 patients. The trial specified 409 events (i.e. recurrence or death) were required to have 92% power to detect a hazard ratio (HR) of 0.70 using a one-sided alpha of 0.014.[2] The HR corresponds to a one-year RFS rate of 58.3% in the placebo group and 68.5% in the pembrolizumab group or a three-year RFS rate of 35.3% in the placebo group and 48.3% in the pembrolizumab group.[1,2] Eggermont et al (2018) stated that if the analysis comparing the effect of pembrolizumab relative to placebo on RFS was statistically significant then the subgroup analysis comparing the treatment effect on RFS stratified by PD-L1 expression levels could be performed using a one-sided alpha of 2.5%.[1] Additionally, it was stated that a hierarchical testing approach would also be applied to all subsequent analyses of DMFS and OS.[1,2]

Interim Analysis: Initially, the trial was not designed to perform an interim analysis.[7] However, a protocol amendment on 02-October-2017 permitted an interim analysis to be performed when 330 RFS events had occurred.[7] The European Medicines Agency (EMA) requested that the Submitter perform an updated analysis of RFS at 02-May-2018, which represents seven additional months of follow-up after the 02-October-2017 data cut-off.[4]

b) Populations

A total of 1,019 patients with resected stage IIIA, IIIB and IIIC melanoma were included in the KEYNOTE-054 trial. Five hundred and fourteen patients were randomized to the pembrolizumab group and 505 patients were randomized to the placebo group. Baseline characteristics are presented in Table 11. The majority of patients in the trial were male (61.6%), stage IIIB (45.8%) and had positive PD-L1 expression (83.8%).

Table 11: Baseline characteristics of patients enrolled in the KEYNOTE-054 trial.

Characteristic	Pembrolizumab (N = 514)	Placebo (N = 505)
Sex — no. (%)		
Male	324 (63.0)	304 (60.2)
Female	190 (37.0)	201 (39.8)
Age		
Median (range) — yr	54 (19–88)	54 (19–83)
<50 yr — no. (%)	193 (37.5)	186 (36.8)
50 to <65 yr — no. (%)	196 (38.1)	193 (38.2)
≥65 yr — no. (%)	125 (24.3)	126 (25.0)
Body-mass index — no./total no. (%)		
<25	155/501 (30.9)	184/501 (36.7)
25 to <30	224/501 (44.7)	194/501 (38.7)
≥30	122/501 (24.4)	123/501 (24.6)
Disease stage — no. (%)		
At randomization		
Stage IIIA	80 (15.6)	80 (15.8)
Stage IIIB	237 (46.1)	230 (45.5)
Stage IIIC with 1–3 positive lymph nodes	95 (18.5)	93 (18.4)
Stage IIIC with ≥4 positive lymph nodes	102 (19.8)	102 (20.2)
According to AJCC 2009 criteria†		
Stage IIIA	77 (15.0)	76 (15.0)
Stage IIIB	240 (46.7)	232 (45.9)
Stage IIIC with 1–3 positive lymph nodes‡	87 (16.9)	95 (18.8)
Stage IIIC with ≥4 positive lymph nodes§	110 (21.4)	102 (20.2)
Type of lymph node involvement — no. (%)†		
Microscopic	187 (36.4)	161 (31.9)
Macroscopic	327 (63.6)	344 (68.1)
No of positive lymph nodes on pathological testing — no. (%)†		
1	227 (44.2)	237 (46.9)
2 or 3‡	177 (34.4)	166 (32.9)
≥4§	110 (21.4)	102 (20.2)
Ulceration — no. (%)†		
Yes	208 (40.5)	197 (39.0)
No	230 (44.7)	251 (49.7)
Unknown	76 (14.8)	57 (11.3)
PD-L1 expression status — no. (%)¶		
Positive	428 (83.3)	425 (84.2)
Negative	59 (11.5)	57 (11.3)
Indeterminate	27 (5.3)	23 (4.6)
BRAF mutation status — no. (%)		
Wild type	233 (45.3)	214 (42.4)
V600E or V600K mutation	210 (40.9)	231 (45.7)
Other mutation	35 (6.8)	31 (6.1)
Unknown	36 (7.0)	29 (5.7)

* There were no significant between-group differences in the characteristics listed here. Percentages may not total 100 because of rounding. AJCC denotes American Joint Committee on Cancer 2009 classification, 7th edition.[14]
† Data were from electronic case-report forms.
‡ One patient with in-transit metastases or satellites and without metastatic nodes was included in this subgroup.
§ This subgroup also included 11 patients with matted nodes as well as 5 patients with in-transit metastases or satellites and at least one positive lymph node.
¶ Membranous expression of programmed death ligand 1 (PD-L1) in tumor and tumor-associated immune cells was assessed by means of a 22C3 antibody assay and was scored on a scale of 0 to 5 (with higher scores reflecting a higher level of expression); a score 2 or higher (i.e., staining on >1% of cells) was considered to indicate PD-L1 positivity.

Data Source: Eggermont 2018[1] From The New England Journal of Medicine, Eggermont et al., Adjuvant Pembrolizumab versus Placebo in Resected Stage III Melanoma, 378:1789-1801. © 2018 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

c) Interventions

Treatment Dosing Schedule
In Part 1 of the study, patients randomized to the pembrolizumab group received a 200 mg dose every three weeks (Q3W) while those in the placebo group received a 200 mg dose of saline solution Q3W. The saline solution was prepared by a local pharmacist and it was dosed and administered in the same manner as pembrolizumab.[2] Patients received 18 doses of either treatment for approximately one year or until disease recurrence, unacceptable toxic effects, a major protocol violation or if consent was withdrawn.

Dose delays, reductions or modifications
Dose delays were permitted for medical or surgical events or for reasons not related to the study therapy. Patients were required to be placed back on their assigned therapy within three weeks of the scheduled interruption or unless otherwise specified by the Study Investigator.[2]

Dose reductions were not allowed during the trial.[2]

It was stated in the trial protocol that pembrolizumab was withheld if any drug-related toxicities and severe or life-threatening AEs occurred.[2] Table 12 describes the dose modifications for treatment-related AEs.

Table 12: Dose modification guidelines for drug-related adverse events in the KEYNOTE-054 trial.

Table 1: Dose Modification Guidelines for Drug-Related Adverse Events

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Treatment Discontinuation
Diarrhea/Colitis	2-3	Toxicity resolves to Grade 0-1.	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue
AST, ALT, or Increased Bilirubin	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose.
	3-4	Permanently discontinue (see exception below)1	Permanently discontinue
Type 1 diabetes mellitus (if new onset) or Hyperglycemia	T1DM or 3-4	Hold pembrolizumab for new onset Type 1 diabetes mellitus or Grade 3-4 hyperglycemia associated with evidence of beta cell failure.	Resume pembrolizumab when patients are clinically and metabolically stable.
Hypophysitis	2-4	Toxicity resolves to Grade 0-1. Therapy with pembrolizumab can be continued while endocrine replacement therapy is instituted	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
Hyperthyroidism	3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue
Hypothyroidi		Therapy with pembrolizumab	Therapy with pembrolizumab can be continued

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Treatment Discontinuation
sm		can be continued while thyroid replacement therapy is instituted	while thyroid replacement therapy is instituted.
Infusion Reaction	3-4	Permanently discontinue	Permanently discontinue
Pneumonitis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	3-4	Permanently discontinue	Permanently discontinue
Renal Failure or Nephritis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	3-4	Permanently discontinue	Permanently discontinue
All Other Drug-Related Toxicity2	3 or Severe	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue

Note: Permanently discontinue for any severe or Grade 3 drug-related AE that recurs or any life-threatening event.

1 For patients with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by greater than or equal to 50% relative to baseline and lasts for at least 1 week then patients should be discontinued.

2 Patients with intolerable or persistent Grade 2 drug-related AE may hold study medication at physician discretion. Permanently discontinue study drug for persistent Grade 2 adverse reactions for which treatment with study drug has been held, that do not recover to Grade 0-1 within 12 weeks of the last dose.

Data source: KEYNOTE-054 trial protocol.[2] From The New England Journal of Medicine, Eggermont et al., Adjuvant Pembrolizumab versus Placebo in Resected Stage III Melanoma, 378:1789-1801. © 2018 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

d) Patient Disposition

The disposition of patients through the KEYNOTE-054 trial is presented in Figure 3. A total of 1,019 patients were randomized to receive either pembrolizumab (N = 514) or placebo (N = 505).[1] In the pembrolizumab group, 1.0% of patients did not receive their assigned treatment because three patients withdrew consent, one was not eligible and one had another reason.[1] In the placebo group, 0.6% of patients did not receive their assigned therapy because two patients withdrew consent and one had early progression.[1]

At the 02-October-2017 data cut-off, 3.7% of patients (N = 19) were still receiving pembrolizumab and 1.2% of patients were still receiving placebo (N= 6).[1] In the pembrolizumab group, 55.4% of patients completed their assigned treatment (N = 282) while 40.9% discontinued their therapy (N=208). The most common reasons for discontinuation among those in the pembrolizumab group were recurrence (52.4%; N=109), AEs (33.7%; N = 70), withdrawing after consultation with a physician (8.7%; N = 18), nonadherence or other reasons (3.4%; N=7) and other cancer (1.9%; N=4). In the placebo group, 58.6% of patients completed their assigned treatment (N = 294) while 40.2% discontinued their assigned therapy (N=202).[1] The most common reasons for discontinuation among those in the placebo group were recurrence (88.6%; N=179), AEs (5.4%; N = 11), withdrawing after consultation with a physician (3.0%; N = 6), other cancer (2.0%; N=4), recurrence or other cancer (0.5%; N=1) and other cancer (0.5%; N=1).

As of the 02-October-2017 data cut-off date, 109 (21.6%) of the 505 patients initially assigned to placebo crossed over into Part 2 of the trial and received pembrolizumab.[4] In contrast, one patient (0.2%) of the 514 patients initially assigned to intervention group was rechallenged with pembrolizumab.[4]

Figure 3: Disposition of patients enrolled in the KEYNOTE-054 trial (02-October-2017 data cut-off).

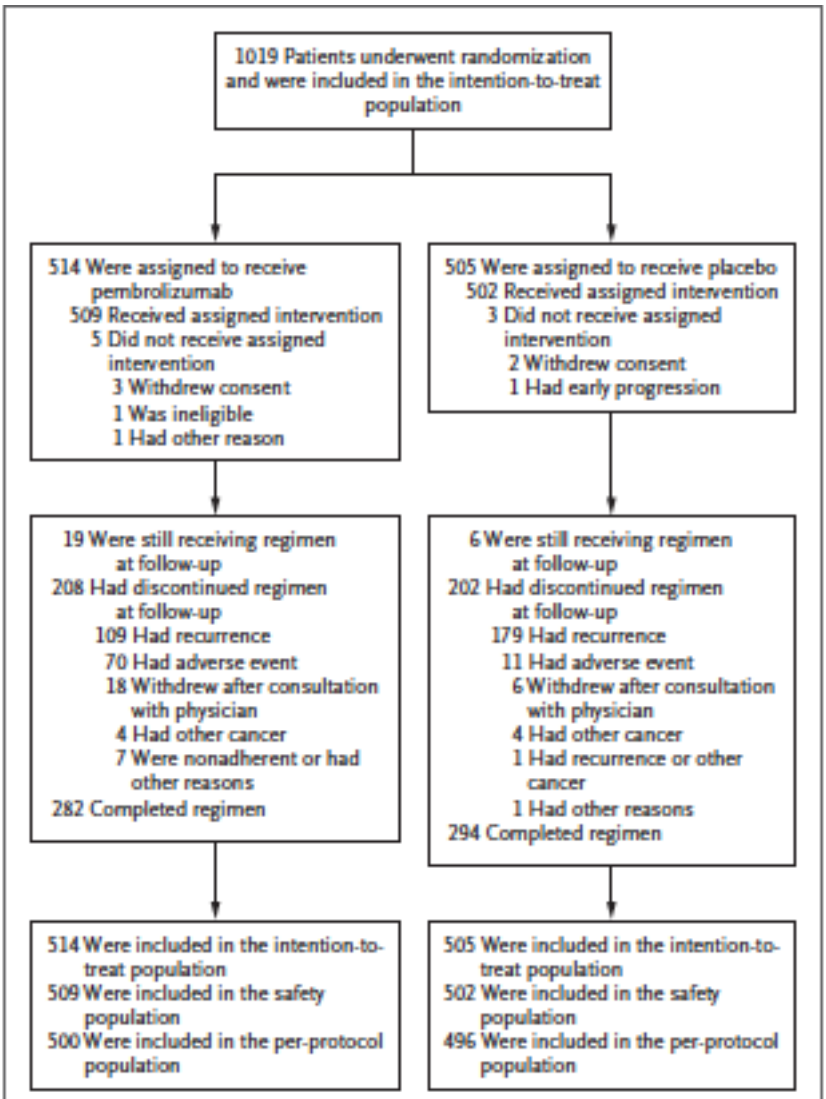


Figure 1. Enrollment, Randomization, and Follow-up.

The intention-to-treat population included all patients who underwent randomization. The safety population included all patients who started the trial regimen to which they had been randomly assigned. The per-protocol population included all eligible patients (i.e., those who did not have a major violation of eligibility criteria) who started the trial regimen to which they had been randomly assigned. In total, 10 patients in the pembrolizumab group (9 of whom started treatment) and 6 patients in the placebo group were found to have major eligibility violations.

Data Source: Eggermont 2018 NEJM.[1] From The New England Journal of Medicine, Eggermont et al., Adjuvant Pembrolizumab versus Placebo in Resected Stage III Melanoma, 378:1789-1801. © 2018 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

e) Limitations/Sources of Bias

Overall, the KEYNOTE-054 trial was a well-designed trial of high quality. However, there are a few limitations that should be taken into consideration, more specifically:

- In addition to being the primary endpoint in the KEYNOTE-054 trial, RFS acts a surrogate outcome for OS. It is necessary to use a surrogate outcome in Part 1 of the KEYNOTE-054 trial because there are no available data on OS. Suciu et al (2018) conducted a study that assessed whether RFS was a valid surrogate outcome for OS in patients with resected stage II to III melanoma.[7] The authors demonstrated that a HR for RFS of 0.77 or less would predict a treatment impact on OS using individual patient data from 11 trials comparing the effect of IFN to observation, two trials comparing IFN to vaccination and one RCT comparing ipilimumab to placebo. The use of RFS as a valid surrogate endpoint for OS in melanoma patients has also been supported by the European Society for Medical Oncology "Magnitude of Clinical Benefit Scale" (ESMO-MCBS).[36,37] Although RFS has been shown to be a valid surrogate outcome for OS, the effect of pembrolizumab as compared to placebo on OS is still unknown.

- The reimbursement request for this review was adjuvant pembrolizumab in stage III melanoma patients following resection and in the retreatment of patients upon loco-regional or distant recurrence more than six months following a completed adjuvant course of pembrolizumab. For this review, our systematic review identified one RCT to provide evidence establishing the efficacy and safety of adjuvant pembrolizumab in patients with stage III melanoma following resection (Part 1 of the KEYNOTE-054 trial). However, we were unable to identify any published RCTs that assessed the retreatment of patients upon loco-regional or distant recurrence more than six months following completed adjuvant course of pembrolizumab. Although evidence from Part 2 of the KEYNOTE-054 may be able to address the efficacy of retreatment with pembrolizumab in the adjuvant setting, the results will not be available until 31-July-2023. Given the current lack of evidence, the Submitter has proposed using the results from the KEYNOTE-006 trial as a "proof-of-concept".[27] The KEYNOTE-006 trial was a phase III RCT that compared the effect of pembrolizumab and ipilimumab on PFS and OS in 834 patients with advanced melanoma. The Submitter states that the results of this trial demonstrate anti-tumour activity upon re-exposure to pembrolizumab. However, due to differences in patient populations, the results of KEYNOTE-006 may not be directly applicable to the adjuvant setting.

- The KEYNOTE-054 trial assessed the effect of adjuvant pembrolizumab compared to placebo. Other potentially relevant comparators were not assessed in this trial (i.e. nivolumab or dabrafenib combined with trametinib). Of note, the Submitter provided an unpublished network meta-analysis (NMA), which indirectly compares pembrolizumab to other comparators including observation, peginterferon alfa-2b (PEG-IFN α-2b), interferon alfa-2b (IFN α-2b) (12 months) and IFN α-2b (24 months). A summary and critical appraisal of the NMA is available in section 7 of this report.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

Efficacy Outcomes

Efficacy analyses were performed in the ITT patient population (N = 1,019) using the 02-October-2017 data-cut off.[1] This data cut-off represents the final efficacy analysis from the primary outcome. The median follow-up was 15.1 months for all patients, 14.7 months in the pembrolizumab group and 15.4 months in the placebo group.[1]

Overall Survival

OS was a secondary outcome in the trial. It was defined as the time from randomization to the date of death.[2] OS estimates were not reported for the 02-October-2017 data cut-off.[1]

Recurrence-Free Survival

Intention-to-treat population

The primary outcome in the trial was RFS. It was defined as the time between randomization and first recurrence (i.e. local, regional or distant metastasis) or death.[2] The definitions of local, regional or distant metastases are provided in Table 13. The RFS curves were estimated using the Kaplain-Meier method and treatment differences were determined using a log-rank test stratified according to disease stage at randomization, at a two-sided alpha level.[1] Additionally, Cox proportional hazard models stratified by disease stage with Efron's method of tie handling were used to calculate HRs with corresponding 98.4% confidence intervals (CIs).[2] A 98.4% CI was used for the ITT analysis because a Lan-DeMets alpha spending function with O'Brien-Fleming stopping rules was applied at the interim analysis.

Table 13: Definitions of local, regional and distant metastases used in the KEYNOTE-054 trial.

Recurrence	Definition
Local recurrence	• Occurs within 2 cm of the tumour bed and must be confirmed either by histology or cytology. • Local recurrence after adequate surgical excision of the primary melanoma is associated with aggressive tumour biologic features and is frequently a harbinger of metastases.
Regional lymphatic and nodal recurrence	• Should be confirmed by histology or cytology. • In transit metastases: defined by the AJCC as any skin or subcutaneous metastases that are more than 2 cm from the primary lesion but not beyond the regional nodal basin. • Regional Nodal Recurrences: Regional nodal failure in a previously dissected basin is usually found at the periphery of the prior surgical procedure.
Distant recurrence	• Patterns of Metastases: Most common sites are non-visceral (i.e., skin, subcutaneous tissue, and lymph nodes) and visceral (i.e. lung, brain, liver, gastrointestinal tract, and bone). • Measurable disease: presence of at least one measurable lesion. • Non-measurable lesions: all other lesions, including small lesions (< 10 mm with spiral CT scan) and other non-measurable lesions.
Abbreviations: AJCC = American Joint Committee on Cancer; CT = computerized tomography. Data Source: Eggermont 2018 NEJM Protocol[2]	

The 12-month RFS rate was higher in the pembrolizumab group (75.4%, 95% CI: 71.3 to 78.9) as compared to the placebo group (61.0%, 95% CI: 56.5 to 65.1).[1] Similar results were observed for the 18-month RFS rate (pembrolizumab: 71.4% [95% CI: 66.8 to 75.4] versus placebo: 53.2% [95% CI: 47.9 to 58.2]).[1]

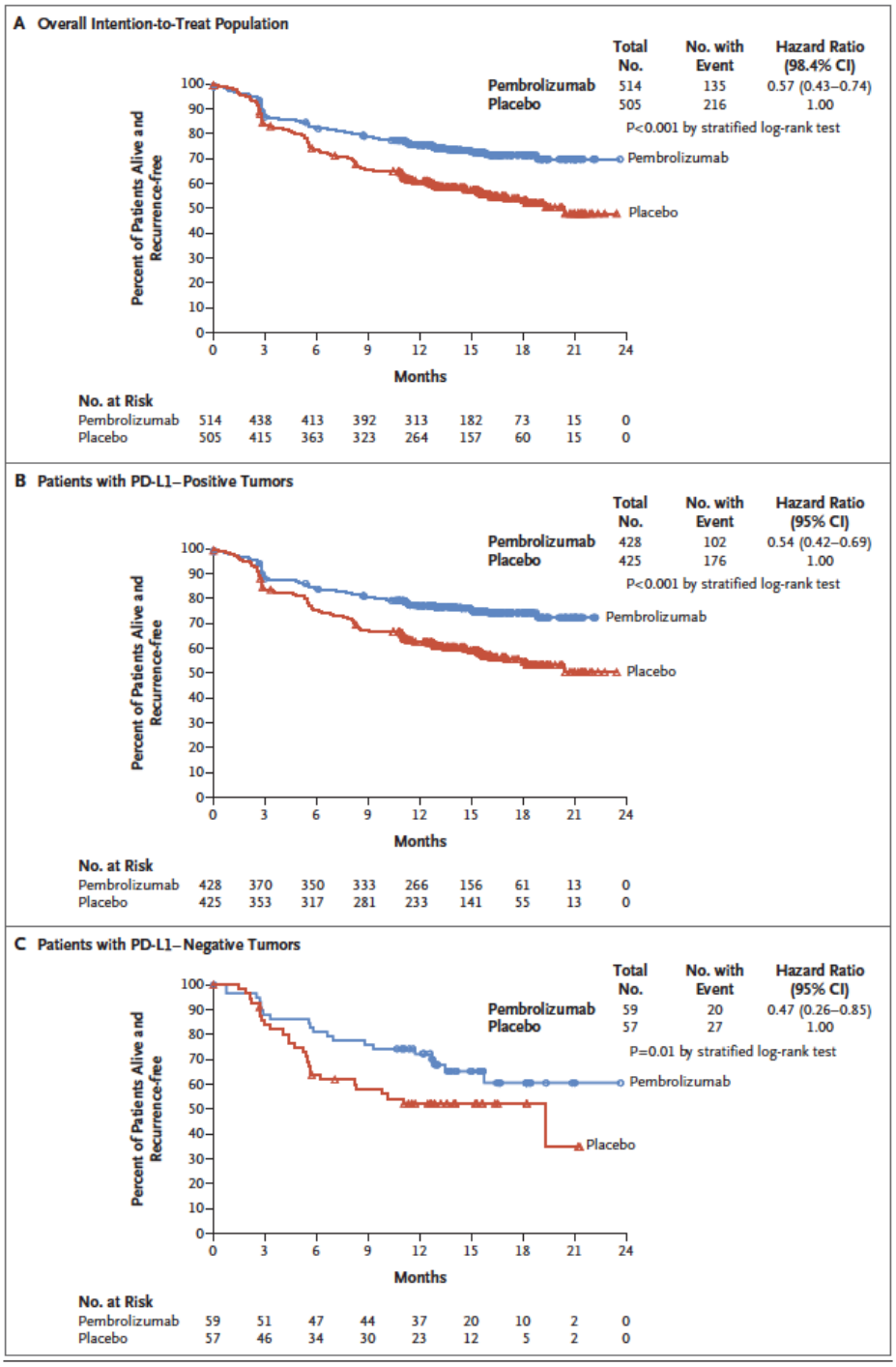
Table 14: Number of RFS events as assessed by local investigators for all patients in the ITT population.

Number of Events (%)	Pembrolizumab (N = 514)	Placebo (N = 505)	Total (N=1019)
Total Number of Events	**135 (26.3)**	**216 (42.8)**	**351 (34.4)**
Loco-regional recurrences	55 (10.7)	77 (15.2)	132 (13.0)
Distant metastases	69 (13.4)	114 (22.6)	183 (18.0)
Concomitant loco-regional and distant metastases	9 (1.8)	24 (4.8)	33 (3.2)
Deaths	2 (0.4)	1 (0.2)	3 (0.3)
No Events	**379 (73.7)**	**289 (57.2)**	**668 (65.6)**
Total	**514 (100)**	**505 (100)**	**1019 (100)**

Data Source: Eggermont et al (2018) NEJM[1]

At the 02-October-2017 data cut off, 135 patients in the pembrolizumab group had first recurrence of disease or died as compared to 216 patients in the placebo group (Table 14). The median RFS in the pembrolizumab group was not reached (Not Reached (NR), 95% CI: NR to NR) and it was 20.4 months (95% CI: 16.2, NR) in the placebo group.[35] Eggermont et al (2018) reported that treatment with pembrolizumab was associated with statistically significant prolonged RFS as compared to placebo (HR: 0.57, 98.4% CI: 0.43 to 0.74; p=0.0001).[1] The Kaplan-Meier curves for RFS are presented in Figure 4.

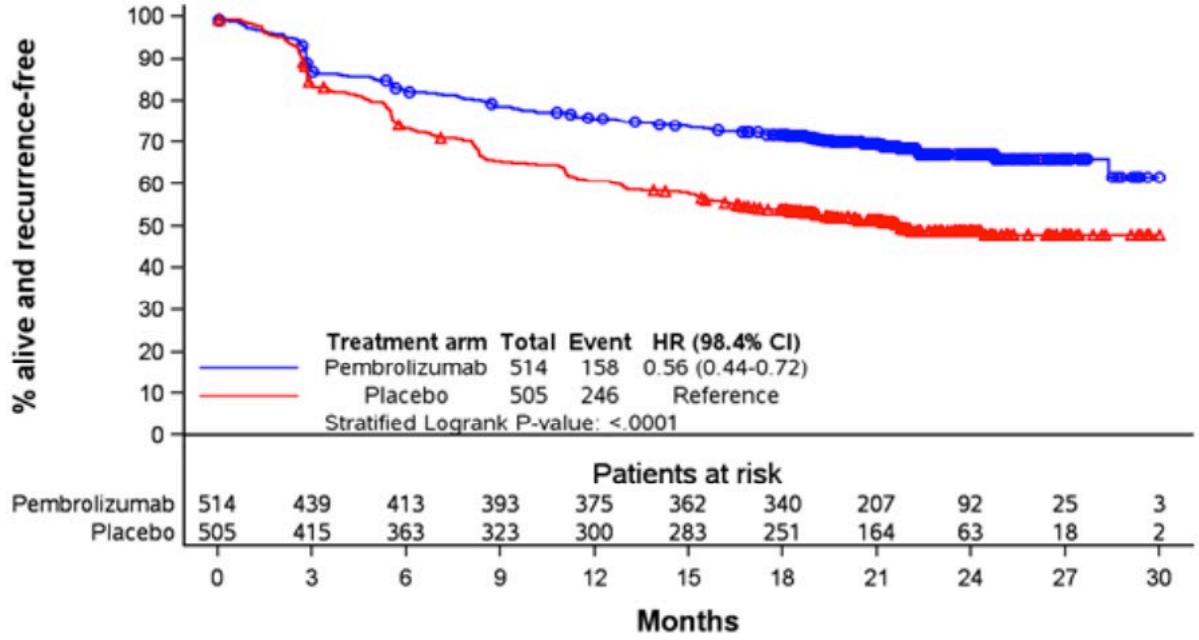
Figure 4: Kaplan-Meier survival curves for RFS as assessed by local investigators for all patients in the ITT population and stratified by PD-L1 at the 02-October-2017 data cut off.



Data Source: Eggermont 2018[1] From The New England Journal of Medicine, Eggermont et al., Adjuvant Pembrolizumab versus Placebo in Resected Stage III Melanoma, 378:1789-1801. © 2018 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

The EMA also requested the Submitter perform an updated analysis of RFS, which was performed based on a data cut-off date of 02-May-2018 and represents a median follow-up of 21.6 months.[4] At the updated data cut-off, 404 events had occurred in the trial, with 30.7% in the pembrolizumab group and 48.7% in the placebo group.[4] The Kaplan-Meier curves for RFS are presented in Figure 5. The median RFS was not reached in the pembrolizumab group (NR, 95% CI: NR to NR) and was 21.7 months (95% CI: 17.1 to NR) in the placebo group.[4] The magnitude of the treatment benefit was sustained at longer follow-up, with pembrolizumab associated with a prolonged RFS as compared to placebo (HR: 0.56, 98.4% CI: 0.44 to 0.72; p<0.0001).[4]

Figure 5: Kaplan-Meier survival curves for RFS as assessed by local investigators for all patients in the ITT population at the 02-May-2018 data cut-off.



Data Source: EMA Report[4]

The EMA reported the additional treatments that patients received after a first recurrence at the 02-May-2018 data cut-off.[4] The results are presented in Table 15. The Submitter noted that surgery was allowed prior to patients enrolling into Part 2 of the trial. Almost 46% percent of patients in the pembrolizumab group (46.2%) had surgery for melanoma versus 38.8% patients in the placebo group.[4] Therefore, patients with loco-regional recurrence may have had complete resection of disease before entering Part 2 of the study.[34] More patients in the pembrolizumab group received anti-CLTA4 agents as compared to placebo (28.2% versus 21.2%) while a similar proportion of patients in the pembrolizumab and placebo groups received BRAF/MEK-inhibitors (28.2% versus 26.1%).[4] However, more patients in the placebo group received an anti-PD-1/anti-PD-L1 therapy as compared to those in the pembrolizumab group (29.5% versus 78.8%).[4]

Table 15: Additional treatments after first recurrence at the 02-May-2018 data cut-off.

	Treatment arm		
	Pembrolizumab (N=156)	Placebo (N=245)	Total (N=401)
Type of additional treatment	N (%)	N (%)	N (%)
Surgery for melanoma under study			
No	84 (53.8)	150 (61.2)	234 (58.4)
Yes	72 (46.2)	95 (38.8)	167 (41.6)
Radiotherapy			
No	119 (76.3)	183 (74.7)	302 (75.3)
Yes	37 (23.7)	62 (25.3)	99 (24.7)
Chemotherapy			
No	144 (92.3)	232 (94.7)	376 (93.8)
Yes	12 (7.7)	13 (5.3)	25 (6.2)
BRAF/MEK-inhibitors			
No	112 (71.8)	181 (73.9)	293 (73.1)
Yes	44 (28.2)	64 (26.1)	108 (26.9)
Anti-CTLA4			
No	112 (71.8)	193 (78.8)	305 (76.1)
Yes	44 (28.2)	52 (21.2)	96 (23.9)
Anti-PD-1 / Anti-PD-L1			
No	110 (70.5)	52 (21.2)	162 (40.4)
Yes	46 (29.5)	193 (78.8)	239 (59.6)
Other targeted agents			
No	155 (99.4)	240 (98.0)	395 (98.5)
Yes	1 (0.6)	5 (2.0)	6 (1.5)
Other systemic immunotherapy			
No	149 (95.5)	231 (94.3)	380 (94.8)
Yes	7 (4.5)	14 (5.7)	21 (5.2)
Other systemic therapy			
No	154 (98.7)	244 (99.6)	398 (99.3)
Yes	2 (1.3)	1 (0.4)	3 (0.7)

Data source: EMA Report[4]

PD-L1 status subgroups

The authors also performed pre-specified subgroup analysis that assessed the effect of PD-L1 status on RFS.[1] Since the ITT analysis of RFS was significant, the authors used a one-sided alpha of 0.025 to test the hypothesis in the PD-L1 positive population.[2] The subgroup analyses were reported using a 95% CI.[2] It should be noted that the subgroup analysis was not pre-specified in the PD-L1 negative population.[4]

PD-L1 was assessed using a 22C3 antibody assay and it was scored on a scale of 0 to 5, where higher scores reflect a higher level of expression.[1] Positive PD-L1 status was defined as a score of 2 or higher (i.e. staining on >1% of cells). Overall, more patients had a positive PD-L1 tumour (83.7%; N=853) in the KEYNOTE-054 trial than a negative PD-L1 tumour (11.4%; N=116) or an indeterminate tumour (4.9%; N=50).[1]

The Kaplain-Meier curves for patients with PD-L1 positive and negative tumours are presented in Figure 4. Among patients with a positive PD-L1 tumour, the 12-month RFS rate was higher in the

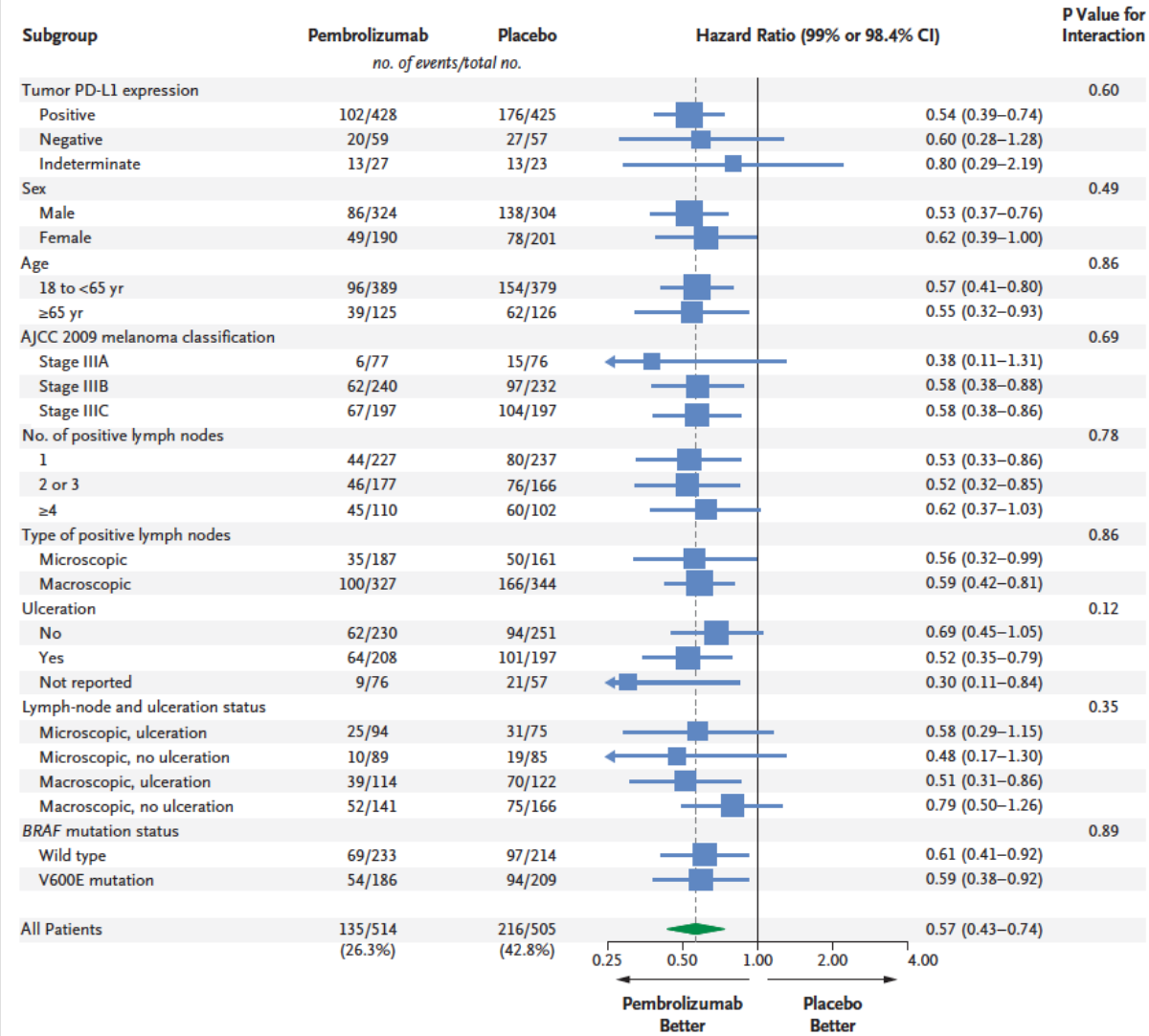
pembrolizumab group (77.1%, 95% CI: 72.7 to 80.9) as compared to the placebo group (62.6%, 95% CI: 57.7 to 67.0).[1] Eggermont et al (2018) reported that treatment with pembrolizumab was associated with a prolonged RFS as compared to placebo in patients with a positive PD-L1 tumour (HR: 0.54, 95% CI: 0.42 to 0.69; P<0.001).[1] Similar results were reported for those with a negative PD-L1 tumour (HR: 0.47, 95% CI: 0.26 to 0.85; p=0.01) but there was no significant difference among those with an indeterminate PD-L1 tumour (HR: 0.88, 95% CI: 0.29 to 2.72, p=0.7709).[1] Eggermont et al (2018) conducted an exploratory univariate subgroup analysis between PD-L1 expression levels and treatment status. The authors reported that the protective effect of pembrolizumab relative to placebo on RFS was similar for patients with a positive PD-L1 tumour, a negative PD-L1 tumour and an intermediate PD-L1 tumour (p for interaction: 0.60).[1] However, this was an exploratory analysis and the results should be interpreted with caution.

Exploratory subgroups

The authors also conducted exploratory subgroup analyses where they assessed the effect of other predictive factors on RFS (Figure 6). For the subgroup analysis, a univariate Cox regression model tested the interaction between predictive factors and treatment groups. The HR with corresponding 99% CI was reported. However, it was noted in the protocol that the subgroup analysis was hypothesis-generating and it is limited by low power.[2] Therefore, the results should be interpreted with caution.

During the pCODR protocol development, the Clinical Guidance Panel (CGP) identified several subgroups of interest, which include: stage of disease, ECOG performance status, recurrence (distant versus local), BRAF mutation status and brain metastases. Among the identified subgroups of interest, Eggermont et al (2018) reported the subgroup analysis that tested the effect of BRAF mutation status and treatment group on RFS.[1] The authors reported that the protective effect of pembrolizumab relative to placebo on RFS was similar for patients with wild type BRAF mutations and V600E BRAF mutations (p for interaction: 0.89).[1]

Figure 6: Subgroup analyses of predictive factors on the effect of RFS for all patients in the ITT population.



Subgroup	Pembrolizumab	Placebo	Hazard Ratio (99% or 98.4% CI)	P Value for Interaction
	no. of events/total no.			
Tumor PD-L1 expression				0.60
Positive	102/428	176/425	0.54 (0.39–0.74)	
Negative	20/59	27/57	0.60 (0.28–1.28)	
Indeterminate	13/27	13/23	0.80 (0.29–2.19)	
Sex				0.49
Male	86/324	138/304	0.53 (0.37–0.76)	
Female	49/190	78/201	0.62 (0.39–1.00)	
Age				0.86
18 to <65 yr	96/389	154/379	0.57 (0.41–0.80)	
≥65 yr	39/125	62/126	0.55 (0.32–0.93)	
AJCC 2009 melanoma classification				0.69
Stage IIIA	6/77	15/76	0.38 (0.11–1.31)	
Stage IIIB	62/240	97/232	0.58 (0.38–0.88)	
Stage IIIC	67/197	104/197	0.58 (0.38–0.86)	
No. of positive lymph nodes				0.78
1	44/227	80/237	0.53 (0.33–0.86)	
2 or 3	46/177	76/166	0.52 (0.32–0.85)	
≥4	45/110	60/102	0.62 (0.37–1.03)	
Type of positive lymph nodes				0.86
Microscopic	35/187	50/161	0.56 (0.32–0.99)	
Macroscopic	100/327	166/344	0.59 (0.42–0.81)	
Ulceration				0.12
No	62/230	94/251	0.69 (0.45–1.05)	
Yes	64/208	101/197	0.52 (0.35–0.79)	
Not reported	9/76	21/57	0.30 (0.11–0.84)	
Lymph-node and ulceration status				0.35
Microscopic, ulceration	25/94	31/75	0.58 (0.29–1.15)	
Microscopic, no ulceration	10/89	19/85	0.48 (0.17–1.30)	
Macroscopic, ulceration	39/114	70/122	0.51 (0.31–0.86)	
Macroscopic, no ulceration	52/141	75/166	0.79 (0.50–1.26)	
BRAF mutation status				0.89
Wild type	69/233	97/214	0.61 (0.41–0.92)	
V600E mutation	54/186	94/209	0.59 (0.38–0.92)	
All Patients	135/514 (26.3%)	216/505 (42.8%)	0.57 (0.43–0.74)	

Figure 3. Forest Plot of Recurrence-free Survival According to Subgroup.

An unstratified univariate Cox model was used to estimate the hazard ratios for the risk of recurrence or death in the pembrolizumab group as compared with the placebo group among all the patients. An unstratified Cox model including the trial group, a covariate of interest (e.g., age 18 to <65 vs. ≥65 years) and the interaction term (e.g., age × treatment) was used to perform the interaction test and estimate the hazard ratios for the subgroups. P values were yielded by the test of the treatment difference in the overall intention-to-treat population or by the test of interaction; for each, the Wald test was used. The sizes of the blue boxes are nonlinearly proportional to the numbers of events. The green diamond is centered on the overall hazard ratio (dashed line) and covers its 98.4% confidence interval. In the subgroup analyses, 99% confidence intervals (blue lines) are presented. Data on lymph-node and ulceration status were not available for 133 patients; data on *BRAF* mutation status were not available for 65 patients, and the *BRAF* mutation present differed from V600E in 112 patients. P<0.001 in the unadjusted analysis of the overall effect of pembrolizumab versus placebo on recurrence-free survival. AJCC denotes American Joint Committee on Cancer 2009 classification, 7th edition.[14]

Data Source: Eggermont 2018[1] From The New England Journal of Medicine, Eggermont et al., Adjuvant Pembrolizumab versus Placebo in Resected Stage III Melanoma, 378:1789-1801. © 2018 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

As previously discussed, patients who were enrolled into the KEYNOTE-054 trial were staged according to the 7th edition of the AJCC (2009). Eggermont et al (2018) reported that there was a protective effect of pembrolizumab on RFS as compared to placebo regardless of the stage of disease according to the AJCC 2009 melanoma classification system (p for interaction: 0.69).[1] Unlike the 7th edition, the updated 8th edition of the AJCC (2017) includes the stage IIID subgroup. The EMA requested the Submitter perform an additional subgroup analysis, where they stratified the effect of pembrolizumab as compared to placebo on RFS according to the AJCC 8th edition melanoma classification system.[4] The protective effect of pembrolizumab relative to placebo on RFS was similar regardless of the patients' stage of disease.[1]

Distant Metastasis-Free Survival

DMFS was a secondary outcome in the trial. It was defined as the time from randomization to the date of first distant metastasis or death.[2] DMFS estimates were not reported for the 02-October-2017 data cut-off.[1]

Quality of Life

The Submitter indicated that there are no validated immune-specific questionnaires for oncology trials.[6] Thus, they assessed patient-reported outcomes (PROs) using the EORTC QLQ-C30 and EQ-5D-3L.[2] The EORTC QLQ-C30 includes five functional scales (i.e. physical, role, emotional, social, and cognitive), three symptom scales (i.e. fatigue, nausea and vomiting and pain), one global health status scale and six single items (i.e. dyspnea, insomnia, appetite loss, constipation, diarrhea and financial difficulties). All scales range from 0 to 100 and a higher score represents better function or quality of life. In the Protocol, it was stated that a 10-point difference on the EORTC QLQ-C30 scale between the two treatment groups was considered a minimally important difference (MID).[2] The EQ-5D assesses general health status and health utility measures. It measures five dimensions of health state: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.[35] It also has a visual analog scale (VAS). Each dimension is assessed using a single question on a three-point scale.[35] The MID for the EQ-5D index was a 0.08-point difference and a 10-point and 7-point difference was considered the MID of the EQ-5D VAS.[5] The data cut-off for the analysis was 02-October-2017.

HRQoL was measured at baseline, every 12 weeks after randomization for two years and then every six months thereafter.[2] For the purpose of this review, data up to week 48 is reported as decreased compliance rates were observed after this week due to patients crossing over to receive pembrolizumab in Part 2 of the trial. Therefore, these data should be interpreted with caution because there is no HRQoL assessment post-treatment for the patients enrolled in the KEYNOTE-054 trial.

The primary HRQoL endpoint was the change in the global health/QoL scale for the EORTC QLQ-C30 and all other analyses were considered descriptive.[2] Patients were included in the analysis if they received ≥ 1 dose of study treatment and completed ≥ 1 HRQoL questionnaire.[5] The Submitter reported that the score change from baseline was compared using a constrained longitudinal data analysis model stratified by randomization strata; and missing data were handled using multiple imputation methods.[5] The differences between groups were determined using non-parametric rank-order tests with a two-sided significance level of 5%.[2]

HRQoL was measured as the change from baseline to week 48 using the EORTC QLQ-C30 global health status/QoL score (defined as a ≥10-point decrease).[5] The compliance rates for the EORTC QLQ-C30 questionnaire were 96.5% in the pembrolizumab group and 97.0% in the placebo group at baseline and the compliance rates decreased for both groups at week 48 (81.8% for pembrolizumab and 82.4% for the placebo groups.[5] At the 02-October-2017 data cut-off, the

baseline global health status was similar for patients in both the pembrolizumab and placebo groups and remained stable over time. The results are presented in Table 16 and Figure 7. At week 48 the MID was not reached in either treatment group for the global health status/QoL score and no significant differences between the two treatment groups were observed.[5]

Table 16: Change from baseline for the EORTC QLQ-C30 Global Health Status/QoL Score at week 48 for patients enrolled in the KEYNOTE-054 trial.

	Baseline		Week 48		Change from Baseline at Week 48	
Treatment	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)†
Pembrolizumab	488	77.13 (18.027)	382	75.76 (18.842)	508	-2.45 (-4.36, -0.53)
Placebo	481	76.80 (17.871)	326	77.04 (18.982)	498	-0.35 (-2.38, 1.68)

Pairwise Comparison	Difference in LS Means (95% CI)	p-Value
Pembrolizumab vs. Placebo	-2.09 (-4.60, 0.41)	0.101

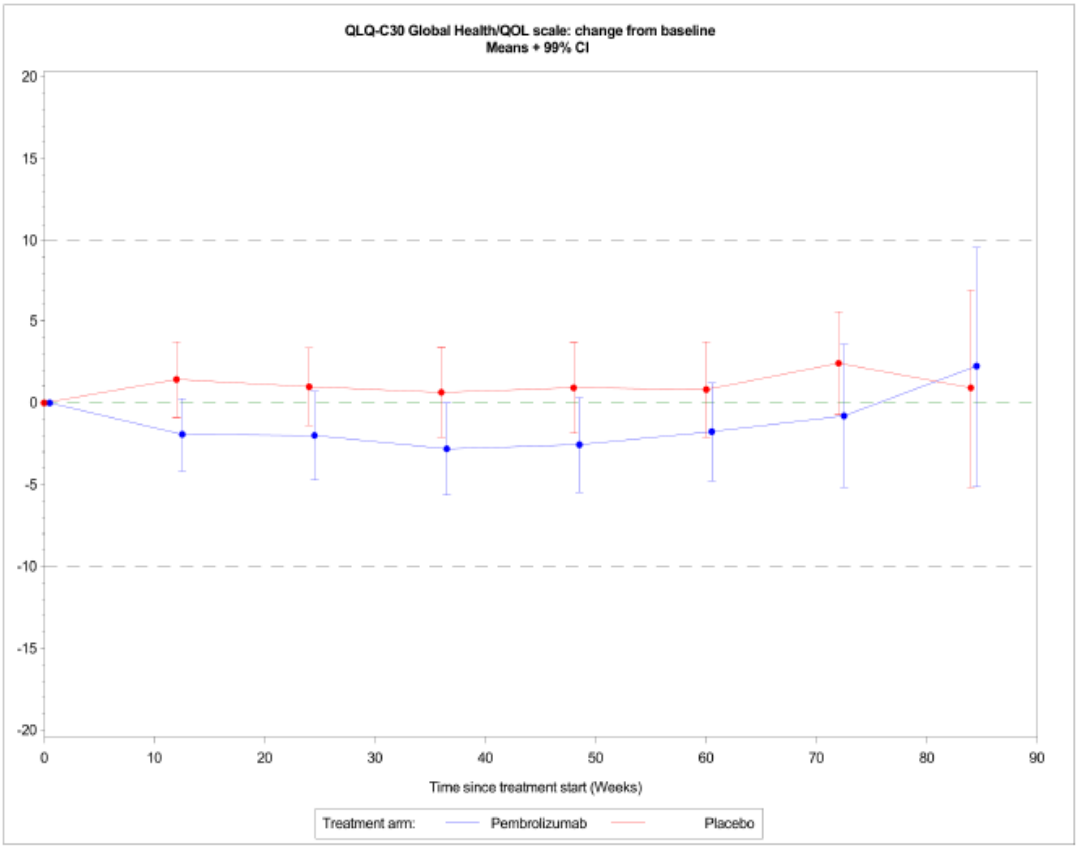
† Based on cLDA model with the PRO scores as the response variable, and treatment by study visit interaction, stratification factors stage (IIIA [>1 mm metastasis] vs. IIIB vs. IIIC 1-3 nodes vs. IIIC >=4 nodes) as indicated at randomization as covariates.

For baseline and Week 48, N is the number of subjects in each treatment group with non-missing assessments at the specific time point; for change from baseline, N is the number of subjects with data available for analysis.

(Database Cutoff Date: 02OCT2017)

Data Source: Health Related Quality of Life Analysis Health Related Quality of Life Analysis[5]

Figure 7: Least-square mean change from baseline in the EORTC QLQ-C30 Global Health Status/QoL over time for patients enrolled in the KEYNOTE-054 trial.



Data source: Coens 2018 ESMO[30] from pan-Canadian Oncology Drug Review manufacturer submission: Keytruda (pembrolizumab), powder for solution for infusion 50 mg, solution for infusion 100 mg/4mL vial. Kirkland (QC): Merck Canada; 2019.[33]

The compliance rates for the EQ-5D index were 95.3% in the pembrolizumab group and 96.0% in the placebo group at baseline while the compliance rates decreased for both groups at week 48 (81.3% for pembrolizumab and 80.6% for the placebo groups).[5] The baseline EQ-5D was similar for patients in both the pembrolizumab and placebo groups and remained stable over time. The results are presented in Table 17 and Figure 8. There were no significant differences between the two treatment groups at week 48 and the MID was not reached.[5] Similar results were observed for the EQ-5D VAS. [5]

Table 17: Change from baseline for the EQ-5D at Week 48 for patients enrolled in the KEYNOTE-054 trial.

	Baseline		Week 48		Change from Baseline at Week 48	
Treatment	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)†
Pembrolizumab	483	0.83 (0.195)	379	0.85 (0.195)	507	0.00 (-0.02, 0.02)
Placebo	479	0.83 (0.174)	320	0.84 (0.217)	499	0.00 (-0.02, 0.02)
Pairwise Comparison					Difference in LS Means (95% CI)	p-Value
Pembrolizumab vs. Placebo					0.00 (-0.03, 0.03)	0.929

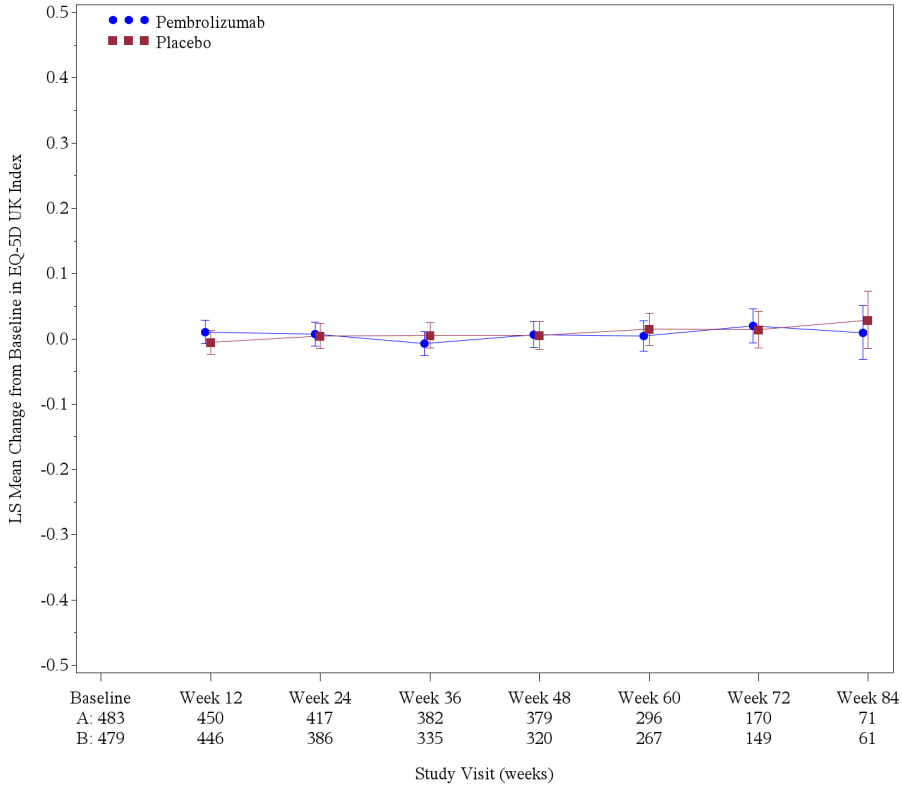
† Based on cLDA model with the PRO scores as the response variable, and treatment by study visit interaction, stratification factors stage (IIIA [>1 mm metastasis] vs. IIIB vs. IIIC 1-3 nodes vs. IIIC >=4 nodes) as indicated at randomization as covariates.

For baseline and Week 48, N is the number of subjects in each treatment group with non-missing assessments at the specific time point; for change from baseline, N is the number of subjects with data available for analysis.

(Database Cut-off Date: 02OCT2017)

Data Source: Health Related Quality of Life Analysis Health Related Quality of Life Analysis[5]

Figure 8: Least-square mean change from baseline in the EQ-5D UK index over time for patients enrolled in the KEYNOTE-054 trial.



Data Source: Health Related Quality of Life Analysis Health Related Quality of Life Analysis[5]

Harms Outcomes

The safety set in the KEYNOTE-054 trial consisted of patients who had received at least one dose of the study treatment. There was a total of 1,011 patients in the safety set, with 509 patients in the pembrolizumab group and 502 patients in the placebo group.[1] At the 02-October-2017 data cut-off, patients received a median of 18 doses (interquartile range [IQR]: 9 to 18) of pembrolizumab and a median of 18 doses (IQR: 8 to 18) of placebo.[1] Additionally, the median number of days on therapy for those in the pembrolizumab group was 357 days (range: 1 to 478) and 357 days (range: 1 to 424) in the placebo group.[4]

Dose discontinuation

More patients in the pembrolizumab group (13.8 %) had one or more AEs that led to a dose discontinuation as compared to those in the placebo group (3.6%).[4] Moreover, 12.2% of patients in the pembrolizumab group discontinued due to a drug-related AEs relative to 1.6% of patients in the placebo group.[6]

Adverse Events

AEs for all patients enrolled in the KEYNOTE-054 trial at the 2-October-2017 data cut off are presented in Table 18.[1] Overall, AEs of any grade occurred at the same frequency among those treated with pembrolizumab or placebo (93.3% versus 90.2%). In contrast, more grade 3 or greater AEs were reported in the pembrolizumab group as compared to the placebo group (31.6% versus 18.5%). More treatment-related AEs (TRAEs) of any grade occurred in the pembrolizumab group as compared to the placebo group (77.8% versus 66.1%) (Table 18).[1] The most common TRAEs of any grade in both the pembrolizumab and placebo groups were fatigue (37.1% versus 33.3%), skin reactions (28.3% versus 18.3%), diarrhea (19.1% versus 16.7%), arthralgia (12.0% versus 11.0%) and nausea (11.4% and 8.6%). Likewise, more grade 3 or greater TRAEs were reported in the pembrolizumab group as compared to the placebo group (14.7% versus 3.4%).

Table 18: Adverse events for all patients enrolled in the KEYNOTE-054 trial at the 02-October-2017 data cut-off.

Event	Pembrolizumab (N = 509)		Placebo (N = 502)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number of patients (percent)			
Any adverse event	475 (93.3)	161 (31.6)	453 (90.2)	93 (18.5)
Treatment-related adverse events†				
Any	396 (77.8)	75 (14.7)	332 (66.1)	17 (3.4)
Fatigue or asthenia	189 (37.1)	4 (0.8)	167 (33.3)	2 (0.4)
Skin reactions	144 (28.3)	1 (0.2)	92 (18.3)	0
Rash	82 (16.1)	1 (0.2)	54 (10.8)	0
Pruritus	90 (17.7)	0	51 (10.2)	0
Diarrhea	97 (19.1)	4 (0.8)	84 (16.7)	3 (0.6)
Arthralgia	61 (12.0)	3 (0.6)	55 (11.0)	0
Nausea	58 (11.4)	0	43 (8.6)	0
Dyspnea	30 (5.9)	1 (0.2)	15 (3.0)	0
Immune-related adverse events, regardless of investigator attribution				
Any	190 (37.3)	36 (7.1)	45 (9.0)	3 (0.6)
Endocrine disorders	119 (23.4)	9 (1.8)	25 (5.0)	0
Hypothyroidism	73 (14.3)	0	14 (2.8)	0
Hyperthyroidism	52 (10.2)	1 (0.2)	6 (1.2)	0
Thyroiditis	16 (3.1)	0	1 (0.2)	0
Hypophysitis, including hypopituitarism	11 (2.2)	3 (0.6)	1 (0.2)	0
Type 1 diabetes mellitus	5 (1.0)	5 (1.0)	0	0
Adrenal insufficiency	5 (1.0)	1 (0.2)	4 (0.8)	0
Respiratory, thoracic and mediastinal disorders	24 (4.7)	4 (0.8)	3 (0.6)	0
Pneumonitis or interstitial lung disease	17 (3.3)	4 (0.8)	3 (0.6)	0
Sarcoidosis	7 (1.4)	0	0	0
Vitiligo or severe skin reactions	27 (5.3)	3 (0.6)	8 (1.6)	0
Vitiligo	24 (4.7)	0	8 (1.6)	0
Severe skin reactions	3 (0.6)	3 (0.6)	0	0
Gastrointestinal conditions	20 (3.9)	10 (2.0)	4 (0.8)	2 (0.4)
Colitis	19 (3.7)	10 (2.0)	3 (0.6)	1 (0.2)
Pancreatitis	2 (0.4)	1 (0.2)	1 (0.2)	1 (0.2)
Hepatobiliary disorders	9 (1.8)	7 (1.4)	1 (0.2)	1 (0.2)
Hepatitis	9 (1.8)	7 (1.4)	1 (0.2)	1 (0.2)
Other immune-related adverse events	15 (2.9)	5 (1.0)	5 (1.0)	0
Nephritis	2 (0.4)	2 (0.4)	1 (0.2)	0
Uveitis	2 (0.4)	0	0	0
Myositis	1 (0.2)	1 (0.2)	1 (0.2)	0
Myocarditis	1 (0.2)	1 (0.2)	0	0

* The safety analysis included all patients who underwent randomization and received at least one dose of trial agent (1011 patients). Listed are the adverse events that were reported between the first dose and 30 days after the last dose; for all serious adverse events and serious immune-related adverse events, a time limit of 90 days after the last dose was used. All adverse events correspond to part 1 of the trial (the 1-year adjuvant-therapy period) and not to part 2 (in which patients with disease recurrence were eligible to cross over or receive repeat treatment with pembrolizumab). The severity of adverse events was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

† The investigators determined whether adverse events were related to a trial agent. Adverse events and immune-related adverse events that occurred in at least 10% of patients or those that were considered to be medically relevant are reported. Patients may have had more than one event.

Data Source: Eggermont 2018[1] From The New England Journal of Medicine, Eggermont et al., Adjuvant Pembrolizumab versus Placebo in Resected Stage III Melanoma, 378:1789-1801. © 2018 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

Serious Adverse Events

The National Institute for Health and Care Excellence (NICE) Report stated that 25.1% of patients in the pembrolizumab group and 16.3% of patients in the placebo group had a serious adverse

event (SAE).[6] Similarly, more treatment-related SAEs occurred in the pembrolizumab group (13.0%) as compared to the placebo group (1.2%).[6]

Adverse Events of Special Interest

More immune-related AEs of any grade occurred in the pembrolizumab group as compared to the placebo group (37.3% vs. 9.0%) (Table 18).[1] More endocrine immune-related AEs occurred in the pembrolizumab group as compared to the placebo group (23.4% vs. 5%). As compared to the placebo group, more grade 3 or 4 immune-related AEs occurred in the pembrolizumab group (0.6% vs 7.1%). Eggermont et al (2018) reported that among the 43 grade 3 or 4 immune-related AEs in the pembrolizumab group, 21 resolved within two months after the last dose of pembrolizumab.[1]

Deaths

In the pembrolizumab group there were two patient deaths; one patient died from treatment-related autoimmune myositis involving respiratory muscles while one patient death was attributed to a drug reaction with eosinophilia and systemic symptoms from the initiation of vemurafenib and cobimetinib.[6] No deaths occurred in the placebo group.[1]

6.4 Ongoing Trials

Table 19: Ongoing trials of pembrolizumab as adjuvant treatment after resection in patients with melanoma.

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes

Trial
EORTC-1325/KEYNOTE-054 Trial
 	
Other identifiers
NCT02362594
2014-004944-37
 	
Characteristics
Double-blind, placebo-controlled, phase 3 RCT
 	
Sample Size
N= 1019
 	
Number of centres and number of countries
123 centres in 23 countries
 	
Patient Enrolment Dates
August 2015 to November 2016
 	
Final Analysis Date
31-July-2023
 	
Funding
Merck
	Key Inclusion Criteria:
	• Upon documented recurrence (i.e. defined as appearance of one or more new melanoma lesions: local, regional or distant), patients may undergo surgery if indicated.
	• **Re-challenge**: Patients originally assigned to the pembrolizumab arm who experienced disease recurrence more than six months after completing one year of therapy could be re-treated with pembrolizumab.
	• **Crossover**: Patients originally assigned to the placebo arm could crossover to receive pembrolizumab. They were eligible if they met the following criteria:
	  • No evidence of brain metastases or any other CNS disease.
	  • No evidence of a second recurrence or a progression before enrolment in Part 2.
	  • ECOG performance status 0 to 2.
		Part 2 of the trial
		Intervention (Unblind)
		Pembrolizumab (200 mg IV Q3W for 2 years)
			Primary:
			• RFS
			• RFS in subgroup of patients with PD-L1-positive tumor expression receiving either pembrolizumab or placebo
			
			Secondary:
			• DMFS
			• DMFS in subgroup of patients with PD-L1-positive tumor expression receiving either pembrolizumab or placebo
			• OS
			• OS in subgroup of patients with PD-L1-positive tumor expression receiving either pembrolizumab or placebo
			• Toxicity profile according to CTCAE v. 4.0
			• To evaluate the PK of pembrolizumab when pembrolizumab is administered 200 mg every 3 weeks
			• To assess for development of ADA
			
			Tertiary:
			• Quality of life
			• Health outcomes evaluation
			• To evaluate predictive biomarkers for treatment difference in outcome
			• PRFS2

Abbreviations: ADA = anti-drug antibodies; CNS = central nervous system; CTCAE = Common Terminology Criteria for Adverse Events; DMFS = distant metastases-free survival; ECOG = Eastern Cooperative Oncology Group; IV = intravenous; PD-L1 = anti-programmed cell death receptor ligand 1; PRFS2 = Progression/recurrence-free survival 2; PK = pharmacokinetics; OS = overall survival; Q3W = every 3 weeks; RFS = Recurrence free survival

7 SUPPLEMENTAL QUESTIONS

7.1 Critical appraisal of a network meta-analysis comparing the efficacy and safety of adjuvant anti-cancer therapies in the treatment of melanoma

Background

The pCODR-conducted literature search identified only one RCT that assessed the efficacy and safety of adjuvant pembrolizumab versus placebo in stage III melanoma patients following resection.[1] Thus, there is a lack of direct evidence comparing pembrolizumab to other active therapies. Given the absence of head-to-head trials, the Submitter provided an unpublished network meta-analysis (NMA). The NMA provided an indirect comparison of pembrolizumab to observation, peginterferon alfa-2b (PEG-IFN α-2b), interferon alfa-2b (IFN α-2b) (12 months) and IFN α-2b (24 months).[8,33]

The objective of this section is to summarize and critically appraise the submitted unpublished NMA, which provides evidence of the efficacy and safety of pembrolizumab as compared to other therapies in patients with stage III melanoma in the adjuvant setting.

Summary of NMA

Objective of NMA
The objective of the NMA was to compare the efficacy and safety of pembrolizumab to other anticancer agents used in the adjuvant setting among patients with stage III melanoma.

Methods

Search and Study Selection
The Submitter conducted a systematic review to identify eligible RCTs. Studies were eligible if they assessed the effect of adjuvant pembrolizumab, PEG-IFN α-2b, IFN α-2b (12 months), IFN α-2b (24 months) to placebo or best supportive care (BSC) on overall survival (OS), recurrence-free survival (RFS) or distant metastasis-free survival (DMFS) in adult patients with stage III melanoma.

The systematic review was conducted on Feburary-2018 using the following sources: Medical Literature Analysis and Retrieval System Online (MEDLINE), Excerpta Medica database (EMBASE) and the Cochrane Central Register of Controlled Trials. In addition, the Submitter also searched the US National Institutes of Health Clinical Trial Registry (http://www.clinicaltrials.gov) and relevant conference proceedings within the past two years (i.e. 2016 and 2017) for trials or articles. 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.

The quality of all included studies was appraised using the Cochrane Collaboration's Risk of Bias tool. The tool assesses sequence generation, allocation concealment, blinding of participants, personnel and outcome assessors, incomplete outcome data, selective outcome reporting and other sources of bias. The quality assessment was conducted by two independent reviewers, and, if any discrepancies occurred, the investigators used a third party to provide consensus.

NMA Methodology

Feasibility Assessment

Prior to conducting the NMA, the Submitter conducted a feasibility assessment to ensure that the included trials provided sufficient evidence to form a network for the target population and outcomes of interest. Moreover, the assessment also explored if the distribution of study, patient, treatment and outcome characteristics were balanced across the included studies in the NMA. The Submitter stated that should the included trials form an evidence network and the studies were similar then a Bayesian NMA could be performed.

NMA

The Submitter reported that the proportional hazards assumption was violated. Typically, NMAs that model survival data from oncology trials use the reported HR, which relies on the proportional hazards assumption. However, this may not be a realistic assumption, especially when the evidence that is used in the NMA comes from different RCTs. Therefore, the Submitter implemented a method proposed by Ouwens et al (2010) and Jansen et al (2011) which models survival data using multidimensional treatment effects rather than synthesizing the constant hazard ratios (HRs).[38,39] This method allows for the proportional hazards assumption to be relaxed and the time-varying HR NMA model will fit the reported data more closely.

The hazard functions of the interventions in a trial are modeled using known parametric survival functions or fractional polynomials, and the difference in the parameters are considered the multidimensional treatment effect, which are synthesized (and indirectly compared) across studies. With this approach, the treatment effects are represented by multiple parameters (multivariate) rather than a single parameter. For the multivariate NMA framework, the Submitter considered the following survival distributions: Weibull, Gompertz, and second-order fractional polynomials including p1=0 or 1 and p2=0 or 1.The time-varying HR estimates from the NMA represent the comparison of the intervention of interest to observation using a follow-up of 24 months, which was the maximum length of follow-up in the KEYNOTE-054 trial. In addition, the Submitter also provided HR point estimates using a three-month interval for each treatment and observation comparison.

Although the proportional hazard assumption was violated, the Submitter reported constant HRs for OS, DMFS, and RFS, which assumes proportional hazards between treatments. This was achieved by using a regression model with a contrast-based normal likelihood for the log HR of each trial in the network. For all other outcomes, the Submitter reported that they used a regression model with a binomial likelihood and logit link to assess the effect of pembrolizumab relative to other anticancer therapies.

The Submitter reported that the best-fitting model was chosen based on the lowest deviance information criterion (DIC). Normal non-informative prior distributions were used for all parameters (mean 0; variance of 10,000). The effect estimates of binary outcomes were expressed as odds ratios (OR) with 95% credible intervals (CrI) while time-to-event outcomes were expressed as HRs with 95% CrIs. Although both fixed and random effects models were considered for the NMA, the Submitter used a fixed effects model because there were insufficient trials to achieve a stable estimate of between-study heterogeneity.

Results

Included studies

The systematic review identified 23 citations which corresponded to 12 unique studies; however, the Submitter narrowed the search results of the systematic review to include relevant comparators that are used in Canada. Thus, 10 citations were included in the NMA which represents four unique trials. These trials include: EORTC 18952, EORTC 18991, KEYNOTE-054 and the Nordic IFN trial.

Trial characteristics

Prior to conducting the NMA, the Submitter assessed the assumptions of the NMA. To do so, the Submitter described the study design of the included trials and the baseline characteristics. The Submitter stated that that there were some differences in baseline characteristics across the four included trials. Details of the included studies are reported in Table 20. Baseline characteristics were well balanced across the included trials, which includes age and sex. Only three trials reported ECOG performance status. Patients who had an ECOG performance status of 0 ranged from 84% to 94% and those who had an ECOG performance status of 1 ranged from 6% to 16%.

The Submitter stated that the patient populations included in the NMA were composed of patients with stage II or stage III melanoma. For instance, the EORTC 18952 and Nordic IFN trials enrolled patients who had either stage II or stage III melanoma; 26% of patients in the EORTC 18952 trial had stage IIb melanoma and 19% of patients in the Nordic-IFN trial had stage II melanoma. Given the mixed patient populations, the Submitter commented that trials were only included in the NMA if they reported a subgroup analysis for the outcome of interest stratified by disease stage. Therefore, the EORTC 18952 trial was excluded from the primary NMA analysis because a subgroup analysis stratifying by disease stage was not available; however, the results of the EORTC 18952 trial were included in subsequent sensitivity analyses.

Moreover, the Submitter identified PD-L1 status, BRAF mutation status, and disease stage as important effect modifiers. They stated that they there were unable to construct a network that assessed the effects of PD-L1 expression level, BRAF carrier status or disease stage (Stage IIIA, IIIB, IIIC) because there were insufficient data.

Table 20: Characteristics of randomized controlled trials included in the feasibility assessment.

Trial ID	Trial design	Start - end dates	Age in years	Disease stage	Performance score	Prior treatment excluded
EORTC 18952	Multicentre, international, open label, phase III RCT	May, 1996 - Ongoing	18-75	IIB-III	--	Patients previously treated with systemic drugs for melanoma, other maliganant diseases (other than basal cell carcinoma, in situ cervical cancer), autoimmune disease, uncontrolled infections, cardiopulmonary disease, liver or renal disease, taking corticosteriods
EORTC 18991	Multicentre, international, open label, phase III RCT	October, 2000 - August, 2003	18-70	III	ECOG 0-1	Patients who have taken prior interferon alpha, prior immunotherapy for melanoma, other concurrent immunologic or biologic therapy, concurrent colony stimulationg factors including epoetin alfa and filgrastim (G-CSF), prior chemotherapy, and concurrent chemotherapy for melanoma, prior hormonal therapy for melanoma, concurrent hormonal therapy, concurrent chronic systemic corticosteroid therapy, previous radiotherapy for melanoma, concurrent radiotherapy, and/or other concurrent investigational drugs are excluded.
KEYNOTE 054	International, double-blind, phase III RCT	July, 2015 - May, 2018 Phase 2 Ongoing	≥18	III	ECOG 0-1	Prior treatment with any anti-cytotoxic CTLA4 monoclonal antibody or PD-1, PD-L1, or PD-L2 or prior participation in any Merck pembrolizumab clinical trial
Nordic IFN trial	Multicentre, international, open label, phase III RCT	November, 1996 June, 2008	>=18	IIB-III	ECOG 0-1	Patients who have had prior adjuvant radiotherapy, chemotherapy, immunotherapy including preoperative infusion or perfusion therapy are ineligible. Patients requiring ongoing treatment with steroids, non-steroidal anti-inflammatory drugs, or other known immunomodulators are ineligible.

Trial ID	Treatment	N	ECOG 0 N(%)	ECOG 1 N(%)	ECOG 2 N(%)	Stage IIa N(%)	Stage IIb N(%)	Stage IIc N(%)	Stage II N(%)	Stage IIIa N(%)	Stage IIIb N(%)	Stage IIIc N(%)	Stage III N(%)
EORTC 18952	IFN alfa-2b	553					141 (25%)			412 (74%)			
	IFN alfa-2b	555					142 (26%)			414 (74%)			
	Obs	279					73 (26%)			206 (74%)			
EORTC 18991	PEG-IFN alpha-2B	627	530 (84%)	97 (16%)									627 (100%)
	Obs	629	531 (84%)	98 (16%)									629 (100%)
KEYNOTE 054	Pembrolizumab	514	485 (94%)	29 (7%)						80 (16%)	237 (46%)	197 (38%)	514 (100%)
	Placebo	505	475 (94%)	30 (6%)						80 (16%)	230 (46%)	195 (39%)	505 (100%)
Nordic IFN trial	Obs	284	241 (85%)	43 (15%)					55 (19%)				229 (81%)
	IFN alfa-2b	285	258 (90%)	27 (10%)					58 (20%)				227 (80%)
	IFN alfa-2b	286	254 (89%)	32 (11%)					53 (18%)				233 (82%)

Trial ID	Treatment	N	PD-L1 < 1%, N(%)	PD-L1 < 5%, N(%)	PD-L1 ≥ 1%, N(%)	PD-L1 ≥ 5%, N(%)	PD-L1 unknown, N(%)	Positive sentinel node biopsy or micrometastasis,n(%)	Clinical detectable nodal metastasis or macrometastasis, n(%)
EORTC 18952	IFN alfa-2b	553						409 (74%)	
	IFN alfa-2b	556						406 (73%)	
	Obs	279						206 (74%)	
EORTC 18991	PEG-IFN alpha-2B	627						271 (43%)	356 (57%)
	Obs	629						272 (43%)	357 (57%)
KEYNOTE 054	Pembrolizumab	514	59 (12%)		428 (83%)		27 (5%)	187 (36%)	327 (64%)
	Placebo	505	57 (12%)		425 (84%)		23 (5%)	161 (32%)	344 (68%)
Nordic IFN trial	Obs	284						229 (81%)	
	IFN alfa-2b	285						227 (80%)	
	IFN alfa-2b	286						233 (81%)	

Data source: NMA Report[8,33]

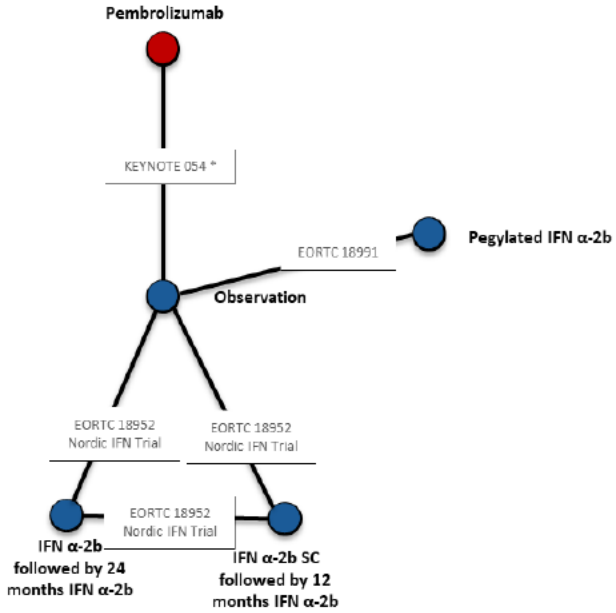
The risk of bias for all the included trials was assessed using the Cochrane Risk of Bias tool. It was reported that the risk of bias was low across the included trials. However, there was an increased risk of performance and detection bias in the Nordic IFN trial because it used an open-label design.

The feasibility assessment for the NMA concluded that connected networks could be created to compare adjuvant pembrolizumab to other relevant comparator in stage III melanoma for RFS using time-varying HRs and constant HRs, discontinuations due to AEs, and grade 3-4 adverse events. Furthermore, due to a lack of reported information NMA would not be possible for OS using time-varying HRs or DMFS using time-varying HRs and constant HRs.

NMA

Figure 9 represents the NMA using a Canadian perspective for all outcomes. As previously mentioned, trials were included in the NMA if they included patients with stage III melanoma or the trial reported a subgroup analysis that stratified by disease stage.

Figure 9: NMA using a Canadian perspective for all outcomes.



*: Comparator is "Placebo", assumed to be equivalent to "Observation"

Data Source: NMA Report[8,33]

RFS

The direct estimates of RFS from the four trials included in the NMA are presented in Table 21. It should be noted that the definition of RFS across trials included in the NMA was not reported. This may increase the uncertainty in the estimates obtained from the NMA.

Table 21: Reported efficacy outcomes of randomized controlled trials included in the feasibility assessment.

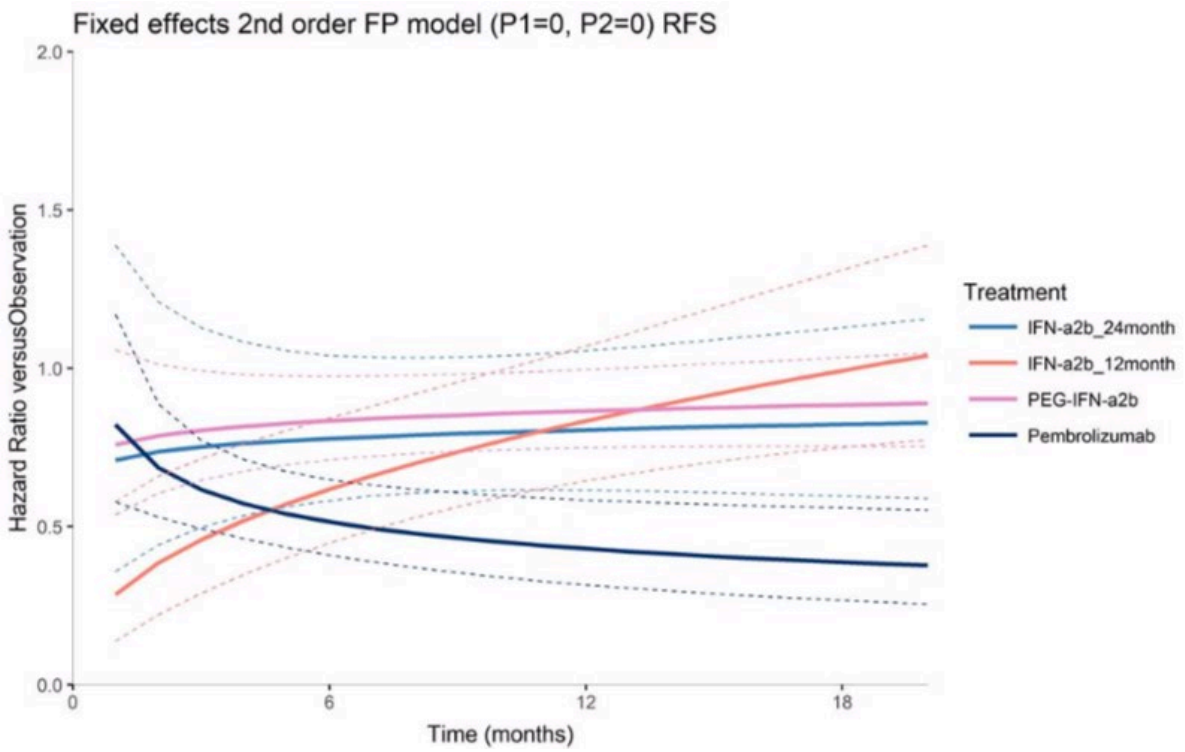
Trial ID	Intervention	Subgroup	N	Median RFS (95%CI)	RFS (95%CI)
EORTC 18952	IFN alpha-2b followed by 12 months IFN alpha-2b	Stage III (N1)	553	--	0.80 (0.56, 1.14)
	IFN alpha-2b followed by 24 months IFN alpha-2b	Stage III (N1)	556	--	0.74 (0.51,1.06
	Observation	Stage III (N1)	279	--	--
	IFN alpha-2b followed by 12 months IFN alpha-2b	Stage III (N2)	553	--	1.04 (0.77, 1.39)
	IFN alpha-2b followed by 24 months IFN alpha-2b	Stage III (N2)	556	--	0.89 (0.66, 1.21)
	Observation	Stage III (N2)	279	--	--
	IFN alpha-2b followed by 12 months IFN alpha-2b	ITT	553	19.9 (14.8, 30.1) NA	0.94(0.75, 1.17)
	IFN alpha-2b followed by 24 months IFN alpha-2b	ITT	308	26 (19.1, 34.4) NA	0.84 (0.64, 1.06)
	Observation	ITT	279	18.6 (12.2, 25) NA	--
EORTC 18991	PEG Interferon-alpha-2b	Stage III	627	34.8 months	0.82 (0.73, 0.96)
	Observation	Stage III	629	25.6 months	--
	PEG Interferon-alpha-2b	Stage III	627	3 years	0.87 (0.76, 1)
	Observation	Stage III	629	2.2 years	--
KEYNOTE-054	Pembrolizumab	Stage III	514	--	0.57 (0.46, 0.70)
	Placebo	Stage III	505	--	--
	Pembrolizumab	PD-L1+	428	--	0.54 (0.42, 0.69

	Placebo	PD-L1+	425	--	--
	Pembrolizumab	PD-L1-	59	--	0.47 (0.26, 0.85)
	Placebo	PD-L1-	57	--	--
	Pembrolizumab	BRAF+	245	--	0.49 (0.36, 0.67)
	Placebo	BRAF+	262	--	--
	Pembrolizumab	BRAF wildtype	233	--	0.64 (0.47, 0.87)
	Placebo	BRAF wildtype	214	--	--
	Pembrolizumab	Stage IIIa	80	--	0.31 (0.12, 0.79)
	Placebo	Stage IIIa	80	--	--
	Pembrolizumab	Stage IIIb	237	--	0.56 (0.41, 0.78)
	Placebo	Stage IIIb	230	--	--
	Pembrolizumab	Stage IIIc (1-3 LN+)	95	--	0.51 (0.31, 0.83)
	Placebo	Stage IIIc (1-3 LN+)	93	--	--
	Pembrolizumab	Stage IIIc (4LN+)	102	--	0.69 (0.47, 1.03)
	Placebo	Stage IIIc (4LN+)	102	--	--
Nordic IFN trial	Observation	ITT	185	--	--
	IFN alpha-2b followed by 12 months IFN alpha-2b	ITT	182	--	0.82 (0.64, 1.06)
	IFN alpha-2b followed by 24 months IFN alpha-2b	ITT	187	--	0.78 (0.61, 1.0)

Data source: NMA Report[8,33]

The results of the NMA comparing pembrolizumab to observation, IFN α2b (12 months), IFN α2b (24 months) or PEG-IFN α2b for time-varying HRs are presented in Figure 10. The Submitter reported that pembrolizumab had a protective effect on RFS compared to all other interventions after three months. In addition, sensitivity analyses were conducted among mixed diseased patients and these analyses showed that pembrolizumab was associated with a prolonged RFS as compared to all other interventions throughout the course of the 18-month follow-up.

Figure 10: Fixed-effects NMA of RFS using time-varying HRs which compare observation to pembrolizumab, IFN α2b (12 months), IFN α2b (24 months) or PEG-IFN α2b



Data source: NMA Report[8,33]

The Submitter also compared pembrolizumab to observation, IFN α2b (12 months), IFN α2b (24 months) or PEG-IFN α2b using constant HRs (Table 22). Using the fixed-effects model, the Submitter stated that pembrolizumab was statistically superior for RFS to observation, IFN α2b (12 months) and PEG-IFN α2b. The Submitter observed similar estimates in sensitivity analyses, where they included mixed stage II and III melanoma patients from the EORTC 18952 trial.

Table 22: Fixed-effects NMA comparing pembrolizumab to observation, IFN α2b (12 months), IFN α2b (24 months) and PEG-IFN α2b on RFS using constant HRs.

Observation	1.22 (0.95, 1.57)	1.28 (1.00, 1.65)	1.12 (0.98, 1.29)	**1.76** **(1.43, 2.16)**
0.82 (0.64, 1.06)	**IFN-a2b (12month)**	1.05 (0.82, 1.35)	0.92 (0.69, 1.23)	**1.44** **(1.03, 1.99)**
0.78 (0.61, 1.00)	0.95 (0.74, 1.22)	**IFN-a2b (24month)**	0.87 (0.66, 1.17)	1.37 (0.99, 1.89)
0.89 (0.77, 1.02)	1.09 (0.81, 1.45)	1.14 (0.85, 1.51)	**PEG-IFN a2b**	**1.57** **(1.22, 2.01)**
0.57 **(0.46, 0.70)**	**0.69** **(0.50, 0.97)**	0.73 (0.53, 1.01)	**0.64** **(0.50, 0.82)**	**Pembrolizumab**

Note: Each cell represents the comparison (hazard ratio and 95% CrI) of the row treatment versus the column treatment.
All bolded values are statistically meaningful at the 0.05 significance level.
DIC: 7.27; Deviance: 3.27

Data source: NMA Report[8,33]

Discontinuations due to adverse events

The Submitter reported that two trials reported data on discontinuations due to AEs (i.e., KEYNOTE-054 and EORTC 18991). Using a fixed effects model, the Submitter observed that pembrolizumab significantly reduced the risk of discontinuations due to AEs as compared to PEG-IFN α2b while the risk of discontinuations due to AEs was increased as compared to observation.

Grade 3-4 AEs

The Submitter reported that two trials included in the NMA reported data on the grade 3 to 4 AEs (i.e., KEYNOTE-054 and EORTC 18991). Using a fixed effects model, the Submitter reported that pembrolizumab significantly reduced the risk of grade 3-4 AEs as compared to PEG-IFN α2b but the risk was increased as compared to observation.

Critical Appraisal of the NMA

The quality of the NMA provided by the Submitter was assessed according to the recommendations made by the ISPOR Task Force on Indirect Treatment Comparisons.[40] Details of the critical appraisal are presented below.

Table 23: Adapted ISPOR Questionnaire to Assess the Credibility of an Indirect Treatment Comparison or Network Meta-Analysis adapted from Jansen et al.[40]

ISPOR Questions	Details and Comments‡
1. Is the population relevant?	**Yes.** The study populations of all the included trials in the NMA matched in review indication, which was to evaluate the efficacy and safety of adjuvant pembrolizumab in patients with stage III melanoma.
2. Are any critical interventions missing?	**Yes, in part.** The Submitter compared pembrolizumab relative to observation, PEG-IFN α-2b, IFN α-2b (12 months) and IFN α-2b (24 months). However, there are other relevant interventions for this indication, which include nivolumab and combination dabrafenib and trametinib.
3. Are any relevant outcomes missing?	**Yes, in part.** The following outcomes were identified as important during the protocol stage: OS, DMFS, RFS, safety outcomes and HRQoL. However, given the lack of data, the Submitter was only able to assess RFS and safety outcomes.
4. Is the context (e.g., settings and circumstances) applicable to your population?	**Yes.** The settings of all the included trials in the NMA were similar.
5. Did the researchers attempt to identify and include all relevant randomized controlled trials?	**Yes.** A summary of the systematic literature review process used in the NMA was reported. The information sources, search strategy and study selection criteria were clearly described.
6. Do the trials for the interventions of interest form one connected network of randomized controlled trials?	**No.** The only closed loop in the NMA is from a three-arm trial.
7. Is it apparent that poor quality studies were included thereby leading to bias?	**No.** The Submitter used the Cochrane Risk of Bias tool to assess the quality of the included trials. Overall, the Submitter stated that there was a low risk of bias among all included trials.
8. Is it likely that bias was induced by selective reporting of outcomes in the studies?	**No.** There was no selective reporting of outcomes.
9. Are there systematic differences in treatment effect modifiers (i.e. baseline patient or study characteristics that impact the treatment effects) across the different treatment comparisons in the network?	**Yes.** The Submitter provided a qualitative assessment of treatment effect modifiers.
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.** The Submitter noted an imbalance in treatment effect modifiers across the different treatment comparisons identified prior to comparing individual study results. There were differences in stage of disease, PD-L1 and *BRAF* mutation status across the trials.
11. Were statistical methods used that preserved within-study randomization? (No naïve comparisons)	**Yes.**
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. The only closed loop in the NMA is from a three-arm trial.
13. In the presence of consistency between direct and indirect comparisons, were	**Not applicable.** There was no closed loop. The only closed loop in the NMA is from a three-arm trial.

ISPOR Questions	Details and Comments‡
both direct and indirect evidence included in the network meta-analysis?	
14. With inconsistency or an imbalance in the distribution of treatment effect modifiers across the different types of comparisons in the network of trials, did the researchers attempt to minimize this bias with the analysis?	**Yes, in part.** Although the Submitter noted an imbalance in treatment effect modifiers across the different treatment comparisons, they were unable to conduct subgroup analyses for all of the effect modifiers due to a lack of data.
15. Was a valid rationale provided for the use of random effects or fixed effect models?	**Yes.** The Submitter noted that fixed and random effects models were considered for the base case and sensitivity analyses. However, due to a limited number of studies included in the NMA, fixed effects models were reported because there were insufficient data to estimate between-study heterogeneity, and therefore the data should be interpreted with caution.
16. If a random effects model was used, were assumptions about heterogeneity explored or discussed?	**Not applicable.**
17. If there are indications of heterogeneity, were subgroup analyses or meta-regression analysis with pre-specified covariates performed?	**Yes.** Subgroup analyses were performed for mixed-disease groups but meta-regression analyses 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 NMA and the violation of the proportional hazard assumption.
18. Is a graphical or tabular representation of the evidence network provided with information on the number of RCTs per direct comparison?	**Yes.** The NMA is presented in Figure 9.
19. Are the individual study results reported?	**Yes.** The individual study results for RFS are reported in Table 19.
20. Are results of direct comparisons reported separately from results of the indirect comparisons or network meta-analysis?	**Yes.** The Submitter has provided the direct comparisons for all of the trials included in the NMA but the data are not presented in this critical appraisal.
21. Are all pairwise contrasts between interventions as obtained with the network meta-analysis reported along with measures of uncertainty?	**Yes.** The pairwise contrasts between interventions as obtained with NMA are reported along with measures of uncertainty.
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?	**Yes, in part.** The NMA reported that pembrolizumab was associated with a protective effect on RFS and safety outcomes compared to observation, PEG-IFN α-2b, IFN α-2b (12 months) and IFN α-2b (24 months). However, HRQoL and OS were not assessed in this NMA due to unavailability of data. Furthermore, there were no comparisons between pembrolizumab and other potentially relevant comparators, such as nivolumab and dabrafenib and trametinib. It should be noted that these agents are approved but not currently reimbursed in Canada. Although the Submitter identified relevant effect modifiers (i.e., stage of disease, PD-L1 and *BRAF* mutation status), they were unable to assess their effect due to a lack of data across the trials included in the NMA. Thus, the heterogeneity across the included trials may have an impact on the findings of the NMA and the reported results need to be interpreted with caution. Therefore, it is difficult

ISPOR Questions	Details and Comments‡
	to determine the overall benefit of this drug as compared to currently available adjuvant therapies in this patient population.
25. Were there any potential conflicts of interest?	Not reported.
26. If yes, were steps taken to address these?	Not reported.

Conclusion

The Submitter submitted an NMA in patients with stage III melanoma that compared adjuvant pembrolizumab to observation, PEG-IFN α-2b, IFN α-2b (12 months) and IFN α-2b (24 months).[8,33] The results of the NMA suggest that pembrolizumab has a prolonged effect on RFS relative to other active therapies after three months of treatment. Similar estimates were shown among those with stage II and stage III melanoma. Furthermore, as compared to PEG-IFN α2b, pembrolizumab reduced the risk of discontinuations due to AEs and grade 3-4 AEs while the inverse was observed when pembrolizumab was compared to observation.

There are a few limitations of the NMA that warrant discussion. First, OS and HRQoL were not assessed in the NMA due to data availability. Second, there was no comparison of pembrolizumab to other relevant comparators, such as nivolumab and dabrafenib-trametinib. Although these comparators are relevant and approved by Health Canada, they are not currently reimbursed in Canada. In response to pCODR, the Submitter communicated that they were unable to compare pembrolizumab to nivolumab because the phase III CheckMate 238 RCT, which compared nivolumab to ipilimumab, could not be included in the NMA.[34] They stated that this trial could not be included because of differences in the administration of ipilimumab and patient populations across trials. In order for the Checkmate 238 trial to be included in the NMA, it needed to be linked to the EORTC 18071 trial, which compared ipilimumab to observation. Ipilimumab was administered for one year in the CheckMate 238 trial versus up to three years in the EORTC 18071 trial. In addition, the CheckMate 238 trial included patients with stages IIIB, IIIC and IV melanoma while the EORTC 18071 trial included patients with stage IIIA-IIIC. Thus, the Submitter stated that they were unable to incorporate the CheckMate 238 trial in the NMA because they could not adjust for differences in treatment duration or patient populations. The Submitter's rationale for not indirectly comparing the effect of pembrolizumab to dabrafenib- trametinib was based on differences in patient populations. Here, treatment with dabrafenib-trametinib was intended for melanoma patients with a BRAF mutation; thus, an NMA comparing pembrolizumab to dabrafenib-trametinib would only provide indirect estimates among patients with a BRAF mutation rather than all patients with stage III melanoma. Lastly, the Submitter was unable to account for the impact of effect modifiers, such as BRAF carrier status and PD-L1 status, due to data availability. Given the aforementioned limitations of the NMA, the results should be interpreted with caution.

8 COMPARISON WITH OTHER LITERATURE

No comparisons with other literature were identified.

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 pembrolizumab for the adjuvant treatment of 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 is comprised of three medical oncologists .The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package, which is available on the 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 AND DETAILED METHODOLOGY

1. Literature search via OVID platform

Database(s): EBM Reviews - Cochrane Central Register of Controlled Trials November 2018, Embase 1974 to 2018 December 20, Ovid MEDLINE(R) ALL 1946 to December 20, 2018
Search Strategy:

#	Searches	Results
1	(Keytruda* or Pembrolizumab* or Lambrolizumab* or HSDB 8257 or HSDB8257 or Merck 3475 or Merck3475 or MK 3475 or MK3475 or Sch 900475 or Sch900475 or DPT0O3T46P).ti,ab,ot,kf,kw,hw,rn,nm.	11003
2	exp Melanoma/ or exp skin neoplasms/	453880
3	(melanoma* or melanotic or melanocarcinoma* or melanomalignoma* or naevocarcinoma* or nevocarcinoma* or pigmentary cancer* or (skin adj3 (cancer* or neoplas* or tumor* or tumour*))).ti,ab,kf,kw.	321154
4	or/2-3	540557
5	1 and 4	4426
6	5 use medall	825
7	5 use cctr	202
8	*pembrolizumab/ or (Keytruda* or Pembrolizumab* or Lambrolizumab* or HSDB 8257 or HSDB8257 or Merck 3475 or Merck3475 or MK 3475 or MK3475 or Sch 900475 or Sch900475).ti,ab,kw,dq.	7184
9	exp melanoma/ or exp skin tumor/	370626
10	(melanoma* or melanotic or melanocarcinoma* or melanomalignoma* or naevocarcinoma* or nevocarcinoma* or pigmentary cancer* or (skin adj3 (cancer* or neoplas* or tumor* or tumour*))).ti,ab,kw,dq.	319786
11	or/9-10	475544
12	8 and 11	2950
13	12 use oemezd	2042
14	13 and conference abstract.pt.	894
15	limit 14 to yr=2013-current	891
16	13 not conference abstract.pt.	1148
17	(Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or Equivalence Trial or Clinical Trial, Phase III).pt.	1110979
18	Randomized Controlled Trial/	1001214
19	exp Randomized Controlled Trials as Topic/	284676
20	"Randomized Controlled Trial (topic)"/	155048
21	Controlled Clinical Trial/	552561
22	exp Controlled Clinical Trials as Topic/	296135
23	"Controlled Clinical Trial (topic)"/	9876
24	Randomization/	177215
25	Random Allocation/	194042
26	Double-Blind Method/	399873
27	Double Blind Procedure/	156410
28	Double-Blind Studies/	262474
29	Single-Blind Method/	76080
30	Single Blind Procedure/	33436

31	Single-Blind Studies/	78027
32	Placebos/	329277
33	Placebo/	328171
34	Control Groups/	111326
35	Control Group/	111233
36	(random* or sham or placebo*).ti,ab,hw,kf,kw.	4013895
37	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.	782685
38	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.	3056
39	(control* adj3 (study or studies or trial* or group*)).ti,ab,kf,kw.	2627380
40	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf,kw.	95165
41	allocated.ti,ab,hw.	178019
42	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf,kw.	115218
43	((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.	25214
44	(pragmatic study or pragmatic studies).ti,ab,hw,kf,kw.	956
45	((pragmatic or practical) adj3 trial*).ti,ab,hw,kf,kw.	11232
46	((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.	17648
47	(phase adj3 (III or "3") adj3 (study or studies or trial*)).ti,hw,kf,kw.	129001
48	or/17-47	5740519
49	15 and 48	251
50	6 or 16	1973
51	48 and 50	385
52	7 or 51	587
53	remove duplicates from 52	477
54	49 or 53	728
55	limit 54 to english	690
56	55 and conference abstract.pt.	302
57	55 not conference abstract.pt.	388

2. Literature search via PubMed

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

Search	Query	Items found
#7	Search (#5 AND publisher[sb]) Filters: English	52
#6	Search (#5 AND publisher[sb])	53
#5	Search (#3 AND #4)	830
#4	Search Melanoma[mh] or skin neoplasms[mh] or melanoma*[tiab] or melanotic[tiab] or melanocarcinoma*[tiab] or melanomalignoma*[tiab] or naevocarcinoma*[tiab] or nevocarcinoma*[tiab] or pigmentary cancer*[tiab] or skin cancer*[tiab] or skin neoplasm*[tiab] OR skin tumor*[tiab] OR skin tumour*[tiab]	211135
#3	Search (#1 OR #2)	2074

Search	Query	Items found
#2	Search Keytruda*[tiab] OR Pembrolizumab*[tiab] OR Lambrolizumab*[tiab] OR HSDB 8257[tiab] OR HSDB8257[tiab] OR Merck 3475[tiab] OR Merck3475[tiab] OR MK 3475[tiab] OR MK3475[tiab] OR Sch 900475[tiab] OR Sch900475[tiab] OR DPT0O3T46P[rn]	2074
#1	Search "pembrolizumab" [Supplementary Concept]	755

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: Keytruda/pembrolizumab, melanoma

   Select international agencies including:

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

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

   Search: Keytruda/pembrolizumab, melanoma

   Conference abstracts:

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

   European Society for Medical Oncology (ESMO)
   http://oncologypro.esmo.org/Meeting-Resources

   Search: Keytruda/pembrolizumab, melanoma - last 5 years

Literature Search Methods

The literature search was performed by the pCODR Methods Team using the search strategy above.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-) with in-process records & daily updates via Ovid; Embase (1974-) via Ovid; The Cochrane Central Register of Controlled Trials (November 2018) via Ovid and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were keytruda and pembrolizumab 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 May 2, 2019.

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) and the European Society for Medical Oncology (ESMO) 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. One member 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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