pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Pembrolizumab (Keytruda) for Non-small Cell Lung Cancer

November 3, 2016

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1 GUIDANCE IN BRIEF

This Clinical Guidance Report was prepared to assist the pCODR Expert Review Committee (pERC) in making recommendations to guide funding decisions made by the provincial and territorial Ministries of Health and provincial cancer agencies regarding pembrolizumab for the treatment of patients with metastatic non-small cell lung carcinoma (NSCLC) whose tumors express PD-L1 (as determined by a validated test) and who have disease progression on or after platinum-containing chemotherapy. 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 for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 (as determined by a validated test) and who have disease progression on or after platinum-containing chemotherapy conducted by the Lung 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 and NSCLC, a summary of submitted Provincial Advisory Group Input on pembrolizumab and NSCLC, and a summary of submitted Registered Clinician Input on pembrolizumab and NSCLC, and are provided in Sections 2, 3, 4, and 5 respectively.

1.1 Introduction

As stated in the Health Canada Product Monograph, pembrolizumab is a high affinity antibody against PD-1, which exerts dual ligand blockade of the PD-1 pathway, including PD-L1 and PDL2, on antigen presenting or tumour cells. By inhibiting the PD-1 receptor from binding to its ligands, pembrolizumab reactivates tumour-specific cytotoxic T lymphocytes in the tumour microenvironment and thereby also reactivates anti-tumour immunity.[1]

On April 15, 2016 pembrolizumab was issued marketing authorization with conditions by Health Canada, pending the results of studies to verify its clinical benefit. Pembrolizumab is indicated for metastatic NSCLC whose tumours express PD-L1 (as determined by a validated test) and who have disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumour aberrations should have disease progression on authorized therapy for these aberrations prior to receiving pembrolizumab.[1]

Pembrolizumab is also been issued marketing authorization without conditions by Health Canada for the treatment of patients with unresectable or metastatic melanoma who have not received prior treatment with ipilimumab. Patients with BRAF V600 mutant melanoma may have received prior BRAF inhibitor therapy.[1]

The recommended dose for unresectable or metastatic melanoma and metastatic NSCLC, as it appears in the Health Canada Product Monograph, is 2 mg/kg administered intravenously over 30 minutes every 3 week. According to the Health Canada Product Monograph, patients should be treated with pembrolizumab until confirmed disease progression or unacceptable toxicity. Atypical responses (i.e., an initial transient increase in tumour size or small new lesions within the first few months followed by tumour shrinkage) have been observed. Clinically stable patients with initial evidence of disease progression should remain on treatment until disease progression is confirmed.[1] Of note, the Health Canada approved indication for NSCLC was based on the

Keynote 001 study, a phase 1 study primarily aimed at evaluating the safety, side-effect profile, and antitumor activity of pembrolizumab. A maximum duration of treatment with pembrolizumab (of 2 years) was introduced in a subsequent phase 2/3 study, Keynote 010 (this trial will be described in detail in the later sections of the report).

According to the Health Canada Product Monograph, patients should be selected for treatment of metastatic NSCLC with pembrolizumab based on the presence of positive PD-L1 expression defined as a Tumour Proportion Score (TPS) ≥ 50%, PDL1 expression with TPS ≥ 50% should be determined by an experienced laboratory using a validated test. The Health Canada Product Monograph states that it is preferred that, a test authorized by Health Canada, or one that is equivalent to that used in clinical trials (e.g. PD-L1 IHC 22C3 pharmDx kit from Dako) should be considered.[1] Of note, PD-L1 IHC 22C3 pharmDx was issued a license (No.: 96396) by Heath Canada on January 15, 2016.

Pembrolizumab is currently available is as a single-use vial containing 50 mg of pembrolizumab.

The submitter, Merck Canada Inc., had requested funding for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 (as determined by a validated test) and who have disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on authorized therapy for these aberrations prior to receiving pembrolizumab. Funding is being requested for patients with a PD-L1 TPS of > 1%, based on the results of KEYNOTE 010, not only in patients with a PD-L1 TPS of > 50% as per the current Health Canada Product Monograph.

The objective of the systematic review is to evaluate the efficacy and safety of pembrolizumab compared to standard therapy in previously treated patients with advanced or metastatic NSCLC whose tumours express PD-L1 and who have progressed on or after platinum-containing chemotherapy and an appropriate tyrosine kinase inhibitor (TKI) for patients with EGFR (epidermal growth factor receptor) mutations or ALK (anaplastic lymphoma kinase) rearrangements.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

Trials

One randomized controlled trial was identified that met the selection criteria of this review.[2] KEYNOTE 010 is an open-label, randomized phase 2/3 trial comparing two doses (2mg/kg versus 10mg/kg) of pembrolizumab to docetaxel in patients with PD-1 positive NSCLC who have progressed on or after platinum-based doublet chemotherapy.

The trial, conducted in 202 academic centres in 24 countries, including Canada, enrolled patients between August 2013 and February 2015, according to the following criteria:

- ≥18 years of age
- Disease progression as per RECIST (version 1.1) after two or more cycles of platinum-doublet chemotherapy and an appropriate TKI for patients with EGFR or ALK mutations
- Measurable disease as per investigator assessed RECIST
- A ECOG performance status of 0 or 1
- Provision of a tumour sample, and PD-L1 tumour expression on at least ≥1% of tumour cells, referred to as a tumour proportion score (TPS) of ≥1%.
- Patients previously treated with a PD-1 checkpoint inhibitor or docetaxel, or with active brain metastases were excluded.

PD-L1 tumour expression testing was carried out at a central laboratory using the Dako PD-L1 immunohistochemistry assay and the murine 22C3 anti-human PD-L1 antibody. A total of 1034 patients met the eligibility criteria and were randomized into the trial. Randomization was stratified according to PD-L1 tumour expression (TPS ≥1% versus TPS ≥50%), geographic site (East Asia versus non-East Asia), and ECOG performance status (0 versus 1). Assigned treatment continued for 24 months in all treatment groups or until disease progression, intolerable side effects, or physician decision or patient withdrawal. Patients randomized to docetaxel were not permitted to crossover to receive pembrolizumab. There were 34 patients who withdrew consent after learning they had been allocated to the docetaxel treatment group.

The primary endpoints of the trial were overall survival (OS) and progression-free survival (PFS); and secondary endpoints included safety, response rate (complete and partial), and duration of response. Exploratory endpoints included patient reported outcomes (using EORTC Quality of Life Questionnaire (QLQ)-C30, the QLQ-Lung Cancer Module (LC-13), and the EuroQoL 5-Dimensions). For efficacy analyses, the assessment of PFS and response was carried out by independent central review. All treatment decisions, however, were made according to investigator assessment of immune-related response criteria. Patients who progressed by investigator assessment criteria were permitted to remain on study treatment until their next radiologic scan taken four to six weeks later.

Of the 1034 randomized patients, 345 patients were allocated to the 2mg/kg pembrolizumab group, 346 were allocated to the 10mg/kg pembrolizumab group, and 343 were allocated to docetaxel. The median duration of treatment was 3.5 months in both pembrolizumab treatment groups, and was two months in the docetaxel group. After discontinuation of study treatment, 422 patients (41%) received subsequent anti-cancer therapy: 138 patients (40%) in the 2mg/kg pembrolizumab group, 133 patients (38%) in the 10mg/kg pembrolizumab group, and 151 patients (44%) in the docetaxel group. In each treatment group the majority of patients received chemotherapy as subsequent treatment.

In the all-patient population (TPS ≥1%), treatment groups were balanced for baseline characteristics. The median age of patients was approximately 63 years, with 24% (n=48) of patients aged 70 years or older. Most patients were Caucasian (72%), former or current smokers (80%), had non-squamous histology (70%), an ECOG performance status of 1 (66%), and had received one line of previous systemic treatment (69%). PD-L1 testing was performed on archived tumour samples in 455 patients (44%) and new tumour samples in 578 patients (56%). There were 442 patients (43%) who had a TPS score of ≥50%: 139 in the 2mg/kg pembrolizumab group, 151 in the 10mg/kg pembrolizumab group, and 152 in the docetaxel group. The distribution of baseline characteristics in this patient subgroup was similar to the all-patient population.

At the time of the primary efficacy analysis, 79%, 78% and 92% of patients had discontinued treatment in the 2mg/kg pembrolizumab, 10mg/kg pembrolizumab, and docetaxel treatment groups, respectively. Similar percentages of discontinuations were observed in the TPS ≥50% patient subgroup. Progressive disease was indicated as the primary reason for treatment discontinuation in all treatment groups.

Overall, the KEYNOTE trial was well conducted owing to its design features (e.g., appropriate randomization methods, the use of independent central review for the assessment of key efficacy outcomes) and clear reporting (e.g., explanation of the disposition of patients through the trial). However, the trial did have limitations, which are summarized below:

- The trial was open label, and as such, patients, investigators and Sponsor personnel involved the trial were aware of treatment assignment, which can

introduce bias and threaten the internal validity of the trial. However, the potential for bias is minimized in KEYNOTE 010 through the use of independent central review of key efficacy outcomes, the blinding of parties to the PD-L1 status of patients, and the use of blinded data-analysts.

- There were 34 patients (9%) who withdrew consent after learning they had been allocated to the docetaxel treatment group. Although this type of attrition is not uncommon in NSCLC trials (and likely minimal considering the number of patients), it does introduce the potential for bias in the assessment of OS, as patients who dropped out could seek out alternative treatments.
- After discontinuing study treatment, 422 patients (41%) received subsequent anti-cancer therapy. The OS results of the trial (a primary endpoint) are likely confounded by these treatments.
- Given the uncertainty that exists around the optimal PD-L1 tumour expression threshold for clinical benefit, it is unfortunate that the trial did not include patients with no expression level, and that prospective efficacy analyses were limited to two patient PD-L1 expression subgroups (TPS ≥1% and ≥50%).
- QOL data were assessed in the KEYNOTE 010 trial but have not been published in the public domain and undergone peer-review. The QOL data reviewed for the pCODR submission is incomplete, and suffers from selective reporting in documents provided by the Submitter.

A brief summary, highlighting the key outcomes of the trial, is provided in Table 1. All efficacy analyses were performed by intent-to-treat and the safety analysis included all patients who received at least one dose of study medication. Patient-reported QOL was assessed using the EORTC QLQ-C30, the QLQ-LC-13, and the EuroQoL 5-Dimensions (EQ-5D). For the QLQ-C30, a mean change from baseline of 10% or greater was considered the minimal clinically important difference (MCID), with lower scores indicative of improvement in symptoms and side effects. For the EQ-5D, possible scores range from -0.594 to 1.0 with a change in score of ≥0.06 deemed the MCID.

Table 1: Highlights of Key Outcomes

KEYNOTE 010[2]	All Patients with PD-L1 TPS of ≥1%			Patients with PD-L1 TPS ≥50%		
Key Efficacy Outcomes[A]	Pembro 2mg/kg (n=344)	Pembro 10mg/kg (n=346)	Docetaxel (n=343)	Pembro 2mg/kg (n=139)	Pembro 10mg/kg (n=151)	Docetaxel (n=152)
Primary Outcome: OS						
Median, months (95% CI)	10.4 (9.4-11.9)	12.7 (10.0-17.3)	8.5 (7.5-9.8)	14.9 (10.4-NR)	17.3 (11.8-NR)	8.2 (6.4-10.7)
HR (95%CI)[B]	0.71 (0.58-0.88)	0.61 (0.49-0.75)	-	0.54 (0.38-0.77)	0.50 (0.36-0.70)	-
p-value	p=0.0008	p<0.0001	-	p=0.0002	p<0.0001	-
Primary Outcome: PFS						
Median, months (95% CI)	3.9 (3.1-4.1)	4.0 (2.7-4.3)	4.0 (3.1-4.2)	5.0 (4.0-6.5)	5.2 (4.1-8.1)	4.1 (3.6-4.3)
HR (95%CI)[B]	0.88 (0.74 to 1.05)	0.79 (0.66-0.94)	-	0.59 (0.44-0.78)	0.59 (0.45-0.78)	-
p-value	p=0.07[C]	p=0.004[C]	-	p=0.0001	p<0.0001	-

KEYNOTE 010[2]	All Patients with PD-L1 TPS of ≥1%			Patients with PD-L1 TPS ≥50%		
HrQoL	n=212	n=210	n=146	n=90	n=103	n=60
QLQ-C30 LS Mean Change from baseline at 12 weeks (95% CI)	-1.2 (-3.7 to 1.4)	-2.5 (-5.1 to 0.0)	-3.8 (-6.7 to 0.9)	1.5 (-2.5 to 5.5)	-3.0 (-6.8 to 0.7)	-6.9 (-11.5 to -2.2)
LS Mean Difference[D] (95% CI); p-value	2.7 (-1.1 to 6.4) p=0.16	1.3 (-2.4 to 5.0) p=0.49	-	8.3 (2.4 to 14.3) p=0.006	3.8 (-1.9 to 9.6) p=0.19	-
Harms Outcomes, n (%)	**Pembro 2mg/kg (n=339)**	**Pembro 10mg/kg (n=343)**	**Docetaxel (n=309)**			
TRAE Grade ≥3	43 (13)	55 (16)	109 (35)			
TRAE (any grade)	215 (63)	226 (66)	251 (81)			
WDTRAE	15 (4)	17 (5)	31 (10)			

Abbreviations: AE = adverse event, CI = confidence interval, HR = hazard ratio, HRQoL = health-related quality of life, LS - least squares; NA - not applicable; NR = not reported, Pembro - pembrolizumab; QLQ-C30 - EORTC Quality of Life Questionnaire C-30; SD = standard deviation, TRAE = treatment-related adverse event, WDTRAE = withdrawal due to treatment-related adverse event; "-" docetaxel is the treatment reference group.

Notes:
[A] Data cut-off date is September 30, 2015.
[B] HR is for pembrolizumab versus docetaxel, where a HR < 1 favours pembrolizumab 2mg/kg or 10mg/kg.
[C] Result is not statistically significant because it did not meet the pre-specified criterion declaring statistical significance for PFS (p<0.001).
[D] Pembrolizumab treatment group versus docetaxel.

Efficacy

After a median follow-up time of 13.1 months (range, 8.6-17.7), a total of 521 patients had died: 172 (50%) in the pembrolizumab 2mg/kg group, 156 (45%) in the 10mg/kg group, and 193 (56%) in the docetaxel group.

Overall, compared to docetaxel, pembrolizumab significantly prolonged OS, regardless of dose, among all patients (TPS ≥1%) but the magnitude of benefit was greater in the TPS ≥50% patient subgroup. The treatment benefit was also evident in all other patient subgroups examined, however, the difference between treatment groups did not reach statistical significance in the following patients subgroups: those with squamous cell histology, mutant EGFR status, aged ≥70 years,[a] and an ECOG status of 0. The subgroups analysis was pre-specified for ECOG PS, EGFR status and age of tumour sample. For tumour histology it was a post-hoc exploratory subgroup analysis. Further, the use of archived versus new tumour sample tissue for PD-L1 testing did not appear to affect treatment benefit.

Considering all patients (TPS ≥1%), a total of 776 PFS events were observed during the follow-up period; 226 (77%) in the 2mg/kg pembrolizumab group, 254 (73%) in the 10mg/kg group, and 256 (75%) in the docetaxel group. No differences in PFS were found between treatment groups. Compared to docetaxel, pembrolizumab at either dose was associated with a PFS benefit among patients with a TPS ≥50%, but not in patients with a TPS score below this expression level. The results of subgroup analyses showed a statistically significant PFS benefit in the following subgroups of patients: male gender, ECOG of 1, and those patients with EGFR wild-type status.

[a] At the request of the pCODR review team, the submitter performed a post-hoc subgroup analysis for patients aged ≥ 70 years. The subgroup analysis for patients ≥65 years was presented in the trial publication and was pre-specified.

Health-related Quality of Life (EORTC-QLQ-C30, EORTC-QLQ-LC13 and EQ-5D)

In all patients (TPS ≥1%) at week 12, differences in the mean change from baseline on the EORTC-QLQ-C30 showed numerical improvements (i.e., less deterioration) of the Global Health Status Score in patients treated with either dose of pembrolizumab compared to docetaxel. These differences, however, did not reach the MCID of >10%. Among patients in the TPS ≥50% subgroup, the difference in mean change did reach statistical significance in the 2mg/kg pembrolizumab group. For the majority of lung cancer symptoms, patients treated with pembrolizumab showed numerical improvements from baseline, while patients treated with docetaxel showed numerical worsening from baseline. Specifically, in all patients (TPS ≥ 1%) at week 12, alopecia, peripheral neuropathy, and sore mouth were statistically significantly improved with pembrolizumab 2mg/kg versus docetaxel. In the TPS ≥50% patient subgroup, dyspnea, hemoptysis, alopecia, and sore mouth were statistically significantly improved with pembrolizumab 2mg/kg versus docetaxel.

Considering all treatment groups, EQ-5D scores generally increased over time, with similar scores observed among the treatment groups at weeks 3 and 6, and lower scores observed in the docetaxel group at weeks 12, 24 and 36 (Table 12). At most assessment periods the mean differences in index scores between pembrolizumab groups versus docetaxel were small (<0.04), except at week 36 where at both doses the difference exceeded the MCID of 0.06 (difference versus docetaxel for both doses=0.18, p=0.01). It should be noted, however, that the number of patients included in the analysis at week 36 included only 14% of trial patients, which limits interpretation of the findings.

Harms Outcomes

Compared to docetaxel, pembrolizumab was associated with fewer all grade and grade 3-5 treatment-related adverse events (TRAE). A higher percentage of patients receiving docetaxel required dose modifications due to TRAE: 42% versus 29% and 30% in the 2mg/kg and 10mg/kg pembrolizumab treatment groups, respectively. Treatment discontinuations due to TRAE were also higher among patients treated with docetaxel: 10% versus 4% and 5% of patients in the 2mg/kg and 10mg/kg groups, respectively, while treatment interruptions were similar among the treatment groups (22% and 24% in the 2mg/kg and 10mg/kg pembrolizumab groups, respectively, versus 24% in the docetaxel group).

Immune-related events of special interest occurred in 20% (69 of 339 patients) of patients receiving pembrolizumab at a dose of 2mg/kg, and 19% (64 of 343 patients) of patients at a dose of 10mg/kg. The most frequent type of events, any grade (2mg/kg versus 10mg/kg dose), included hypothyroidism (8% at both doses), pneumonitis (5% versus 4%), and hyperthyroidism (4% versus 6%). Of these events, only pneumonitis and severe skin reactions occurred at a severity of grade 3 or higher in greater than 1% of patients.

The trial reported 11 deaths attributable to study treatment. There were three deaths (<1%) in the 2mg/kg pembrolizumab group, three deaths (<1%) in the 10mg/kg pembrolizumab group, and 5 deaths (2%) in the docetaxel group.

1.2.2 Additional Evidence

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

Patient Advocacy Group Input

Input on pembrolizumab for the treatment of patients with metastatic NSCLC) whose tumors express PD-L1 (as determined by a validated test) and who have disease progression on or after

platinum-containing chemotherapy was provided by three patient advocacy groups: a submission from Lung Cancer Canada (LCC) and a joint submission from British Columbia Lung Association (BCLA) and Ontario Lung Association (OLA).

From a patient perspective, lung cancer impacts many aspects of day-to-day life for people living with it. Specifically, it affects the respondents' ability to work, travel, socialize and participate in leisure and physical activities. It also affects their relationships with family and friends, emotional well-being and may cause financial hardship. It was reported by both patient and caregiver respondents that high symptom burden of lung cancer is difficult to manage. These symptoms may include: loss of appetite, cough, pain, and shortness of breath. Moreover, one of the most common symptom burden for lung cancer patients is fatigue or lack of energy. For the vast majority of this patient population, the current standard of care are chemotherapy or radiation. Chemotherapy is viewed as a necessary, but feared treatment. The infusions themselves presented challenges beyond travel time and hospital visits; some respondents reported feeling sick even before the infusion was completed and that significant recovery time was needed after each chemotherapy infusion.

Respondents who do not have experience with the drug under review reported that key treatment outcomes they would most like to address are: to stop or slow the progression of the disease, to reduce or eliminate side effects (e.g., reduce pain, fatigue, cough and shortness of breath), and to improve appetite and energy. They would also like there to be less or no cost burden associated with new treatments.

For respondents who have experience with pembrolizumab, a majority of respondents reported no side effects to mild side effects that are easily managed. In a few cases there have been stronger side effects that had to be managed either by over-the-counter drugs or prescription drugs. Most respondents, however, found that the management was tolerable and did not interfere with their day-to-day life. In some cases, there was uncertainty with distinguishing the side effects of pembrolizumab from other causes. Many of the respondents mentioned that they went from feeling really sick before treatment, to feeling better within days of their first treatment up to their first few treatments. Respondents also stated that pembrolizumab allows them to have a high quality of life, provides them with the time to do the things that they love the most and extends that time with their family. Infusion time is less frequent because pembrolizumab is infused every three weeks compared to every two weeks for nivolumab, and in their opinion, could be viewed as an advantage in terms of time and hospital resources.

Provincial Advisory Group (PAG) Input

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

Clinical factors:

- Clarity of patients eligible, including for patients who have not received platinum-based doublet chemotherapy or who have received oral targeted therapies
- Clarity on dose and duration of treatment
- The need for PD-L1 testing, timing of the testing and the accuracy of the test results

Economic factors:

- Drug wastage
- Implementation of PD-L1 testing, which is not currently funded

Registered Clinician Input

Two clinician input on pembrolizumab for NSCLC were received:

1. Dr. Sandeep Sehdev
2. A joint submission from Dr. Rosalyn Juergens and Dr. Quincy Chu, on behalf of Lung Cancer Canada, Medical Advisory Committee, with five other clinicians.

Overall, the clinicians providing input noted that pembrolizumab is more effective and better tolerated than chemotherapy. They felt that pembrolizumab provides another immunotherapy treatment option, with shorter infusion time and less frequent dosing schedule than nivolumab, for patients who have disease progression and whose tumours express PD-L1. They identified that testing for PD-L1 expression is important but that the turn-around time for test results would delay initiation of treatment.

Summary of Supplemental Questions

The following supplemental questions were identified during the development of the review protocol as relevant to the pCODR review of pembrolizumab for NSCLC:

1. What is the accuracy of programmed death ligand 1 (PD-L1) diagnostic antibody assays?
2. What is the clinical utility of PD-L1 testing in patients with NSCLC?
3. What is the effectiveness of programmed cell death protein 1 (PD-1)/PD-L1 checkpoint inhibitors for treating patients with NSCLC with different levels of PD-L1 expression?

The limited literature search did not identify any evidence to inform on the accuracy of available PD-L1 diagnostic antibody assays (i.e., sensitivity, specificity, and detection rate), or the clinical utility of PD-L1 testing compared to no testing (i.e., clinical benefits and harms of testing) in patients with NSCLC. Seven reports, considered higher-quality evidence, were identified that addressed the effectiveness of PD-1/PD-L1 inhibitors in treating NSCLC patients with different levels of PD-L1 expression. Of these, two were HTAs that narratively summarized the evidence from individual randomized trials, and five were systematic reviews that included a meta-analysis of trials (randomized and non-randomized) that examined outcomes by PD-L1 expression. In the absence of evidence on the accuracy and clinical utility of PD-L1 testing, however, it is questionable whether combining trial data is actually appropriate and yields relevant, accurate and reliable findings. Therefore, the findings of these meta-analyses have not been summarized in this report. The results of individual randomized trials assessing the effectiveness of PD-1/PD-L1 checkpoint inhibitors for treating patients with NSCLC with varying levels of PD-L1 expression are presented in Sections 6 and 8 of this report.

Comparison with Other Literature

See Section 8 for further details on the comparison with other literature section.

1.2.3 Factors Related to Generalizability of the Evidence

Table 2 addresses the generalizability of the evidence and an assessment of the limitations and sources of bias can be found in Sections 6.3.2.1e. The use of pembrolizumab in the general Canadian lung cancer population can be guided by specific details of the KEYNOTE-10 clinical trial, clinical experience with this class of monoclonal antibodies against the PD-1 immune checkpoint receptor, and the natural history of advanced non-small cell lung cancer (NSCLC). Key issues to consider:

Table 2: Assessment of generalizability of evidence for pembrolizumab in patients with previously treated NSCLC[2]

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
Population	Performance Status	The trial limited eligibility to patients with an ECOG performance status of 0 or 1. All patients with PD-L1 ≥1: ECOG 0: n=348 (33%) ECOG 1: n=678 (66%) Subgroup analyses were conducted (a priori) by performance status for OS and PFS. Patients with ECOG status of 2 were excluded from the trial.	Does performance status limit the interpretation of the trial results (efficacy or toxicity) with respect to the target population (e.g., Canadian clinical practice, patients without the factor, etc.)?	The clinical trial was restricted to patients ECOG 0-1 and specifically excluded patients with ECOG ≥2. Similar criteria have been used in other studies with PD-1 and PD-L1 immune checkpoint inhibitors. In general, patients with ECOG 0-2 constitute those in the outpatient setting while ECOG 3-4 patients are usually hospitalized. Systemic therapies with higher response rates and limited toxicity (e.g. oral targeted therapy in EGFR or ALK mutated NSCLC) have been considered appropriate for hospitalized patients. While drug is reasonably well tolerated, overall response rates to pembrolizumab in KEYNOTE-10 were 18%. Median time to response was 9 weeks with only partial responses noted as the best observed response. The Clinical Guidance Panel noted that response rate is not necessarily the best measure of efficacy for this class of drugs. However, the lack of immediate benefit may make these drugs unsuitable for use in hospitalized patients. The use of pembrolizumab should therefore be restricted to the outpatient setting for patients with ECOG 0-1 as per the clinical trial. Real world experience with this class of drugs has suggested that patients with ECOG = 2 have similar drug tolerance; clinical judgement should therefore be used when offering pembrolizumab to patients with ECOG = 2.
	Age	The trial eligibility criteria were not limited by patient age. Median age of patients was 63 years. 429/1033 (42%) patients were ≥ 65 years Subgroup analyses were conducted (a priori) by age group for OS and PFS. An ad-hoc analysis requested by the review team suggested the following: The number and proportion of subjects ≥70 years old are evenly distributed across treatment groups: 79 (23.0%), 86 (25.0%), 83 (24.0%) for docetaxel, pembrolizumab 2 mg/kg and 10 mg/kg arms, respectively. There is no statistical evidence that the hazard ratios were different in these 2 subgroups. The p-values for treatment-by-sub-group interaction for OS and PFS, based on the Q-statistic, was p=0.3727 for OS (pembrolizumab 2 mg/kg vs. docetaxel) and	Does the age in the trial limit the interpretation of the trial results with respect to the target population?	The KEYNOTE-10 trial did not restrict patient age. The median age on trial was 63 which is comparable to the Canadian population. Patients ≥70 years old composed 23-25% of all treatment arms with similar OS benefit. Therefore, pembrolizumab can be considered for all adult patients.

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
		p=0.7426 for OS (pembrolizumab 2 mg/kg vs. docetaxel)"		
	Organ dysfunction	The trial limited eligibility to patients with adequate organ function, including hematological, renal, hepatic, endocrine, and coagulation.	Did the exclusion of patients with organ dysfunction limit the interpretation of the trial results with respect to the target population (e.g., Canadian clinical practice, patients without the factor, etc.)?	Patients on trial were required to have adequate organ function. Hepatic or renal impairment does not appear to increase toxicity of pembrolizumab. Drug related organ failure is also extremely rare. Besides in the setting of specific disease characteristics described below, pembrolizumab can be used with adequate monitoring in the most settings of stable organ dysfunction. The few exceptions include pneumonitis requiring steroid use, interstitial lung disease, and a patient history of autoimmune disease.
	Metastatic Sites	The trial excluded patients with active brain metastases and carcinomatous meningitis, and included patients with stable metastases.	Did the exclusion of patients with certain sites of metastatic disease limit the interpretation of the trial results with respect to the target population (e.g., Canadian clinical practice, patients without the factor, etc.)?	Patients with uncontrolled brain metastases or carcinomatous meningitis were excluded from the trial. This is similar to most drugs as systemic therapies often have poor CNS penetration. Patients with stable brain metastases were eligible and some cases even showed improvement of intracranial disease without the addition of local therapy. Other sites of metastases should not be considered contraindications for therapy unless they are contributing to a poor ECOG status.
	Ethnicity or Demographics	The trial was conducted in Canada and 23 other countries: Argentina, Australia, Belgium, Brazil, Chile, Czech Republic, Denmark, France, Germany, Greece, Hungary, Italy, Japan, Lithuania, Netherlands, Portugal, Russia, South Africa, South Korea, Spain, Taiwan, UK, and US. All patients with PD-L1 ≥1: East Asia: n=190 (18%) Not East Asia: n=843 (82) White: n=747 (72%) Asian: n=217 (21%) Black: n=28 (3%) Other: n=12 (1%)	If the trial was conducted outside of Canada, is there a known difference in effect based on ethnicity that might yield a different result in a Canadian setting? Also, if the demographics of the study countries differ from Canada, the average treatment effect in the trial might not be representative of a Canadian setting.	The clinical study of pembrolizumab was conducted world-wide, including several Canadian centres, with similar efficacy across populations. This would be representative of the ethnic diversity across Canada.
	Biomarkers	The trial enrolled patients who were PD-L1 positive; patients further grouped by PD-L1 tumour proportion score (TPS), ≥1% vs. ≥50%. Randomization was stratified, and efficacy analyses were conducted by PD-L1 TPS status.	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	The trial enrolled patients with tumor staining for the PD-L1 protein. Patients on KEYNOTE-10 were required to have a tumor proportion score (TPS) of PD-L1 ≥1%. Sixty-six percent of patients screened for the trial had TPS ≥1%. Those with TPS ≥50% (28% of all screened patients) seemed to derive even greater benefit with pembrolizumab. Patient tumours were screened with the

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
		PD-L1 TPS ≥1%: n=1033 PD-L1 ≥50%: n=442 PD-L1 1-49%: n=591	substantial group of patients excluded from the trial to whom the results could be generalized?	22C3 PD-L1 antibody. There is ongoing debate as to whether this is the best assay. The BluePrint Consortium is actively comparing several commercial PD-L1 assays. Until these results are published, PD-L1 assays with comparable performance to the 22C3 antibody should be considered reasonable to access pembrolizumab. The expectation is that two thirds of eligible Canadian patients will test ≥1% TPS regardless of NSCLC histologic or molecular subtype. There is no comparative evidence to support the efficacy or harm of pembrolizumab in patients with <1% TPS. Based on opinion, there do not appear to be any concerns about drug safety in this patient population.
Intervention	Treatment Intent	The intent of treatment in the trial was palliative.	Are the results of the treatment generalizable to an alternative treatment intent? (i.e., if the trial is palliative in intent, could the therapy also be used in the adjuvant setting or vice versa?)	Based on the KEYNOTE-10 study alone, the efficacy of pembrolizumab cannot be generalized beyond palliative intent therapy in previously treated patients. Clinical studies of pembrolizumab in the adjuvant setting are currently being conducted but no conclusions can be drawn at the present time.
	Line of therapy	The trial was conducted in previously treated patients (i.e., platinum doublet, or TKI without previous PD-1/PD-L1 immunotherapy).	Are results of the trial generalizable to patients who have been previously treated with oral targeted therapies (e.g. afatinib, crizotinib, etc.) but not platinum-based chemotherapy?	All patients received pembrolizumab after failure of at least 1 platinum-doublet based therapy, and failure of an oral tyrosine kinase inhibitor (TKI) if patients had EGFR or ALK mutated NSCLC. Mutated patients accounted for <10% of the total trial population. There are currently second and third generation TKI's available that have shown efficacy after failure of a previous TKI. These agents would likely be the preferred choice after failure of first line TKI therapy for gene mutated patients. If subsequent lines of TKI therapy are unavailable, then treatment with a platinum-doublet should be considered next line of therapy. PD-1 inhibitors like pembrolizumab can be considered an option after platinum-doublet therapy has failed in all patients (mutated or wild-type), or if traditional second-line therapies are intolerable or not accessible. All have to fail platinum doublet, except in patients who cannot tolerate the platinum portion of their treatment.
	Administration of intervention	Two different doses of pembrolizumab were studied: 2mg/kg vs. 10 mg/kg.	Are the results of the trial generalizable to a different dose or administration schedule?	Similar OS is observed between 2 mg/kg and 10 mg/kg pembrolizumab dosing given every 3 weeks. Similar toxicity as seen for both doses. The lower dose would be preferred from a health economic perspective. The lower dose is also the Health Canada approved

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
		No difference in efficacy outcomes (OS, PFS) was found between the two doses of pembrolizumab.		recommended dose for NSCLC. No other dosing schedule has been studied.
	Optimal Duration of Treatment and treatment discontinuation	PAG is seeking clarity on the duration of treatment and treatment discontinuation. Treatment continued for 24 months in all treatment groups or until disease progression, intolerable side effects, or physician decision or patient withdrawal. The median duration of treatment was 3.5 months in both pembrolizumab treatment groups, and was two months in the docetaxel group.	What is the optimal duration of treatment and treatment discontinuation?	This remains unclear given current studies and according to the Keynote 010 study patients were treated until progression, intolerable toxic effects or for a maximum 24 months. Patients can be treated beyond initial evidence of progression given the possibility of pseudo-progression on immunotherapy, although this phenomenon appears less common in lung cancer (~5%) then other diseases such as melanoma.
Comparator	Standard of Care	The comparator in the trial was docetaxel, which is a standard of care in Canada.	Is docetaxel is an appropriate comparator?	For patients with non-EGFR or ALK-mutated NSCLC, docetaxel would be considered an appropriate comparator. Docetaxel is the standard second line chemotherapy for squamous histology patients. Most non-mutated patients with non-squamous histology receive a platinum-pemetrexed doublet in the first line setting making docetaxel appropriate for second line.
	Dose and Schedule	Docetaxel 75 mg/m^2, iv over 1 hour every 3 weeks.	Is the dose and/or schedule used in the trial relevant in the Canadian setting?	The Health Canada approved dose for metastatic NSCLC is 100mg/m^2 IV infusion q 3 weeks). However, toxicity and treatment related deaths are greater with docetaxel at a dose of 100mg/m^2 when compared to a dose of 75mg/m^2. The 75 mg/m2 dose of docetaxel every 3 weeks used in the study is the commonly used clinical dose across Canada.
Outcomes	Appropriateness of Primary and Secondary Outcomes	The primary (OS, PFS) and secondary outcomes (Response, Duration of Response) of the trial are appropriate.	Are the primary and secondary outcomes appropriate outcomes for the trial?	Overall survival and progression free survival are considered standard primary outcomes for palliative intent therapy. The secondary outcomes response rate and duration of response are also appropriate and meaningful. For the PD-1 inhibitor class of drugs, the true benefit seems to arise from the duration of response rather than response rate, which is very different from traditional cytotoxic chemotherapy or TKI therapy.
Setting	Countries participating in the Trial	The trial was conducted in 23 countries other than Canada (see above for list).	If the trial was conducted in other countries, is there any known difference in the practice pattern between those	Many Canadian cancer centres participated in the KEYNOTE-010 clinical trial.

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
			countries and Canada? Differences in the patterns of care might impact the clinical outcomes or the resources used to achieve the outcomes.	
	Location of the participating centres	The trial was conducted in academic centres only.	If the trial was conducted only in academic centres are the results applicable in the community setting?	While the trial was conducted in academic centres, the relatively low grade 3-5 treatment related toxicities means that even community treatment centres could handle administration of the drug with appropriate training. Pembrolizumab and related drugs are already used in the community setting for the treatment of melanoma. This sentiment is echoed in the Registered Clinician Input section of the document that included a response from a community oncologist.
	Supportive medications, procedures, or care	Concomitant medications were received by 95% of patients in the trial. There were 10% of patients who received levothyroxine sodium (13% and 14% in the pembrolizumab 2mg/kg and 10mg/kg groups, respectively and 5% in the docetaxel group) and <1% of patients who received infliximab (10mg/kg pembrolizumab group).	Are the results of the trial generalizable to a setting where different supportive medications, procedures, or care are used?	Supportive medications like steroids and thyroxine are routinely used by most physicians who would prescribe systemic therapy.

1.2.4 Interpretation

Burden of Illness and Need

Lung cancer is the most common type of cancer in Canada. In 2015, it was estimated that 26,600 new cases of lung cancer would be diagnosed and 20,900 deaths from lung cancer would occur. NSCLC is the most common type of lung cancer, comprising 85% of lung cancers. The majority of new cases of lung cancer are expected to arise in people over 60 years of age, with an estimated 16,300 new cases in the age group between 60 years and 79 years and 12,300 deaths.[3,4]

The two main histological subtypes of NSCLC are squamous cell carcinoma and adenocarcinoma. Non-squamous cell lung cancer comprises about 70% of NSCLC while squamous cell cancer comprises 30%. Cigarette smoke is a known risk factor but adenocarcinomas are frequently diagnosed in non-smokers with lung cancer. The goals of treatment for patients with advanced stage NSCLC are primarily palliative; namely to prolong life while maintaining or improving quality of life. Over the last 2 decades, modest improvement to patient survival and quality of life has been achieved through the emergence of new therapies. Cytotoxic chemotherapy drugs like pemetrexed and docetaxel can prolong survival by several months. However, few patients are fit to tolerate the side effects of therapy. Arguably the greatest therapeutic success in lung cancer has come from oral targeted therapeutics that have shown tremendous benefit in ~15% of the NSCLC population in Canada who harbour targetable lung cancer-associated gene mutations. These molecular subsets are especially enriched for non-smokers with adenocarcinoma histology.

On average, less than one third of Stage IV NSCLC patients receive any systemic therapy. Of these patients, less than half are eligible for subsequent lines of systemic therapy. Therapies that are well tolerated and improve survival, especially in patients that are EGFR/ALK wildtype and exposure to cigarette smoke, are desperately needed.

Effectiveness

The KEYNOTE-10 study is a Phase II/III open-label randomized clinical trial comparing the efficacy of two doses of pembrolizumab versus docetaxel, in previously treated patients with advanced stage, incurable NSCLC (both squamous and non-squamous histologies). To be eligible for the study, at least 1% of tumor cells needed to express the PD-L1 protein. Both doses of pembrolizumab (2 mg/kg and 10 mg/kg) demonstrated a statistically significant and clinically meaningful improvement in median overall survival (10.4 and 12.7 months respectively) versus docetaxel (8.5 months). This represented a 29-39% reduction in the risk of death with pembrolizumab compared to docetaxel across common NSCLC subtypes. With increasing PD-L1 expression the degree of benefit seen with pembrolizumab versus docetaxel increased, where high expressors that had >50% of tumor cells expressing the PD-L1 protein, the risk of death with pembrolizumab was reduced almost 50% compared to docetaxel (HR 0.54, p=0.0002). However, patients with low PD-L1 expression >1 to 24% also derived clinical benefit with pembrolizumab with improved OS versus docetaxel (OS HR=0.74; p=0.01; PFS=HR 1.08, p=0.74; ORR=8.6%, p=0.76). There was no statistically significant difference in PFS with pembrolizumab (2 mg/kg and 10 mg/kg) 3.9-4.0 months versus docetaxel (4.0 months) and did not differ by tumour histology or in the cohort with high PD-L1 expression of >50%. Among pembrolizumab responders, the durability of the response extends beyond that observed with docetaxel chemotherapy, with the median duration of response not reached in the pembrolizumab arm, versus 6 months with docetaxel.

Across all pre-specified subgroups, with the exception of EGFR mutated NSCLC, derived an OS benefit with Pembrolizumab vs docetaxel. For patients with EGFR mutated NSCLC there was no difference in OS compared to docetaxel. Also to note that the OS benefit of pembrolizumab versus docetaxel was seen in both archival and new biopsies that stained positive for PD-L1. Thus both tissue samples are acceptable for PD-L1 testing.

Pembrolizumab compared to docetaxel demonstrated less numerical deterioration of the Global Health Status Score, and specifically for lung cancer specific symptoms. There was a trend towards less deterioration of quality of life (EQ-5D) in the pembrolizumab arms compared to docetaxel.

Safety

Both doses of pembrolizumab were significantly better tolerated than docetaxel. Grade 3-5 toxicity was observed in 13-16% of the pembrolizumab arms compared to 35% in the docetaxel arm. Pembrolizumab was associated with less side effects commonly associated with cytotoxic chemotherapy such as fatigue, stomatitis, diarrhea, and neutropenia. However, as expected, pembrolizumab was associated with a higher rate of immune-related toxicities which are commonly seen in drugs of this class. The toxicity profile with pembrolizumab is different from classic cytoxic chemotherapy and thus will require physician education and institutional education around recognition of toxicities and management. These toxicities can be managed effectively if recognized early, although endocrinopathies that occur with this class of agents are often not reversible.

1.3 Conclusions

The Clinical Guidance Panel concluded that there is a net clinical benefit to pembrolizumab in the treatment of patients with advanced or metastatic NSCLC following platinum doublet combination chemotherapy. This conclusion is based on one high-quality randomized controlled trial that demonstrated a clinically and statistically significant benefit in overall survival for pembrolizumab compared with docetaxel. Responses with pembrolizumab appeared to be more durable and had a better adverse event profile compared to docetaxel.

This recommendation takes into account:

- The requirement for biomarker testing for all eligible patients: a minimum of 1% PD-L1 positive lung cancer tumor cells in patient biopsy samples was a requirement for enrollment in the clinical trial. The optimal test has yet to be determined; until then, the Dako murine 22C3 anti-human PD-L1 antibody is a reasonable standard. As the field evolves, the appropriate validated assay may change. Easy access to testing in clinical diagnostic laboratories will be essential to accessibility of this drug. Either archival or fresh tumour biopsies are acceptable for PD-L1 testing.
- Non blinded clinical trial; even after independent review, pembrolizumab demonstrated a statistically significant and clinically meaningful improvement in overall survival compared to an acceptable standard of care in Canada.
- Treatment responses, durability of response, and drug tolerability are superior with pembrolizumab compared to docetaxel.
- There is insufficient data to compare the efficacy of pembrolizumab to other commonly used therapies in the second line setting including oral TKI's, non-docetaxel chemotherapy, and other PD-1 inhibitors approved for use in lung cancer.
- There is insufficient evidence to support the use of pembrolizumab in patients with an ECOG 3-4 uncontrolled brain metastases or carcinomatous meningitis.
- The trial failed to demonstrate statistically significant differences in Quality of Life between pembrolizumab and Docetaxel treatment arms. However, there was a trend towards less deterioration of quality of life in the pembrolizumab arms. This is further supported by the patient input, registered clinician input and by ongoing clinical experience with these drugs.

- Clinical trials to date have studied the use of these drugs in ECOG 0-1 patients. ECOG 2 patients have been specifically excluded from clinical trials, however in real practice differences between ECOG 1 and 2 can be quite subjective.
- Pembrolizumab may be administered in the community and academic setting with adequate training in the monitoring and management of immune-related toxicity.
- Of the currently Health Canada approved treatment options in Canada for NSCLC, possible treatment options after progression of pembrolizumab may include: docetaxel, erlotinib, pemetrexed, nivolumab, docetaxel/ramucirumab depending on histology, known/unknown driver mutation, and prior treatment(s). Of note, all patients have to fail platinum doublet (except in patients who cannot tolerate the platinum portion of their treatment), and targeted therapy if applicable, prior to receiving pembrolizumab.
- PAG provided feedback on the initial recommendation and noted that the final recommendation for nivolumab in patients with NSCLC was for patients who "have disease progression on or after cytotoxic chemotherapy," whereas the initial recommendation for pembrolizumab was for patients with NSCLC "who have disease progression on or after platinum doublet chemotherapy." The CGP noted that some patients may not be eligible for platinum doublet chemotherapy, but would be eligible for first line non-platinum chemotherapy and, thus, the wording of the initial recommendation would exclude these patients from the opportunity to get pembrolizumab (as in the initial recommendation for pembrolizumab). The CGP acknowledged that both studies with nivolumab were following platinum doublet as was Keynote 010 with pembrolizumab. In light of the fact that these are both PD 1 inhibitors, the CGP agreed that the language around pembrolizumab for NSCLC and nivolumab for NSCLC recommendations should align.
- PAG also provided feedback on the initial recommendation that indicated a need for guidance on the use of pembrolizumab in patients in whom tissue biopsy is not feasible or where the tissue specimen is inadequate to determine PD-L1 status. The CGP noted that the results of the KEYNOTE 010 study cannot be generalized to patients with unknown PD-L1 status (for whom tissue biopsy is not feasible or where the tissue specimen is inadequate), as these patients were specifically excluded from the clinical trial. Furthermore, the CGP noted that, in both of the clinical trials of nivolumab (Checkmate 017 and Checkpoint 057), these patients were not excluded from trial entry. Therefore, a PD-1 inhibitor, nivolumab, would be available to patients for whom tissue biopsy is not feasible or for whom the tissue specimen is inadequate to determine PD-L1 status.
- Registered clinicians provided feedback on the initial recommendation and noted that re-treatment with pembrolizumab was allowed in the Keynote 010 trial in patients who relapsed or progressed after they had stopped pembrolizumab due to either a complete response or after two years of treatment with pembrolizumab; that is in a Second Course Phase of the Keynote 010 trial, patients could receive up to 12 months of pembrolizumab if they experienced an investigator-determined confirmed radiographic disease progression according to Immune-Related Response Criteria after stopping their initial treatment with pembrolizumab due to achievement of a confirmed complete response or have experienced 35 administrations of pembrolizumab. The CGP agreed that while there is no indication of how many patients were retreated or benefit achieved in this setting, the trial was open to retreatment, if necessary, and as indicated in the registered clinician feedback. Therefore, under these circumstances, CGP felt that it would be reasonable to retreat patients who progressed after pembrolizumab was stopped either due to a complete response or after 2 years, as per trial protocol.

2 BACKGROUND CLINICAL INFORMATION

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

2.1 Description of the Condition

In Canada, 2 out of every 5 people are expected to develop cancer in their lifetime. Furthermore, 1 out of 4 Canadians are expected to die of cancer. Lung cancer is the most common type of cancer in Canada. In 2015, it was estimated that 26,600 new cases of lung cancer would be diagnosed and 20,900 deaths from lung cancer would occur. The incidence and mortality rates for lung cancer were 51.9/100,000 and 40.2/100,000 respectively.[4] NSCLC is the most common type of lung cancer, comprising 85% of lung cancers. The majority of new cases of lung cancer are expected to arise in people over 60 years of age, with an estimated 16,300 new cases in the age group between 60 years and 79 years and 12,300 deaths.[3,4] The advanced age group and advanced stage population contain a disproportionately greater number of patients with poor performance status, as well as a higher likelihood of significant co-morbidities that impact patients' ability to tolerate conventional chemotherapy regimens.[5]

2.2 Accepted Clinical Practice

Introduction: The two main histological subtypes of NSCLC are squamous cell carcinoma and adenocarcinoma. Squamous cell carcinomas account for 30-40% of all NSCLC, and are more common in men than women.[6] Adenocarcinomas are the most common non-squamous cell carcinoma, and occur more frequently in women than men. Adenocarcinomas are frequently diagnosed in non-smokers with lung cancer. The goals of treatment for patients with advanced stage NSCLC are primarily palliative; namely to prolong life while maintaining or improving quality of life. Factors that influence the choice of initial therapy depend on the clinical condition (performance status, co-morbidities, etc.) of the patient, the histological subtype of NSCLC and the presence of driver mutations for which a specific inhibitor may be available.

First-line systemic therapy in tumors without identified driver mutations: In the setting of NSCLC without an eligible driver mutation, platinum based doublet chemotherapy combinations remain the mainstay of first line systemic treatment. Platinum combinations provide palliative benefit with a modest incremental improvement in median survival measured in months over the course of the last few decades.[7-10] A variety of first-line platinum doublets have shown comparable efficacy in terms of response rates, survival improvement and improvement in quality of life. Third generation cytotoxic agents such as vinorelbine, gemcitabine, pemetrexed, paclitaxel and Docetaxel, when paired with platinum agents, have shown modest incremental gains over older regimens.[10-12] Histological sub classifications of NSCLC have proven to have implications for therapy. The use of pemetrexed combinations appears to preferentially benefit patients with non-squamous histologies. Alternatively, this agent appears to be inferior to gemcitabine in the first line treatment of squamous NSCLC when combined with a platinum agent.[13] This difference has been attributed to differential levels of thymidylate synthase expression.[14,15] The addition of maintenance therapy following first line therapy with pemetrexed or the EGFR TKI, erlotinib, have demonstrated modest incremental gains in survival.[16,17] Platinum doublets in combination with targeted therapy in the form of bevacizumab have demonstrated an improvement in progression free survival without consistently translating into an overall survival benefit in the first line setting.[18,19] While a meta-analysis identified an improvement in overall survival with this strategy, there remains uncertainty as to whether the identified survival gains are superior to those provided by the addition of maintenance chemotherapy to the first-line setting.[20,21] Furthermore,

the cost of bevacizumab and its associated toxicities has dissuaded its widespread adoption in clinical practice in Canada.

Systemic therapy in tumors with identified driver mutations: Activating mutations have been increasingly recognized as key drivers in certain histological subtypes. EGFR activating mutations and fusion genes involving ALK have well elucidated roles in the pathogenesis of NSCLC.[22,23] Agents that selectively target these pathways have been shown to induce superior response rates and progression free survival benefits in patients whose cancers harbor these mutations. Several trials and a meta-analysis have confirmed the benefit of EGFR TKI therapy in the first line, second line and maintenance therapy in patients with EGFR mutated tumors without demonstrating an advantage to overall survival - attributed to the extensive cross over in this population.[24] Although in patients with Exon 19 deletion subtype, a recent pooled analysis showed improved OS with first line afatinib compared to chemotherapy.[25] In patients with ALK mutated tumors, crizotinib — an oral small molecule inhibitor of ALK, MET and ROS1 kinase - has demonstrated superior ORR and PFS when compared to standard first line platinum doublet therapy and second line chemotherapy.[26,27] The second generation ALK inhibitor, ceritinib, has demonstrated the ability to overcome resistance to crizotinib. Data from phase I and phase II trials suggests that this drug induces durable responses and meaningful benefit in terms of progression free survival in both crizotinib resistant and crizotinib naive patients.[28-30] The exact sequencing of these agents in relation to chemotherapy is not yet clearly established.[31] Nevertheless, there is increasing clinical consensus that the utilization of these agents upfront provides improved quality of life and delays the necessity of initiating cytotoxic chemotherapy with its inferior tolerability profile in well-selected populations.

Second-line systemic therapy: The typical treatment approach for those patients with NSCLC who do not have a driver mutation and who have received first line chemotherapy is to receive second line chemotherapy if they maintain a good performance status and are willing to receive additional chemotherapy. Single agent therapy with pemetrexed or Docetaxel in this situation is based on a modest improvement in survival as well as quality of life when compared to best supportive care.[32,33] For those patients who receive biomarker driver therapy initially, second line systemic therapy typically consists of second line platinum-based chemotherapy and pemetrexed in third line for those who maintain a performance status. While erlotinib may be used in some patients, in whom it is difficult to determine mutation status due to inaccessibility of tissue for testing, it has less importance in clinical practice compared to Docetaxel and pemetrexed as most patients are now assessed for mutation status before first line is initiated and receive treatments based on their mutation status.

Third-line and subsequent systemic therapy: In this population, antineoplastic systemic therapy is typically dependent on patient performance status as well as patient motivation. In the era of targeted therapies, Gefitinib demonstrated non-inferiority to Docetaxel in the second or subsequent line of treatment.[34] Erlotinib has shown improved survival and symptom control in the second line or later line treatment when compared to best supportive care.[35] More recently, afatinib has been shown to provide greater benefit than erlotinib in the treatment of squamous cell cancers.[36] Of note, as of April 12, 2016, afatinib is not yet approved in Quebec, but may be approved in the near future. A trial of a previously unused agent is reasonable in the absence of contraindications and if a suitable clinical trial is unavailable. Supportive care therapy including palliative radiation and early referral to the palliative care team along with psychosocial and spiritual supportive care are considered appropriate throughout the spectrum of treatment and have been shown to improve survival.[37,38]

Elderly and poor performance status patients: In patients who are elderly or have poor performance status, chemotherapy can increase the risk of serious adverse events. Phase III trials have suggested a clinically meaningful benefit including improved overall survival with

chemotherapy. Hence, the choice of therapy needs to be tailored to the patient's overall condition and performance status. Subset analysis of a trial comparing pemetrexed and Docetaxel in the second line treatment of non-small cell lung cancer identified a similar survival advantage with acceptable toxicity profile in patients who were elderly compared to those who were younger than 70 years of age.[39]

Patient population and attrition with subsequent lines of therapy: Retrospective analyses have suggested that there is an attrition in the number of patients who receive systemic therapy as they proceed from first line therapy to second or subsequent lines of therapy. For second line therapy, it is estimated that close to 50% of patients receiving first line therapy will receive second line therapy and approximately 30% of patients receiving first line therapy will proceed to third line regimens.[40,41] These studies nevertheless are limited in terms of their generalizability because they have typically been retrospective and single institution in nature. These and other factors may make the results less relevant to the Canadian context.

2.3 Evidence-Based Considerations for a Funding Population

Immunotherapies: Innate immunity and immune-editing are becoming increasingly recognized as key aspects in the development and persistence of cancer cells in the body. The PD-1 receptor on activated T cells interacts with ligands, PD-L1 and PD-L2, expressed by tumor cells and infiltrating immune cells. NSCLC tumor cells have been noted to over express PD-L1. Interaction between PD-L1 on tumor cells with PD-1 receptors on T cells inhibits T cell activation and promotes tumor immune escape and avoids elimination by the immune system. Nivolumab is a PD-1 antibody, which is currently under pCODR review as of April 15, 2016. A promising role for nivolumab in the treatment of advanced NSCLC was suggested by activity observed in the phase I Checkpoint 003 clinical trial that demonstrated durable responses in heavily pretreated patients with advanced NSCLC. At dose levels of 3mg/kg, durable responses were seen with survival at 1 year, 2 years and 3 years, which appeared better than with prior systemic therapies across all tumor histologies.[42]

These promising results subsequently resulted in two phase III randomized clinical trials, evaluating a role for immunotherapy in the second line setting for patients with advanced NSCLC that have published their interim analysis data.

Another phase I study has suggested impressive and durable responses with another PD-1 inhibitor, pembrolizumab, in a subset of patients with high levels of PD-L1 expression.[43] In 2015, based on the results of these trials, the FDA granted approval for use of nivolumab and pembrolizumab in the treatment of advanced (metastatic) NSCLC. Trials combining immunotherapies are ongoing, attesting to the increasingly significant role of immunotherapy in lung cancer.[3]

A randomised, open-label, phase 2/3 trial by Merck comparing two doses of pembrolizumab to Docetaxel was conducted;[2] the main difference between the CheckMate 017 and 057 and Keynote 010 is the eligibility criteria of the studies,[44,45] as Keynote 010 accepted only patients with PD-L1 expression on at least 1% of tumour cells.

Biomarker: A reliable biomarker has not yet been elucidated for use with immunotherapies. While, there is some data from clinical trial evaluation of PD-1 and PD-L1 blocking antibodies in NSCLC to suggest an enhanced benefit in tumors with increased immunohistochemical expression of PD-L1, the data has not been clear or consistent. Diagnostic PD-L1 immunohistochemistry assays vary between pharmaceutical companies and different thresholds for PD-L1 positivity ranging between 1 and 50 percent have been evaluated in clinical trials. Furthermore, there appears to be considerable heterogeneity in PD-L1 expression within tumors and between tumor sites, as well as

a potential for this expression to change over time and with other therapies; though the use of either fresh or archival tissue for PD-L1 testing does not seem to impact clinical outcomes with pembrolizumab in NSCLC.[2] Moreover, responses to PD-1 inhibition have been identified in small subsets of patients reported to be PD-L1 negative across trials. These factors have called into question the suitability of PD-L1 expression as a reliable biomarker for response to PD-1 axis inhibitor therapy. Of note, the optimal PD-L1 test has yet to be determined.

2.4 Other Patient Populations in Whom the Drug May Be Used

Currently, pembrolizumab is approved by Health Canada for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab therapy and, if BRAF V600 mutation positive, following a BRAF or MEK inhibitor as per proposed indication; and for the treatment of patients with metastatic NSCLC whose tumours express PD-L1 (as determined by a validated test) and who have disease progression on or after platinum containing chemotherapy. Patients with EGFR or ALK genomic tumour aberrations should have disease progression on authorized therapy for these aberrations prior to receiving pembrolizumab. Pembrolizumab has been issued marketing authorization without conditions for the treatment of patients with unresectable or metastatic melanoma who have not received prior treatment with ipilimumab. Subjects with BRAF V600 mutant melanoma may have received prior BRAF inhibitor therapy.[1] There are several ongoing trials evaluating its role in a variety of other tumour types such as head and neck squamous cell cancers, gastrointestinal cancers, as well as hematological malignancies.[46] The wide availability of these trials allows for a broad population to access this and similar agents in the controlled setting of a clinical trial without the need for off label use.

3 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

Input on pembrolizumab (Keytruda) for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 and who had disease progression on or after platinum-containing chemotherapy was provided by three patient advocacy groups: submission from Lung Cancer Canada (LCC) and a joint submission from British Columbia Lung Association (BCLA) and Ontario Lung Association (OLA). Their input is summarized below.

BCLA and OLA conducted one phone interview with a patient living with lung cancer, as well they gathered information from eight respondents (six patients and two caregivers) who completed on-line surveys developed through Fluid Survey, which was promoted through their respective websites and membership databases. The surveys were completed by both patients and caregivers over the past 12 months. No patients within this evidence group submission have used pembrolizumab.

LCC conducted a national survey of lung cancer patients and caregivers in August 2015. There were 91 patient and 72 caregiver respondents who completed the survey. All of the patient respondents who completed the survey have or have had lung cancer, and all of the caregiver respondents are currently caring for, or have previously cared for patients with lung cancer. To provide context around patients' experiences with lung cancer and their treatments, LCC included focus groups and individual interviews from recent submissions that were submitted to the pCODR program. A total of 27 patient and 18 caregiver respondents were gathered from these submissions. LCC also conducted an environmental scan of online forums to gather patient and caregiver feedback regarding pembrolizumab. The comments from 13 patient and nine caregiver respondents were included. LCC also provided an updated literature review from previous submissions. Specifically for this submission, four patient and one caregiver were interviewed between April and May 2016. All of these respondents have experience with pembrolizumab.

From a patient perspective, lung cancer impacts many aspects of day-to-day life for people living with it. Specifically, it affects the respondents' ability to work, travel, socialize and participate in leisure and physical activities. It also affects their relationships with family and friends, emotional well-being and may cause financial hardship. It was reported by both patient and caregiver respondents that high symptom burden of lung cancer is difficult to manage. LCC indicated that these symptoms may include: loss of appetite, cough, pain, and shortness of breath. Moreover, one of the most common symptom burden for lung cancer patients is fatigue or lack of energy. For the vast majority of this patient population, the current standard of care are chemotherapy or radiation. According to LCC, chemotherapy is viewed as a necessary, but feared treatment. The infusions themselves presented challenges beyond travel time and hospital visits; some respondents reported feeling sick even before the infusion was completed and that significant recovery time was needed after each chemotherapy infusion.

Respondents who do not have experience with the drug under review reported that key treatment outcomes that respondents would most like to address are: to stop or slow the progression of the disease, to reduce or eliminate side effects (e.g., reduce pain, fatigue, cough and shortness of breath), and to improve appetite and energy. They would also like there to be less or no cost burden associated with new treatments.

For respondents who have experience with pembrolizumab, a majority of respondents reported no side effects to mild side effects that are easily managed. In a few cases there have been stronger side effects that had to be managed either by over-the-counter drugs or prescription drugs. Most respondents, however, found that the management was tolerable and did not interfere with their day-to-day life. In some cases, there was uncertainty with distinguishing the side effects of

pembrolizumab from other causes. Many of the respondents mentioned that they went from feeling really sick before treatment, to feeling better within days of their first treatment up to their first few treatments. Respondents also stated that pembrolizumab allows them to have a high quality of life, provides them with the time to do the things that they love the most and extends that time with their family. LCC indicated that the infusion time is less frequent because pembrolizumab is infused every three weeks compared to every two weeks for nivolumab, and in their opinion, could be viewed as an advantage in terms of time and hospital resources.

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

3.1 Condition and Current Therapy Information

3.1.1 Experiences Patients have with Advanced or Metastatic Non-Small Cell Lung Cancer

BCLA and OLA reported that lung cancer impacts many aspects of day-to-day life for people living with it. Specifically, it affects: the respondents' ability to work, travel, socialize and participate in leisure and physical activities. It also affects their relationships with family and friends, independence, emotional well-being and their financial situation. LCC also found that, in a survey of Canadian patients with advanced lung cancer, it was reported that two-thirds of respondents feel their symptoms interfered with daily activities; anxiety or worry is common, reported as "frequent" or "constant" in 27%. Rates of depression in advanced lung cancer patients varied between 16-50%, which is seen to be consistently higher than other cancer sites.

For some, it was reported that it strips them of their ability to do anything on their own. One respondent stated: "*this disease has affected all parts of my life. I am not able to go outside on cold days, I am no longer able to drive, and must use volunteer drivers to get to my appointments, I am dependent on my neighbours to get my mail each day and take my weekly trash out. I have lost a significant amount of weight and am tired, weak and without energy. I am no longer able to do the activities I enjoy. It is very hard to be positive and hopeful*."

According to BCLA and OLA, the symptoms and problems that patients experience as a result of lung cancer are the following: pain (could be very intense at times), shortness of breath, cough, weakness, fatigue and being bed-ridden. BCLA and OLA indicated that symptoms are not fixed or consistent, but rather change frequently, which can also can be difficult to manage.

Similarly, LCC noted that Stage IV lung cancer patients experience the highest burden of symptoms. Based on a literature search conducted by LCC, these can include loss of appetite, cough, pain, and shortness of breath, and were found to have significant impact on the quality of life predictors.

In addition, LCC found that financial hardship was experienced by 41% of respondents in the Canadian study. Approximately 69% of respondents believed their illness imposed a significant hardship on those close to them.

LCC also observed that lung cancer patients experience a high amount of stigma a social burden of being a self-inflicted disease despite the fact that many who are diagnosed with lung cancer no longer or have never, smoked. For one respondent, she was someone who did "*everything right*," she ate organic food, exercised for 40 years, was never overweight and didn't smoke. She was

"shocked" when she received her diagnosis and said "*I was very upset*."

3.1.2 Patients' Experiences with Current Therapy for Advanced or Metastatic Non-Small Cell Lung Cancer

LCC reported that for the vast majority of this patient population, the current standard of care are chemotherapy or radiation. According to LCC, chemotherapy is viewed as a necessary, but feared treatment. Specifically, respondents indicated chemotherapy treatment as being "scary." One respondent stated: "*Chemo kicks the crap out of your body and mind. You feel absolutely horrible. [For a] half year of your life you feel like hell for a week, every three weeks. It's not for wimps!*"

BCLA and OLA conducted an interview with one patient who underwent radiation and chemotherapy. The respondent also reported using the following supportive treatments: glycopyrronium bromide, salmeterol xinafoate/fluticasone propionate, and salbutamol sulphate.

Respondents who completed the on-line survey conducted by BCLA and OLA reported using the following treatments, including supportive therapies: tiotropium, salmeterol xinafoate/fluticasone propionate, budesonide/formoterol fumarate dihydrate, roflumilast, prednisone, salbutamol sulphate, ipratropium bromide, salmeterol xinafoate, glycopyrronium bromide, and indacaterol maleate. According to BCLA and OLA, current treatments provide some relief for: fatigue, shortness of breath, cough, appetite loss and low energy, but side effects such as: palpitations, dry mouth, mouth sores, vision and urinary problems and impact on mood need to be better managed. For one respondent, it was reported that the radiation has left them with an extremely sore and painful throat. One respondent stated: "*I have been burned from my treatments from front to back. I now struggle to swallow, but must eat to re-gain weight and energy. I have also lost the feeling in the tips of my fingers and toes. This makes it difficult for me to pick up items, especially money / change when paying for something*."

LCC also observed that response rates for chemotherapy are low, approximately 20% - 30%, with temporary improvement in symptoms and quality of life in up to two thirds of patients. According to respondents, the burden of chemotherapy was felt during all stages of the treatment. Moreover, the burden of chemotherapy extends beyond the patient. Many caregivers must take time off from work to care for the patient receiving treatment.

1. Diagnosis: Chemotherapy carried a psychologic burden even before receiving the first dose. Those that did not have to go through chemotherapy expressed it as a "*relief*". One respondent stated: "*When I was first diagnosed, the fear of traditional chemotherapy and radiation was overwhelming.*" Patients used words such as "*cytotoxic killer*" and "*poison*" to describe chemotherapy.

2. Infusion: The infusions themselves presented challenges beyond travel time and hospital visits. Some respondents reported feeling sick even before the infusion was completed.

3. Recovery: Significant recovery time was needed after each chemotherapy infusion. For respondents, this meant "*two bad weeks and one good week.*" It was also reported that walking and activity were difficult. One respondent stated: "*I was so sick on infusion chemo. I wasn't functional*," In addition to being sick and tired, this respondent also noted that he would have mood swings and get irritated easily. His wife relied on him to drive her to work, but the chemotherapy significantly impacted the family. Other respondents found that chemotherapy took away precious time that they could spend with loved ones due to the side effects. Even when the more acute side effects subsided, their susceptibility to infections due to low white blood counts made spending time with friends

and family difficult. One respondent stated that the social element is very important to helping her stay positive.

4. Lasting effects of chemotherapy: One respondent that was on chemotherapy felt that you never recover. To this date, four years after chemotherapy she still experiences fatigue and has not yet been able to return to work. Another respondent also felt that the combination of chemotherapy and radiation has left her mom with permanent hearing loss.

5. "Looking sick": LCC reported that not only did respondents feel sick on chemotherapy, they also looked sick. On chemotherapy, they tended to stay at home and some experienced hair loss. Hair loss was a major issue for female respondents. In contrast, LCC reported that respondents felt and looked well on the oral therapies. Respondents and their families felt that "*No one could tell I [they] had cancer*."

BCLA and OLA reported that respondents would like their treatments to provide enough help that they will experience improved independence and require less assistance from others. The desire for: fewer medical appointments, and less financial cost burden (i.e. secondary costs of lung cancer and treatments). As an example of this cost burden, BCLA and OLA noted that due to the weight loss and need for good nutrition, one patient respondent was instructed to buy certain foods (such as Ensure – a nutritional supplement) which can be expensive for those living on a fixed income or pension.

Similarly, LCC submits that immunotherapies offer a real chance to lessen the burden of lung cancer. The new options for treatment of NSCLC are significant not only because they have higher efficacy, but could also address the substantial symptoms faced by NSCLC patients.

3.1.3 Impact of Advanced or Metastatic Non-Small Cell Lung Cancer and Current Therapy on Caregivers

BCLA and OLA conducted surveys with two caregiver respondents. According to BCLA and OLA, caregivers of patients living with lung cancer experience many of the same negative impacts on their lives as the patients themselves. Caregiver respondents also indicated that caring for patients has affected their work, finances, relationships with family and friends, physical and leisure activities, independence, and ability to travel and socialize.

BCLA and OLA highlighted an overarching theme was the emotional toll of watching patients with lung cancer suffer in pain, and knowing there is little you can do to alleviate the discomfort and pain.

LCC gathered responses from caregivers from the following sources: 72 caregiver respondents who completed the survey; 18 caregiver respondents from focus groups from previous submissions; nine caregivers from an environmental scan of online forums; and an additional one (1) caregiver who was interviewed specifically for their thoughts relating to this submission.

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

1) The stigma unique to lung cancer places an additional emotional burden on caregivers. In the Faces of Lung Cancer Report (FOLCR), caregivers seemed to feel the stigma more acutely than patients. In addition to this, 38% of responding caregivers felt that they had to advocate more strongly for their family members because of a lung cancer diagnosis. One respondent stated:

"*Everyone assumes that lung cancer is self-inflicted and somehow people who get it deserve their lot. All I heard when people asked if my mom smoked was: "your mother deserves to die.' It is such an ignorant position and a stigma that doesn't affect any other disease that I can tell, including others with high lifestyle correlations (type II diabetes, heart disease etc.). It's frustrating that if my mom had been diagnosed with breast cancer, she would have been considered a hero, but because it was lung cancer, people don't even want to talk to me about it*."

2) Lung cancer is further handicapped by late diagnosis. Across Canada, most lung cancer is diagnosed in Stage IV (Statistics Canada, Canadian Cancer Registry) – LCC believes this is potentially when the physical and emotional demands of caregiving are at their peak. The FOLCR indicated that 82% of caregivers said their caregiving experience was somewhat to very stressful. The most common source of stress for caregivers was dealing with the caregivers declining health.

3) Lung cancer carries a significant economic toll on household finances. Work and relationships often gave way to the challenge of providing care. LCC reported that 59% of caregivers reduced the number of hours they worked and a further 8% quit their jobs. Moreover, 50% of caregivers reported a negative impact on their household financial situation. With patients also reducing their number of working hours or being unable to continue with work, this trend threatens to have a significant impact on the economy by taking not one but two members out of the workforce. This is more significant for younger lung cancer patients.

4) High symptom burden of lung cancer is difficult to manage for both patients and caregivers. LCC indicated that one of the most common symptom burden for lung cancer patients is fatigue or lack of energy. This finding is aligned with the ones that caregivers and patients in the FOLCR found hardest to manage, and had the highest impact on quality of life. Fatigue was also the top treatment side-effect that both patients (68%) and caregivers (43%) found most difficult to manage. This was followed by pain, concentration or memory issues and nausea – each with a combined patient and caregiver rating of 31%.

5) Anxiety and more anxiety when lung cancer turns into a waiting game. According to LCC, lung cancer doesn't wait for anybody, but lung cancer care can be a waiting game. By far the biggest stressor for caregivers is fear. The anxiety felt with a loved one's disease was the feeling, more than any other, that was most associated with their lung cancer experience (50%) and this was reported by more caregivers (61%) than the patients themselves (42%) in the FOLCR. When her husband was diagnosed with lung cancer, AL said, "*he was really sick, we just about lost him. I was really scared, I didn't know what would happen*." The fear and anxiety with lung cancer itself is enough. By adding wait times, such as for multiple biopsies and testing, that fear and anxiety is compounded.

LCC noted that caregiver respondents often feel helpless and anxious and are scrambling to look for things that allow them to help. Appetite improvement played a key role in relieving caregiver anxiety. Patients being able to eat better while on pembrolizumab was significant for caregivers.

3.2 Information about the Drug Being Reviewed

3.2.1 Patient Expectations for and Experiences To Date with pembrolizumab (Keytruda)

None of the respondents from BCLA and OLA had experience with pembrolizumab. BCLA and OLA reported that key treatment outcomes with the drug under review that respondents would most

like to address are: to stop or slow the progression of the disease, to reduce pain, fatigue, cough and shortness of breath, and to improve appetite and energy.

Respondents would expect the drug under review to reduce or eliminate the following current side effects: pain, fatigue, nausea, shortness of breath, appetite loss, low energy, inability to fight infection, burning of skin and impact to mood. They would also like there to be less or no cost burden associated with new treatments.

On a practical level, respondents would like the ability to have treatments at home, so it would remove the need for the patient or the caregiver to take time off of work. In their view, this would also lead to less disruption of the daily routine.

According to LCC, four patients and one caregiver had experience with pembrolizumab. In their feedback, LCC clarified that phone interviews were conducted with four patients and one caregiver who had experience with pembrolizumab. However the environmental scans of online blogs and forums only included feedback from those who have had experience with pembrolizumab; from this source, the comments from 13 patient and nine caregiver respondents all whom had experience with pembrolizumab were included. Therefore in total, 17 patients and 10 caregivers who have had experience with pembrolizumab were included in the LCC submission.

LCC reported that stable is an important point to emphasize as patients have high expectations of immunotherapy. They hear about complete responders and pin great hopes of being the same. Education needs to occur to ensure that patients and their families understand that stable is still a win. One respondent remarked that "*When you have cancer, perspective can be everything*." The respondent reported that while her tumour never did shrink despite multiple rounds of treatment, after each scan the results were stable. This was "*my new normal*" and "*better than the alternative*." Even small chores and "*getting back to the basics of life*" were a triumph.

Many of the respondents interviewed for this submission indicated that they wanted to help increase lung cancer awareness or serve as a peer to others living with lung cancer. This is significant not only because they want to contribute and help, but they are able to help. Many lung cancer patients are very sick - pembrolizumab has offered patients the chance to be well and active.

The majority of respondents interviewed and reviewed during the environmental scan have reported no side effects to mild side effects that are easily managed. In a few cases there have been stronger side effects that had to be managed either by over-the-counter drugs or prescription drugs. Most respondents, however, found that the management was tolerable and did not interfere with their day-to-day life. In some cases, there was uncertainty with distinguishing the side effects of pembrolizumab from other causes. One respondent felt tingling in her ankles and feet but thought it was left over from her chemotherapy. Another respondent wondered if her reactions were due to her many allergies or the drug.

Many of the respondents mentioned that they went from feeling really sick before treatment, to feeling better within days of their first treatment up to their first few treatments. One respondent had a severe cough and had also lost weight, after his treatment he reported there was no adjustment period. His cough slowly went away and it has "*allowed me to have a more normal family life; it's allowed me to live*." He, along with his wife, are able to stay in contact with their daughter and son more often as a result.

Another respondent reported that her side effects were "*really, really light*." She has experienced some dizziness and some itchiness, but otherwise pembrolizumab has "*given me my life back*." She likes to exercise and the only thing holding her back now is due to aging. This respondent also reported that she had lost weight while waiting to receive treatment and was

down to 100 lbs and her daughter (caregiver) was really scared, that she may "*keel over*." After treatment, she has been able to return to her normal weight. Another respondent reported that her husband would tell her to "*just make something and I will try to eat it*." After treatment, his appetite has not returned to normal but he is able to eat more. That helped relieve anxiety. As one respondent happily reported, "*I'm back to being fat!*"

One respondent stated that he went from mostly fatigue on chemotherapy, to minor rash and diarrhea on erlotinib to nothing on pembrolizumab, "*I've had three years symptom and side effect free.*" It was reported that this has allowed him to be able to do everything from playing sports to spending time with his children and feeling normal in every way. His kids don't really understand what it is like to be a stage IV lung cancer patient since their dad's quality of life has been good compared to the norm. He also stated: "*I feel selfish and spoiled. I was getting used to being stage IV; my family sometimes forgets that I have cancer*."

For some respondents, the ability to get out of bed, put clothes on like a "*real person*" and "*fix my hair*" was significant. As one respondent stated: "*When you are on chemotherapy you can be at home but there is no difference to being in the hospital. You still can't do things*." For another respondent, this meant being a father to their young children, "*32 months on Keytruda, everything went down 96%. I'm spoiled…my daughter gets to treat [stage IV lung cancer] as a chronic illness. She wants to be an oncologist*." For others it means playtime with grandchildren. Even when fatigue sets in, it is still better than the alternatives from traditional therapies.

Respondents were often concerned with taking time off for their disease. On chemotherapy, the side effects can be so strong, that there is no chance a patient can work. For those that responded on pembrolizumab, the question of returning to work became an option not possible for many lung cancer patients. For one respondent this was a very big concern and he was happy that his treatments allowed him to continue to teach at a Canadian University, coach Little League, and play hockey. Other respondents shared a similar desire.

According to LCC, pembrolizumab becomes a second and potentially preferred option to nivolumab. LCC noted that this is mainly due to the fact that pembrolizumab is infused every three weeks compared to every two weeks for nivolumab; this advantage has a significant impact on patients' time. 25% of immunotherapy patients could be on treatment for more than a year, which could mean less infusions will be less taxing on the hospital's resources as well.

LCC noted that these respondents realize there is still no cure for lung cancer, but the availability of more treatments gives them their life back. One respondent stated: "*No matter how well a particular treatment may be working, there is still a "shadow lingering over you. [We] need to be careful not to tout [Keytruda] as a cure.*" Notwithstanding, LCC submits that pembrolizumab allows respondents to have a high quality of life, provides them with the time to do the things that they love the most and extends that time, until the next treatment is found. The extra time they are afforded is viewed to be of value to patients.

3.3 Additional Information

LCC believes that there needs to be more professional and patient education as this is still a new type of treatment.

According to LCC, in order to receive pembrolizumab, patients need to undergo a biopsy that is then tested for PDL-1 expression. This can create additional wait times for patients. As one respondent said, "*you don't just get the test right away*." There is a wait before getting the biopsy and then a wait for it to be tested before getting the results. In some cases, this has

taken over a month. One respondent reported that the wait for her biopsy was about 10 days; then the wait for the test result was another three weeks. "*The entire process was extremely hard to deal with*." In other cases, patients do not have archival tissue but their tumours cannot be re-biopsied. In addition, clinical evidence shows that patients who are not PDL-1 positive may still benefit from immunotherapy, as the PDL-1 test is not a biomarker.

LCC submits that the high cost of immunotherapy is a concern for many stakeholders. One caregiver respondent said that her boyfriend has been paying 100% out of pocket for pembrolizumab. "*We are very fortunate that his income has allowed him to do so for a few months, but our financial situation grows increasingly more dismal*." Without some form of funding mechanism, drugs such as these will be out of reach for many if not most of those who so desperately want and need it. LCC proposes that funding be considered for both nivolumab and pembrolizumab as it would allow for marketplace competition and could result in more competitive pricing for both treatments.

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 non-small cell lung cancer (NSCLC):

Clinical factors:

- Clarity of patients eligible, including for patients who have not received platinum-based doublet chemotherapy or who have received oral targeted therapies
- Clarity on dose and duration of treatment
- The need for PD-L1 testing, timing of the testing and the accuracy of the test results

Economic factors:

- Drug wastage
- Implementation of PD-L1 testing, which is not currently funded

Please see below for more details.

4.1 Factors Related to Comparators

Docetaxel is the standard of care in second-line treatment of advanced or metastatic lung cancer.

At the time of the PAG input, nivolumab was under review for NSCLC. If the recommendation is to fund pembrolizumab for NSCLC and when a funding decision is made, nivolumab may already be in use. PAG is seeking information, if available, on the comparison of pembrolizumab and nivolumab.

4.2 Factors Related to Patient Population

There is a large number of patients with lung cancer. However, it was noted that the number of patients who have failed platinum based chemotherapy and whose tumours express the PD-L1 would be a smaller subgroup. PAG is seeking information on the clinical benefit and significance of pembrolizumab based on the results of the subgroup analysis of KEYNOTE-010 trial.

PAG is seeking clarity on whether the KEYNOTE-010 trial data could be generalized to patients who have been previously treated with oral targeted therapies (e.g. afatinib, crizotinib, etc.) but not platinum-based chemotherapy. PAG is also seeking clarity on whether the outcomes of the KEYNOTE 010 trial were similar for patients with squamous cell and non-squamous cell histologies.

If pembrolizumab is recommended for funding, PAG indicated that the funding criteria for oral targeted therapies would need to be re-evaluated as there would be a shift of current second and third-line treatments to third and fourth-line. PAG is seeking information on sequencing of the currently available treatments for lung cancer in all lines of therapy and the place in therapy for pembrolizumab versus other PD-1 inhibitors and oral targeted therapies. PAG is also seeking guidance on the appropriate treatments after progression on pembrolizumab, recognizing that evidence may not be available at this time.

PAG noted that there may be interest in using pembrolizumab in the first-line treatment of NSCLC, but recognizes this would be out of scope of this review.

4.3 Factors Related to Dosing

PAG identified that the frequency of administration for pembrolizumab is similar to docetaxel. However, the KEYNOTE-010 trial studied two different doses of pembrolizumab and the funding request is for the 2mg/kg dose. PAG is seeking clarity on the appropriate dose as there may be interest to use the higher dose.

4.4 Factors Related to Implementation Costs

PAG noted that PD-L1 testing is not readily available or conducted routinely, although it was noted that there will be six centralized facilities set up to conduct the test. There are concerns on the timing of conducting the test, the turn-around times for the test results, and accuracy of the test results as well as co-ordinating with these facilities and the possible need for another biopsy. PAG is seeking clarity on the benefits of PD-L1 testing compared to not conducting the PD-L1 testing prior to treatment of NSCLC with pembrolizumab, given that the testing is not required for treatment with nivolumab, another PD-1 inhibitor, and not required for the treatment of melanoma with pembrolizumab.

PAG has concerns for incremental costs due to drug wastage, specifically in centers where vial sharing would be difficult because there could only be one patient in the day. However, any unused portion would be discarded as the stability of reconstituted drug is poor.

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

PAG is seeking clarity on the duration of treatment and treatment discontinuation.

4.5 Factors Related to Health System

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

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

The potential for another biopsy to acquire adequate tissue sample size for PD-L1 testing and the need for the PD-L1 test requires co-ordination of health care resources with the facilities that can conduct the PD-L1 testing.

4.6 Factors Related to Manufacturer

The high cost and large potential budget impact of pembrolizumab will be barriers to implementation. Additional costs may be incurred due to testing for PD-L1 especially if a repeat biopsy is required.

5 SUMMARY OF REGISTERED CLINICIAN INPUT

Two clinician inputs on pembrolizumab for NSCLC were received: one from an individual oncologist and one joint submission from seven oncologists.

Overall, the clinicians providing input noted that pembrolizumab is more effective and better tolerated than chemotherapy. They felt that pembrolizumab provides another immunotherapy treatment option, with shorter infusion time and less frequent dosing schedule than nivolumab, for patients who have disease progression and whose tumours express PD-L1. They identified that testing for PD-L1 expression is important but that the turn-around time for test results would delay initiation of treatment.

Please see below for a summary of specific input received from the registered clinicians.

5.1 Current Treatment(s) for Advanced or Metastatic Non-Small Cell Lung Cancer

The clinicians providing input identified that the current treatments available for patients who have failed platinum doublet chemotherapy include docetaxel, nivolumab and best supportive care.

5.2 Eligible Patient Population

One clinician providing input indicated that currently in Ontario only about 25% of patients eligible for first line chemotherapy receive treatment and identified that the number of patients eligible for treatment will be modest in relative terms, but possibly large in absolute terms given the high incidence of lung cancer in general.

The clinicians from the joint submission believe that physicians would use pembrolizumab in NSCLC patients who have progressed beyond first line treatment. They estimated that between 200-250 patients in B.C., 200 to 250 patients in Alberta and approximately 500 patients in Ontario could be eligible for both immunotherapies currently approved by Health Canada for NSCLC.

5.3 Identify Key Benefits and Harms with Pembrolizumab

One clinician providing input stated that pembrolizumab is more effective than chemotherapy in tumours expressing PD-L1 and, in his experience, has been much better tolerated than chemotherapy. He noted that the immune mediated toxicities (potential harm) are modest in comparison with earlier CTLA4 inhibitors and are manageable. He noted that with the option of either pembrolizumab or nivolumab in this setting, current second line chemotherapy would almost never be utilized, though may be still of value (given low costs) in the third line setting in the very few patients still fit enough for possible third line therapy later.

The clinicians from the joint submission identified that in clinical practice, physicians have observed a similar side effect profile between pembrolizumab and nivolumab, which are consistent with the clinical trials. Their patients on immunotherapy generally experience significantly lower side effects over those on chemotherapy and some patients even have no side effects. The benefit of treatment is the durability of the response in patients in whom a response is seen. Over 20% of patients are multi-year survivors which is not the norm in stage IV lung cancer.

5.4 Advantages of Pembrolizumab Over Current Treatments

The clinicians providing input felt that immunotherapy is superior to chemotherapy in terms of efficacy

with the possibility of very long remission and patient quality of life with its markedly superior therapeutic index and better tolerability, especially for patients with co-morbidities.

The clinicians providing input noted that pembrolizumab is administered every three weeks whereas nivolumab is administered every two weeks and that pembrolizumab has a shorter infusion time than nivolumab. They felt that these advantages could be significant on patient time and hospital resource utilization as about 25% of patients on PD-1 inhibitors could be on treatment for more than a year.

5.5 Sequencing and Priority of Treatments with Pembrolizumab

The clinicians providing input believe that pembrolizumab would be used on progression after platinum doublet chemotherapy, upon confirmation of a positive PD-L1 status, for patients who are not EGFR or ALK positive. One clinician providing input noted that a minority of patients who have progressed after second line treatment with pembrolizumab would be considered for docetaxel in the third line setting.

In addition, the clinicians from the joint submission identified that for patients who are EGFR or ALK positive, physicians prefer to use another targeted therapy upon progression. For patients who do not have another targeted therapy option or are unable to tolerate the targeted therapy, after progression on platinum-doublet chemotherapy, physicians would require PD-L1 testing to help aid in their decision as to whether to use PD-1 inhibitors. They noted that patients with EGFR or ALK mutations seem to have a similar benefit from immunotherapy if they have PD-L1 expression.

The clinicians providing input noted that there is a place for both PD-1 inhibitors options. If a patient has PD-L1 expression, then the clinicians could choose pembrolizumab over nivolumab due to a shorter infusion timing and better dosing schedule. Clinicians felt that nivolumab is still a good option for patients that have a negative PD-L1 test result.

5.6 Companion Diagnostic Testing

The clinicians providing input identified that testing for PD-L1 expression is necessary and that the test is not similar to EGFR or ALK tests where it can be used to determine suitability for targeted therapies. In this case, a negative test does not mean that a patient would not respond to PD-1 inhibitors and should not be used to exclude patients from receiving immunotherapy.

The clinicians providing input noted that testing has an impact on speed to treatment and use of resources. Currently, PD-L1 testing cannot be done locally except at five academic centres spread across Canada and tissue must be sent out to one of these labs or to DynaCare, resulting in significant delays. In Ontario, the time from a test request to treatment can be up to three weeks. The clinicians providing input noted felt that this wait could be detrimental to patients' prognosis, as the average duration of treatment is three to four months. In cases where there is a potential for delay in testing, physicians need to be able to have nivolumab as an option. Although archived tissue could be used to confirm status, if tissue is not available from the original biopsy, the patient would need to be re-biopsied.

The clinicians providing input felt that PD-L1 testing in Canada could be standardized and implemented efficiently since the Health Canada approval of pembrolizumab is for "Metastatic non-small cell lung carcinoma (NSCLC) whose tumours express PD-L1 (as determined by a validated test)". They feel that laboratories will not have to use certain antibodies, kits or testing platforms and therefore, the test could be available sooner but noted that it is most practical for PD-L1 testing to be performed by central laboratories to assure the best tissue management and to integrate PD-L1 testing into the current algorithm of EGFR and ALK testing. The results could be available as early as 1-2 days following ALK reporting, which will allow for timely clinical planning of second line immunotherapy treatments.

5.7 Additional Information

None provided.

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the efficacy and safety of pembrolizumab (Keytruda) compared to standard therapy in previously treated patients with advanced or metastatic non-small cell lung cancer (NSCLC) whose tumours express PD-L1 and who have progressed on or after platinum-containing chemotherapy and an appropriate tyrosine kinase inhibitor (TKI) for patients with EGFR (epidermal growth factor receptor) mutations or ALK (anaplastic lymphoma kinase) rearrangements.

Supplemental Questions and Comparison with Other Literature 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 and section 8.

Supplemental Questions:

1. What is the accuracy of programmed death ligand 1 (PD-L1) diagnostic antibody assays?

2. What is the clinical utility of PD-L1 testing in patients with non-small cell lung cancer?

3. What is the effectiveness of programmed cell death protein 1 (PD-1)/PD-L1 checkpoint inhibitors for treating patients with non-small cell lung cancer with different levels of PD-L1 expression?

Comparison with Other Literature Topics:

- KEYNOTE trial 001: A summary of the efficacy results by level of PD-L1 expression in the phase I KEYNOTE trial of pembrolizumab.
- CheckMate trials 017 and 057: A comparison, in terms of eligible patient populations, drug dosing and schedules, adverse event profiles, and efficacy results by PD-L1 expression, between the KEYNOTE 010 trial of pembrolizumab and the CheckMate trials evaluating nivolumab.

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

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

Table 3. Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
RCTs	Adult patients (≥18 years) with advanced/metastatic NSCLC with tumours expressing PD-L1 who have progressed on platinum-containing chemotherapy and appropriate TKI for EGFR	Pembrolizumab	• Docetaxel • Pemetrexed • Erlotinib • Platinum doublet chemotherapy • Nivolumab	• OS • PFS • QOL • ORR (CR, PR) • Duration of response • Time-to- response • AE ○ Endocrinopathies

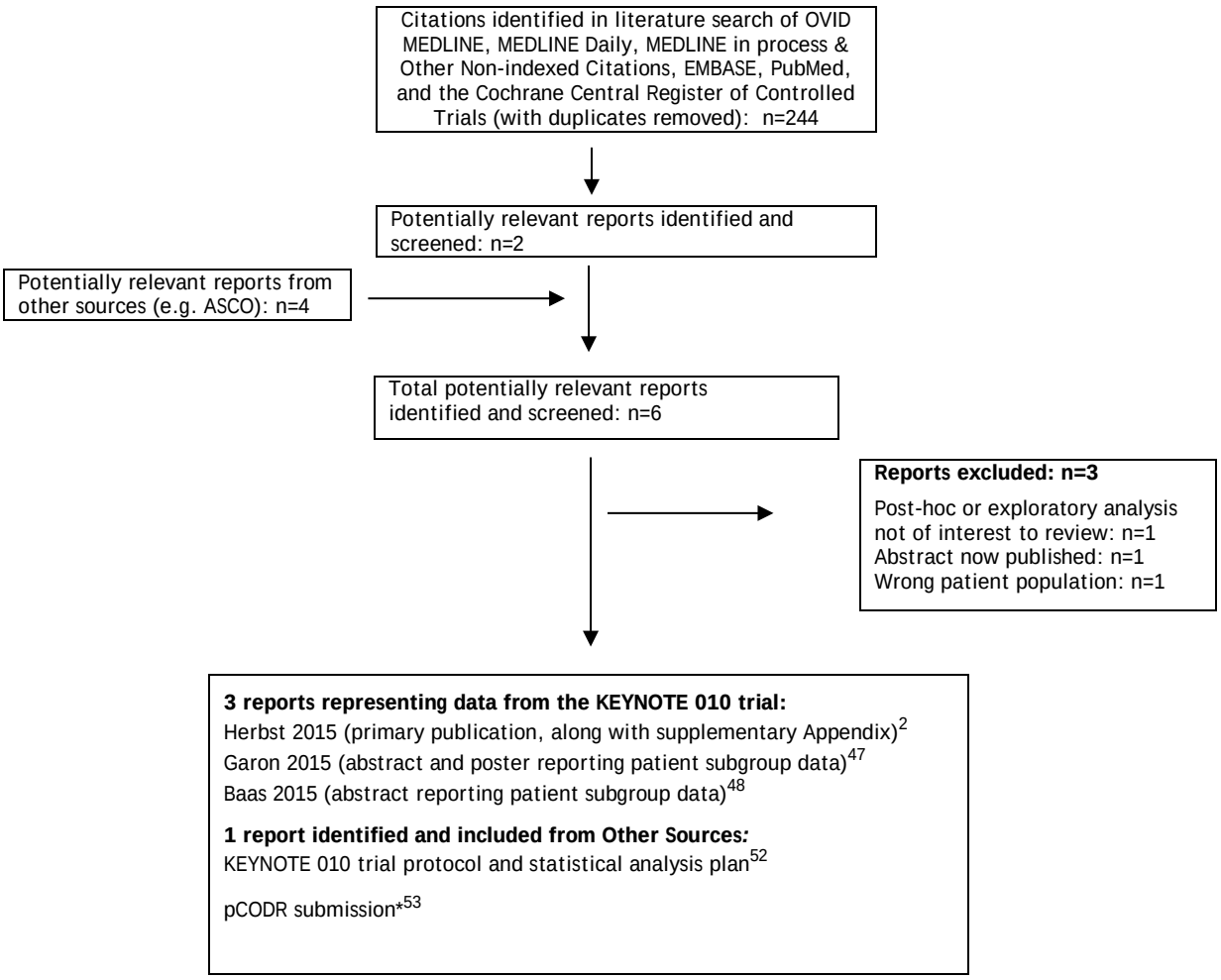
Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
	mutation or ALK rearrangement. Subgroups: • Histologic type (squamous versus non-squamous cell) • PD-L1 tumour percentage score • EGFR status • ALK status • ECOG PS • Age • Smoking status • Tumour sample (archival versus new)			○ Immune-related AE ○ Infusion reactions • SAE • Withdrawal due to adverse events
Abbreviations: AE - adverse events; ALK - anaplastic lymphoma kinase; CR - complete response; ECOG - Eastern Cooperative Oncology Group; EGFR - epidermal growth factor receptor; NSCLC - non-small cell lung cancer; ORR - objective response rate; OS - overall survival; PD-L1 - programmed death-ligand 1; PFS - progression-free survival; PR - partial response; PS - performance status; QOL - quality of life; RCT - randomized controlled trial; SAEs - serious adverse events.				
Notes: * Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions.				

6.3 Results

6.3.1 Literature Search Results

Of the six potentially relevant reports identified for full-text review, three reports were included in the pCODR systematic review[2,47,48] and three reports were excluded.[49-51] Studies were excluded for the following reasons: they were either post-hoc or exploratory analyses of trial data not of interest to this review,[49] they were earlier abstracts of the KEYNOTE 010 trial, which is now published,[51] or were identified as the wrong patient population upon full-text review.[50]

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



**Note: Additional data related to the KEYNOTE 010 trial were also obtained through requests to the Submitter by pCODR.*

6.3.2 Summary of Included Studies

One randomized controlled trial was identified that met the selection criteria of this review.[2] KEYNOTE 010 is an open-label, randomized phase 2/3 trial comparing two doses (2mg/kg versus 10mg/kg) of pembrolizumab to docetaxel in patients with PD-1 positive NSCLC who have progressed after platinum-based doublet chemotherapy. Key characteristics of KEYNOTE 010 are summarized in Table 4, and specific aspects of trial quality are detailed in Table 5.

6.3.2.1 Detailed Trial Characteristics

Table 4: Summary of trial characteristics of the included KEYNOTE 010 trial.

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
KEYNOTE 010[2] Phase 2/3, open-label, RCT (1:1:1 ratio) N randomized=1034 N treated=991 202 Academic centres in 24 countries including Canada Patient enrolment: August 28, 2013-February 27, 2015 Data cut-off date: September 30, 2015 (final analysis) Funded by Merck and Company	Key Inclusion Criteria: • Age ≥ 18 years • Stage IIIB/IV NSCLC • PD-L1 positive[A] with TPS of ≥1% • Disease progression per RECIST version 1.1 after ≥2 cycles of platinum-doublet chemotherapy and appropriate TKI for EGFR or ALK mutation • ECOG 0 or 1 • Provision of tumour sample[B] Key Exclusion Criteria: • Previous treatment with PD-1 checkpoint inhibitor or docetaxel • Active brain metastases or carcinomatous meningitis • Active autoimmune disease, interstitial lung disease or history of pneumonitis requiring systemic steroids	Pembrolizumab 2 mg/kg iv over 30 minutes every 3 weeks vs. Prembrolizumab 10mg/kg iv over 30 minutes every 3 weeks vs. Docetaxel 75 mg/m^2 iv over 1 hour every 3 weeks[C] In all patients, treatment was continued for 24 months or until disease progression,[D] intolerable toxic effects, physician decision, physician decision or other reasons.	Primary:[E] • Overall survival • Progression-free survival[F] Secondary: • Response rate[G] • Duration of response[H] • Safety

Abbreviations: ALK - anaplastic lymphoma kinase - ECOG - Easter Cooperative Oncology Group; EGFR - epidermal growth factor receptor; NSCLC - non-small cell lung cancer; PD-L1 - programmed death-ligand 1; PD-1 - programmed cell death receptor 1; RCT - randomized controlled trial; TKI - tyrosine kinase inhibitor; TPS - tumour proportion score; vs - versus.

Notes:
[A] PD-L1 expression assessed by central laboratory with immunohistochemistry assay (Dako; CA, USA) with murine 22C3 anti-human PD-L1 antibody (Merck; NJ, USA).
[B] Originally, any tumour sample was permitted in the trial, but the protocol was amended to require new tumour sample for PD-L1 testing except in the event where taking a biopsy was too risky for the patient. A new tumour sample required no intervening treatment between the time the sample was taken and initiation of study treatment. The only exception was for patients taking TKI before biopsy were permitted to resume this treatment after sample collection. A total of 456 patients were enrolled based on archival samples.
[C] Corticosteroid premedication was permitted in this treatment group; patients in this group were not permitted to crossover to receive pembrolizumab.

[D] Patients who progressed according to investigator assessed immune-related response criteria could remain on treatment until a confirmatory scan was done 4-6 weeks later.
[E] The statistical plan of the trial accounted for four primary outcomes; PFS and OS in patients with TPS ≥1%, and PFS and OS in patients with TPS ≥50%.
[F] Defined as time from randomization to radiologically confirmed progressive disease or death due to any cause.
[G] Defined as percentage of patients with complete or partial response as per RECIST criteria version 1.1.
[H] Defined as time from first evidence of response until disease progression or death.

Table 5: Select quality characteristics of the KEYNOTE 010 trial[2] comparing two different doses of pembrolizumab to docetaxel in patients with previously treated NSCLC with tumour PD-L1 expression of at least ≥1%.

Study	Treatment vs. Comparator	Primary outcomes	Required sample size	Sample size	Randomization method	Allocation concealment	Blinding	ITT Analysis	Final analysis	Early termination	Ethics Approval
KEYNOTE 010[2]	Pembrolizumab 2mg/kg vs. Pembrolizumab 10mg/kg vs. Docetaxel	OS PFS	*TPS ≥50% Subgroup*:[A] 460 patients required for 200 deaths (across all treatment groups) in patients with a TPS of ≥50% required to provide 81% power to detect a HR=0.55 using a one-sided alpha=0.00825 using the Hochberg procedure for multiple comparisons[D] *TPS ≥1% (total patient population)*: Expected 920 patients enrolled with 550 deaths, providing 80% power to detect a HR=0.70 using a one-sided alpha=0.825.[52]	1034	Central IVRS,[B] stratified[C] using block size of 6	No[D]	Outcome assessment and data analysis[D]	Yes	Yes	No	Yes

Abbreviations: HR - hazard ratio; IVRS - interactive voice response system; TPS - PD-L1 tumour proportion score.

Notes:

[A] That statistical analysis plan accounted for four primary outcomes (OS and PFS in both the TPS ≥50% patient subgroup and the total patient population). The statistical power of the trial, however, was based on the death rate in the TPS ≥50% patient subgroup; the assumptions were as follows: that half of the total sample would have TPS ≥50%; an OS benefit in this subgroup would provide enough power to show benefit for all primary endpoints; a median OS of 9 months in the docetaxel group (HR=0.60 for docetaxel vs. pembrolizumab); an enrolment period of 16 months; a minimum of 8 months of follow-up to observe the required event rate; and a dropout rate of 2% over 12 months.

[B] Allocation schedule was generated using a computerized randomized list generator.

[C] Patients were stratified by ECOG performance status (0 vs. 1), region (east Asia vs. not east Asia), and extent of tumour PD-L1 expression (TPS ≥50% vs. 1-49%). TPS was added as a stratification variable after 441 patients were randomized (the time when the PD-L1 immunohistochemistry assay cut point was established).[43]

[D] OS, PFS, and response were assessed by independent central review for efficacy analyses. Patients, investigators and the Sponsor were blinded to PD-L1 expression. The trial statistician was blinded to treatment assignment until the final efficacy analyses were completed.

a) Trials

KEYNOTE 010 is an open-label, randomized phase 2/3 trial conducted in 202 academic centres in 24 countries including Canada.[2] The trial's design reflects the uncertainty that existed at the time regarding the lowest effective dose of pembrolizumab, the importance of PD-L1 testing, and the optimal primary endpoint.

Patient enrolment occurred between August 2013 and February 2015. The trial included patients according to the following criteria:

- ≥18 years of age
- Disease progression as per RECIST (version 1.1) after two or more cycles of platinum-doublet chemotherapy and an appropriate TKI for patients with EGFR or ALK mutations
- Measurable disease as per investigator assessed RECIST
- A ECOG performance status of 0 or 1
- Provision of a tumour sample, and PD-L1 tumour expression on at least ≥1% of tumour cells, referred to as a tumour proportion score (TPS) of ≥1%.

Excluded from the trial were patients previously treated with a PD-1 checkpoint inhibitor or docetaxel, and patients with active brain metastases or carcinomatous meningitis, or those with active autoimmune disease, interstitial lung disease, or history of pneumonitis requiring systemic steroids.

At the start of the trial, either archived or new tumour samples were accepted for the purpose of PD-L1 testing. During the trial, however, the protocol was amended to only accept new tumour samples unless a new tumour biopsy was considered too risky for a patient. New tumour samples required no intervening treatment between the time of biopsy and the start of study treatment. The only exception to this requirement was in the case of patients on TKI, who were permitted to resume such treatment after biopsy. PD-L1 tumour expression testing was carried out at a central laboratory using the Dako PD-L1 immunohistochemistry assay and the murine 22C3 anti-human PD-L1 antibody. During patient enrolment, 2222 patients were screened that had assessable tumour samples. Of these patients, 1475 (66%) had a TPS score of ≥1% and included 633 patients (28%) with a score of ≥50%. A total of 1034 patients met the eligibility criteria and were randomized into the trial.

Patients were randomized in a 1:1:1 ratio to one of three treatment groups using central randomization methods. The randomization procedure was stratified according to extent of PD-L1 tumour expression (TPS ≥1% versus TPS ≥50%), geographic site (East Asia versus non-East Asia), and ECOG performance status (0 versus 1). The TPS was added as a stratification variable after 441 patients had been randomized, which is the time when tumour expression of ≥50% was established as a threshold for clinical benefit.[43] The trial was open label, and as such, patients, investigators and Sponsor personnel involved with treatment or clinical evaluations were aware of treatment assignment. The PD-L1 status of patients, however, was blinded to all three parties.

Merck and Company funded the trial and reported a role in all aspects of its conduct including study design, maintaining the trial database, data analysis and interpretation, and writing of the final publication. All authors had access to the trial data; and 10 of the 19 authors disclosed potential conflicts of interest related to the Sponsor.

The primary endpoints of the trial were overall survival (OS) and progression-free survival (PFS), the latter defined as the time from randomization to radiologically confirmed progressive disease or death. The secondary endpoints of the trial included safety, response rate (complete and partial), and duration of response, defined as the first evidence of response until disease progression or death.

For efficacy analyses, the assessment of PFS and response was carried out by independent central review. All treatment decisions, however, were made according to investigator assessment of immune-related response criteria. Patients who progressed by investigator assessment criteria were permitted to remain on study treatment until their next radiologic scan taken four to six weeks later.

b) Populations

Of the 1034 patients randomized in the trial, 345 patients were allocated to the 2mg/kg pembrolizumab group, 346 were allocated to the 10mg/kg pembrolizumab group, and 343 were allocated to docetaxel. In the all-patient population (TPS ≥1%), the treatment groups were balanced for baseline characteristics (Table 6). The median age of patients was approximately 63 years, with 24% (n=48) of patients aged 70 years or older. Most patients were Caucasian (72%), former or current smokers (80%), had non-squamous histology (70%), an ECOG performance status of 1 (66%), and had received one line of previous systemic treatment (69%). PD-L1 testing was performed on archived tumour samples in 455 patients (44%) and new tumour samples in 578 patients (56%).

Of the 1034 patients in the trial, 442 patients (43%) had a TPS score of ≥50%: 139 in the 2mg/kg pembrolizumab group, 151 in the 10mg/kg pembrolizumab group, and 152 in the docetaxel group. The distribution of baseline characteristics in the TPS ≥50% patient subgroup (Table 6) was similar to the all-patient population.

c) Interventions

Patients allocated to the pembrolizumab treatment groups (2mg/kg or 10mg/kg) received the drug intravenously over 30 minutes once every three weeks. Docetaxel was administered at 75 mg/m^2 intravenously over one hour once every three weeks, and also included corticosteroid premedication. Treatment continued for 24 months in all treatment groups or until disease progression, intolerable side effects, or physician decision or patient withdrawal. Patients randomized to docetaxel were not permitted to crossover to receive pembrolizumab. There were 34 patients who withdrew consent after learning they had been allocated to the docetaxel treatment group.

A total of 991 of 1034 patients received at least one dose of study drug; however, the median dose received by patients was not reported in the trial publication. The Submitter indicated the median dose received by patients was [redacted] mg and [redacted] mg in the 2mg/kg and 10mg/kg pembrolizumab groups, respectively, and [redacted] mg in the docetaxel treatment group. *(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.)* The median duration of treatment was 3.5 months in both pembrolizumab treatment groups, and was two months in the docetaxel group. Concomitant medications were received by 95% of patients. There were 10% of patients who received levothyroxine sodium (13% and 14% in the pembrolizumab 2mg/kg and 10mg/kg

groups, respectively and 5% in the docetaxel group) and <1% of patients who received infliximab (10mg/kg pembrolizumab group). After discontinuation of study treatment, 422 patients (41%) received subsequent anti-cancer therapy.

d) Patient Disposition

The disposition of patients through the KEYNOTE 010 trial is summarized in Table 7. At the time of the primary efficacy analysis, 79%, 78% and 92% of patients had discontinued treatment in the 2mg/kg pembrolizumab, 10mg/kg pembrolizumab, and docetaxel treatment groups, respectively. Similar percentages of discontinuations were observed in the TPS ≥50% patient subgroup. Progressive disease was indicated as the primary reason for treatment discontinuation in all treatment groups. Aside from reporting that <1% of treatment discontinuations resulted from protocol deviations, the trial publication did not comment on other protocol deviations occurring during the course of the trial. A request was made to the Submitter for this information. They indicated there were 61 protocol deviations that were considered clinical relevant to the Data Monitoring Committee. These deviations related to missing baseline radiographic images (n=21), entry criteria (n=15), informed consent (n=5), and prohibited medications (n=20), and were considered not to compromise the integrity of data analyses due to the use of pre-specified censoring rules.

The intent-to-treat efficacy population includes 1033 of the 1034 randomized patients. One patient allocated to the 2mg/kg pembrolizumab group was found to have pre-baseline scans that were not compliant with the trial protocol. This patient was omitted from efficacy analyses because tumour response assessment was not possible but was included in the analysis of safety. The safety analysis population included 991 patients.

The subsequent anti-cancer therapy received by 422 patients is summarized in Table 8. There were 138 patients (40%) from the 2mg/kg pembrolizumab group, 133 patients (38%) from the 10mg/kg pembrolizumab group, and 151 patients (44%) from the docetaxel group who received some form of anti-cancer therapy post-study. In each treatment group the majority of patients received chemotherapy as subsequent treatment. Considering both pembrolizumab groups, the most common regimens received by patients were docetaxel (21%), pemetrexed (6%), carboplatin (6%), and gemcitabine (5%). In the docetaxel group, the regimens most commonly received by patients were gemcitabine (9%), pemetrexed (6%), carboplatin (6%) and retreatment with docetaxel (4%). In terms of immunotherapy, more patients in the docetaxel group received nivolumab (9%) compared to patients in the pembrolizumab groups (0.3% and 1.4% for 2 mg/kg and 10 mg/kg respectively).

e) Limitations/Sources of Bias

Overall, the KEYNOTE trial[2] was well conducted owing to the use of appropriate methods to randomize patients, clear explanation of the disposition of patients through the trial, the use of independent central review for the assessment of key efficacy outcomes, and conducting all efficacy analyses by assigned treatment. However, the trial did have limitations, which are summarized below:

1. The trial was open label, and as such, patients, investigators and Sponsor personnel involved the trial were aware of treatment assignment, which can introduce bias and threaten the internal validity of the trial. However,

the potential for bias is minimized in KEYNOTE 010 through the use of independent central review of key efficacy outcomes, the blinding of parties to the PD-L1 status of patients, and the use of blinded data-analysts.

2. Although patient subgroup efficacy analyses were pre-specified, some groups (i.e., EGFR mutant status) included a smaller number of patients, which can have influence on the treatment effects observed. The results should such analyses require further validation.

3. There were 34 patients (9%) who withdrew consent after learning they had been allocated to the docetaxel treatment group. Although this type of attrition is not uncommon in NSCLC trials (and likely minimal considering the number of patients), it does introduce the potential for bias in the assessment of OS, as patients who dropped out could seek out alternative treatments, including other checkpoint inhibitors (through participation in other clinical trials, for example).

4. After discontinuing study treatment, 422 patients (41%) received subsequent anti-cancer therapy. The OS results of the trial are likely confounded by these treatments.

5. Given the uncertainty that exists around the optimal PD-L1 tumour expression threshold for clinical benefit, it is unfortunate that the trial did not include patients with no expression level, and that prospective efficacy analyses were limited to two patient PD-L1 expression subgroups (TPS ≥1% and ≥50%).

6. QOL data were assessed in the KEYNOTE 010 trial but have not been published in the public domain and undergone peer-review. The QOL data reviewed for the pCODR submission is incomplete, and suffers from selective reporting in documents provided by the Submitter. Further, the open-label design of the trial makes interpretation of the QOL data difficult.

Table 6: Baseline characteristics of patients in the KEYNOTE 010 trial[2] comparing two different doses of pembrolizumab to docetaxel in patients with previously treated NSCLC with tumour PD-L1 expression of at least ≥1%.

Baseline Characteristics	Total Patient Population (PD-L1 TPS of ≥1%)			Patients with PD-L1 TPS ≥50%		
	Pembro 2mg/kg (n=344)	Pembro 10mg/kg (n=346)	Docetaxel (n=343)	Pembro 2mg/kg (n=139)	Pembro 10mg/kg (n=151)	Docetaxel (n=152)
Age, median (range)	63 (56-69)	63 (56-69)	62 (56-69)	62 (56-69)	64 (58-70)	60 (54-69.5)
Male, n (%)	212 (62)	213 (62)	209 (61)	81 (58)	89 (59)	93 (61)
Race, n (%)						
White	246 (72)	250 (72)	251 (73)	102 (73)	111 (74)	117 (77)
Asian	73 (21)	72 (21)	72 (21)	27 (19)	28 (19)	29 (19)
Black	13 (4)	8 (2)	7 (2)	5 (4)	5 (3)	1 (1)
Region, n (%)						
East Asia	64 (19)	64 (18)	62 (18)	21 (15)	25 (17)	26 (17)
Not East Asia	280 (81)	282 (82)	281 (82)	118 (85)	126 (83)	126 (83)
ECOG PS, n (%)						
0	112 (33)	120 (35)	116 (34)	47 (34)	47 (31)	49 (32)
1	229 (67)	225 (65)	224 (65)	91 (65)	104 (69)	102 (67)
Histology, n (%)						
Squamous	76 (22)	80 (23)	66 (19)	29 (21)	41 (27)	26 (17)
Non-squamous	240 (70)	244 (71)	240 (70)	95 (68)	98 (65)	111 (73)
PD-L1 TPS, n (%)						
>50%	139 (40)	151 (44)	152 (44)	139 (100)	151 (100)	152 (100)
1-49%	205 (60)	195 (56)	191 (56)	0	0	0
Tumour Sample, n (%)						
New	197 (57)	193 (56)	188 (55)	NA		
Archived	147 (43)	153 (44)	155 (45)			
Smoking status, n (%)						
Former or current	279 (81)	285 (82)	269 (78)	112 (81)	122 (81)	113 (74)
Never	63 (18)	60 (17)	67 (20)	26 (19)	29 (19)	34 (32)
Stable brain metastases, n (%)	56 (16)	48 (14)	48 (14)	32 (23)	23 (15)	23 (15)
EGFR mutant, n (%)	28 (8)	32 (9)	26 (8)	8 (6)	13 (9)	12 (8)
ALK translocation positive, n (%)	2 (1)	4 (1)	2 (1)	2 (1)	2 (1)	1 (1)
No. lines advanced disease, n (%)						
1	243 (71)	235 (68)	235 (69)	97 (70)	104 (69)	109 (72)
2	66 (19)	69 (20)	75 (22)	30 (22)	26 (17)	25 (16)
≥3	27 (8)	34 (10)	29 (8)	10 (7)	16 (11)	15 (10)
Previous systemic therapy for advanced disease, n (%)						
Chemotherapy[A]	335 (97)	337 (97)	339 (99)	137 (99)	146 (97)	149 (98)
Immunotherapy	2 (1)	1 (<1)	1 (<1)	1 (1)	1 (1)	0
EGFR TKI	40 (12)	56 (16)	47 (14)	14 (10)	20 (13)	21 (14)
ALK inhibitor	3 (1)	5 (1)	2 (1)	3 (2)	3 (2)	1 (1)

Abbreviations: ALK = anaplastic lymphoma kinase; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; PD-L1 - programmed cell death-ligand 1; NA - not available; Pembro - pembrolizumab; TPS - tumour proportion score; TKI - tyrosine kinase inhibitor; TPS - tumour proportion score.

Notes:
[A]Patients who progressed within 1 year of completing platinum-based adjuvant therapy were also eligible.

Table 7: Patient disposition in the KEYNOTE 010 trial[2] comparing two different doses of pembrolizumab to docetaxel in patients with previously treated NSCLC with tumour PD-L1 expression of at least ≥1%.

Patient Disposition, n (%)	All Patients with PD-L1 TPS of ≥1% (n=1034)			Patients with PD-L1 TPS ≥50% (n=442)		
	Pembro 2mg/kg	Pembro 10mg/kg	Docetaxel	Pembro 2mg/kg	Pembro 10mg/kg	Docetaxel
Randomized n	345 (100)	346 (100)	343 (100)	139 (100)	151 (100)	152 (100)
Received randomized treatment	339 (98)[A]	343 (99)	309 (90)[E]	137 (99)	151 (100)	133 (88)
Discontinued randomized treatment	271 (79)	271 (78)	317 (92)	93 (67)	105 (70)	142 (93)
Remaining on study	74 (21)	75 (22)	11 (3)	46 (33)	46 (30)	5 (3)
ITT efficacy population	344 (99)[B]	346 (110)	343 (100)	139 (100)	151 (100)	152 (100)
Safety population	339 (98)	343 (99)	309 (90)	137 (99)	151 (100)	133 (88)
Primary reasons for treatment discontinuation:						
Progressive disease	124 (36)	126 (36)	89 (26)	34 (24)	49 (32)	40 (26)
Adverse events	34 (10)	32 (9)	47 (14)	17 (12)	12 (8)	17 (11)
Withdrew consent	5 (14)	10 (3)	45 (13)	3 (2)	6 (4)	22 (14)
Death	21 (6)	21 (6)	21 (6)	9 (6)	5 (3)	6 (4)
Physician decision	82 (24)[C]	74 (21)[C]	113 (33)[C]	28 (20)	30 (20)	56 (37)
Protocol deviation	2 (1)	1 (<1)	1 (<1)	1 (<1)	0	1 (<1)
Other	3 (1)	7 (2)	1 (<1)	1 (<1)	3 (2)	0
Completed treatment[D]	NA	NA	15 (4)	NA	NA	5 (3)

Abbreviations: ITT - intent-to-treat; NA - not applicable; Pembro - pembrolizumab; PD-L1 - programmed cell death-ligand 1; TPS - tumour proportion score.

Notes:

[A] Three patients had clinical progression that made them ineligible before treatment, two patients did not meet all the eligibility criteria but were incorrectly randomized to study treatment, and one patient was not treated because of physician decision.

[B] One patient was randomized and received pembrolizumab 2mg/kg but it was later found that their pre-baseline scans were not compliant with protocol. This patient remained on treatment and was included in safety analyses but was excluded from efficacy analyses.

[C] Primary attributable to clinical progression: 98%, 97% and 74% in the pembrolizumab 2mg/kg, 10mg/kg and docetaxel treatment groups, respectively.

[D] Patients who discontinued docetaxel after receiving the maximum number of cycles approved by local authorities were considered to have completed treatment.

[E] 34 patients withdrew consent after learning they were allocated to the docetaxel treatment group.

Table 8: Subsequent anti-cancer therapy in the KEYNOTE 010 trial[2] comparing two different doses of pembrolizumab to docetaxel in patients with previously treated NSCLC with tumour PD-L1 expression of at least ≥1%.

Subsequent anti-cancer therapy, n (%)	All Patients (PD-L1 TPS of ≥1%)		
	Pembro 2mg/kg (n=334)	Pembro 10mg/kg (n=346)	Docetaxel (n=343)
Any	138 (40)	133 (38)	151 (44)
Type[A]			
Chemotherapy[B]	119 (35)	100 (29)	93 (27)
Docetaxel	82 (24)	60 (17)	14 (4)
Pemetrexed	17 (5)	26 (8)	21 (6)
Carboplatin	16 (5)	25 (7)	
Immunotherapy[B]	2 (<1)	6 (2)	45 (13)
Nivolumab	1 (<1)	5 (1)	30 (8.7)
EGFR-TKI[B]	29 (8)	23 (7)	42 (12)
Erlotinib	26 (8)	17 (5)	36 (11)
ALK inhibitor[B]	2 (<1)	5 (1)	4 (1)
Crizotinib	1 (<1)	4 (1)	4 (1)
Other	14 (4)	20 (6)	11 (3)

Abbreviations: ALK - anaplastic lymphoma kinase; EGFR - epidermal growth factor receptor; PD-L1 - programmed cell death-ligand 1; Pembro - pembrolizumab; TPS - tumour proportion score.

Notes:
[A] Patients could have received more than one type of subsequent therapy, as well as more than one type of regimen.
[B] Not a complete list. Single-agent regimen unless otherwise specified.

6.3.2.1 Detailed Outcome Data and Summary of Outcomes

In the KEYNOTE 010 trial,[2] efficacy analyses for OS, PFS, and response rate were performed by intent-to-treat. For duration of response, all patients who had a best overall response of complete or partial response were included in analyses. The Kaplan Meier method was used to generate survival curves for all time-to-event outcomes including OS, PFS and duration of response. Differences in OS and PFS between treatment groups were analyzed using a log-rank test stratified by randomization variables. Hazard ratios (HR) and 95% confidence intervals (CIs) were generated using Cox proportional hazards models.

The trial was powered to show a difference in OS in the subgroup of patients with a TPS score of ≥50%. The statistical plan accounted for four primary endpoints; OS and PFS in all patients (i.e., TPS ≥1%), and OS and PFS in the TPS score ≥50% patient subgroup. The Hochberg procedure was employed to control the type 1 error rate for multiple comparisons; thus, the one-sided p-value used for declaring statistical significance was p=0.00825 for OS and p<0.001 for PFS. Two interim analyses, the first for futility and the second for demonstrating superiority of pembrolizumab in both PFS and OS endpoints, were pre-specified and performed by an independent unblinded statistician. Additional subgroup analyses were also planned a priori, and included age, sex, ECOG performance status, EGFR mutation status, and age of tumour sample. The data cut-off date for the primary efficacy analysis was September 30, 2015. It was reported that data analysts were blinded to treatment assignment until after final data analyses were completed. In 2016,

results of post-hoc efficacy analyses, which examined efficacy by additional PD-L1 expression subgroups, were published in abstract form.[47,48] Efficacy outcomes were analyzed for the 591 patients (57%) in the trial who had a TPS score of 1-49%;[47] and for the following additional TPS categories: 1-24%, 25-49%, 50-74%, and ≥75%.[48] For the latter analysis,[48] the pembrolizumab treatment groups were pooled together (i.e., pembrolizumab vs. docetaxel). The findings of these analyses have been summarized below for the primary outcomes (OS and PFS), but should be interpreted within the limitations of retrospective design. Refer to Table 5 for a more detailed summary of statistical and sample size considerations in the trial.

Patient–reported QOL was considered an exploratory endpoint of the trial, and was assessed using the EORTC Quality of Life Questionnaire (QLQ)-C30, the QLQ-Lung Cancer Module (LC-13), and the EuroQoL 5-Dimensions (EQ-5D). All three instruments are validated and commonly used in oncology. The QOL data from the KEYNOTE 010 trial have not been published; thus the Submitter provided all QOL data summarized in this report.

The QLQ-C30 measures overall QOL and different aspects of patient functioning. It comprises five function scales (physical, emotional, cognitive, social and role), three symptom scales (fatigue, pain, and nausea and vomiting), and a global health and QOL scale. The QLQ-LC13 is specific to lung cancer, and assesses lung cancer symptoms (coughing, hemoptysis, dyspnea, and pain) and side effects from treatment (hair loss, neuropathy, sore mouth and dysphagia). For both instruments, assessments were completed at baseline and at week 12. A mean change from baseline of 10% or greater (for continuous endpoints) is considered the minimal clinically important difference (MCID), with lower scores indicative of improvement in symptoms and side effects. Considering all treatment groups, compliance rates over 90% were reported at baseline, and rates were above 80% at week 12.

The EQ-5D was used to measure overall health status during treatment and follow-up phases of the KEYNOTE 010 trial. The EQ-5D Health State Index assesses health across five dimensions that include mobility, self-care, usual activities, pain or discomfort, and anxiety or depression. Each dimension has three possible outcomes: no problems, some problems, and extreme problems. EQ-5D index scores were calculated using the time trade-off method and incorporated utility weights by nationality (i.e., used US-based scores for US patients, UK-based scores for UK patients, and EU-based scores for all other patients) and were analyzed based on intent-to-treat. Possible scores range from -0.594 to 1. A change in score of ≥ 0.06 has been established as the MCID in US cancer patients. Considering all treatment groups, compliance rates were over 90% at baseline, over 70% at week 12, and were under 40% by week 36. At all assessment periods, compliance was much lower in the docetaxel treatment group.

The analysis of safety included all patients who received at least one dose of study medication.

Efficacy Outcomes

The key efficacy outcomes of the KEYNOTE 010 trial[2] are summarized in Table 9.

Overall Survival

At the time of the primary efficacy analysis, after a median follow-up time of 13.1 months (range, 8.6-17.7), a total of 521 patients had died: 172 (50%) in the pembrolizumab 2mg/kg group, 156 (45%) in the 10mg/kg group, and 193 (56%) in the docetaxel group. Among the TPS ≥50% patient subgroup there were 204 patient deaths (refer to Table 9 for deaths by treatment group).

Among all patients (TPS ≥1%), median OS for the 2mg/kg pembrolizumab, 10mg/kg pembrolizumab, and docetaxel groups were 10.4 months, 12.7 months, and 8.5 months, respectively (HR for 2mg/kg pembrolizumab versus docetaxel=0.71, 95% CI, 0.58-0.88; p=0.0008; HR for 10mg/kg pembrolizumab versus docetaxel=0.61, 95% CI, 0.49-0.75; p<0.0001). Compared to docetaxel, the survival benefit associated with pembrolizumab was 1.9 months at a dose of 2mg/kg and 4.2 months at a dose of 10mg/kg.

Among the TPS ≥50% patient subgroup, median OS for the 2mg/kg pembrolizumab, 10mg/kg pembrolizumab, and docetaxel groups were 14.9 months, 17.3 months, and 8.2 months, respectively (HR for 2mg/kg pembrolizumab versus docetaxel=0.54, 95% CI, 0.38-0.77; p=0.0002; HR for 10mg/kg pembrolizumab versus docetaxel=0.50, 95% CI, 0.36-0.70; p<0.0001). Compared to docetaxel, the survival benefit associated with pembrolizumab was approximately 6.7 months at a dose of 2mg/kg and 9.1 months at a dose of 10mg/kg.

Overall survival was similar between the 2mg/kg and 10mg/kg pembrolizumab groups, in both all patients (TPS ≥1%; HR=1.17; 95% CI, 0.94-1.45) and the TPS ≥50% patient subgroup (HR=1.12; 95% CI, 0.77-1.62).

Overall, compared to docetaxel, pembrolizumab significantly prolonged OS, regardless of dose, among all patients (TPS ≥1%) but the magnitude of benefit was greater in the TPS ≥50% patient subgroup. The treatment benefit was also evident in all other patient subgroups examined, however, the difference between treatment groups did not reach statistical significance in the following patients subgroups: those with squamous cell histology, mutant EGFR status, aged ≥70 years,[b] and an ECOG status of 0. The subgroups analysis was pre-specified for ECOG PS, EGFR status and age of tumour sample. For tumour histology it was a post-hoc exploratory subgroup analysis. Further, the use of archived versus new tumour sample tissue for PD-L1 testing did not appear to affect treatment benefit.

In the TPS 1-49% patient subgroup (n=591),[47] OS favoured the pembrolizumab treatment groups, but a statistically significant benefit was only detected at the 10mg/kg dose. Median OS was 9.4 months in the 2mg/kg pembrolizumab group, 10.8 months in the 10mg/kg pembrolizumab group, and 8.6 months in the docetaxel arm (HR for 2mg pembrolizumab versus docetaxel=0.79, 95% CI, 0.61-1.04; HR for 10mg/kg versus docetaxel=0.71, 95% CI, 0.53-0.94). No difference in treatment effect was observed between the pembrolizumab doses (HR=1.15, 95% CI, 0.88-1.52).

When TPS was further categorized,[48] the percentage of trial patients in each TPS category was: 46% (TPS 1-24%), 12% (TPS 25-49%), 15% (TPS 50-74%), and 28% (≥75%). In the pembrolizumab group, OS, PFS and ORR generally increased with increasing TPS, with the longest OS and PFS, and highest ORR observed in patients with TPS ≥75%; however, not all these differences were statistically significant. Of

[b] At the request of the pCODR review team, the submitter performed a post-hoc subgroup analysis for patients aged ≥ 70 years. The subgroup analysis for patients ≥65 years was presented in the trial publication and was pre-specified.

interest to note, patients in the TPS 1-24% category also derived clinical benefit with pembrolizumab with improved OS compared to docetaxel (OS HR=0.74; p=0.01; PFS HR=1.08, p=0.74; ORR=8.6%, p=0.76).

Progression-free Survival

Among all patients (TPS ≥1%), a total of 776 PFS events were observed during the follow-up period; 226 (77%) in the 2mg/kg pembrolizumab group, 254 (73%) in the 10mg/kg group, and 256 (75%) in the docetaxel group. No differences in PFS were found between treatment groups (Table 9).

In the TPS ≥50% patient subgroup there were a total of 304 PFS events (refer to Table 9 for events by treatment group). PFS was significantly longer with either dose of pembrolizumab compared to docetaxel; median PFS was 5 months, 5.2 months, and 4.1 months in the 2mg/kg, 10mg/kg, and docetaxel groups, respectively (HR for 2mg/kg versus docetaxel=0.59, 95% CI, 0.44-0.78; p=0.0001; HR for 10mg/kg versus docetaxel=0.59, 95% CI, 0.45-0.78; p<0.0001). Compared to docetaxel, the PFS benefit associated with pembrolizumab was 0.9 months at a dose of 2mg/kg and 1.1 months at a dose of 10mg/kg.

Progression-free survival was similar between the 2mg/kg and 10mg/kg pembrolizumab groups, in both all patients (TPS ≥1%; HR=1.09; 95% CI, 0.92-1.30) and the TPS ≥50% patient subgroup (HR=1.01; 95% CI, 0.75-1.36).

Overall, compared to docetaxel, pembrolizumab at either dose was associated with a PFS benefit among patients with a TPS ≥50%, but not in patients with a TPS score below this expression level. The results of subgroup analyses showed a statistically significant PFS benefit for the following subgroups of patients: male gender, ECOG of 1, and those patients with EGFR wild-type status.

In the TPS 1-49% patient subgroup,[47] PFS favoured pembrolizumab, but no statistically significant differences were found between treatment groups. Median PFS was 3.1 months in the 2mg/kg pembrolizumab group, 2.3 months in the 10mg/kg pembrolizumab group, and 3.9 months in the docetaxel arm (HR for 2mg pembrolizumab versus docetaxel=1.07, 95% CI, 0.85-1.34; HR for 10mg/kg versus docetaxel=0.99, 95% CI, 0.78-1.25).

Response and Duration of Response

The response rate, which was defined as the percentage of patients with a complete or partial response, was significantly higher in both pembrolizumab treatment groups compared to docetaxel for all patients (18% in both pembrolizumab groups, versus 9%) and the TPS ≥50% patient subgroup (30% versus 29% versus 8%). All observed responses were partial responses (Table 9). Median time-to-response was nine weeks in each treatment group.

Considering all patients, as well as the TPS ≥50% patient subgroup, the duration of responses was longer with pembrolizumab, regardless of dose, compared to docetaxel. The median duration of response was not reached for either pembrolizumab treatment group and was six months and eight months in the docetaxel group for all patients and the TPS ≥50% patient subgroup, respectively.

Quality of Life

EORTC-QLQ-C30

In all patients (TPS ≥1%) at week 12, differences in the mean change from baseline on the QLQ-C30 showed numerical improvements (i.e., less deterioration) of the Global Health Status Score in patients treated with either dose of pembrolizumab compared to docetaxel (Table 11). These differences, however, did not reach the MCID of >10%. Among patients in the TPS ≥50% subgroup, the difference in mean change reached statistical significance in the 2mg/kg pembrolizumab group compared to docetaxel (difference in mean change=8.3, 95% CI, 2.4 to 14.3; p=0.006).

EORTC-QLQ-LC13

In general, for the majority of lung cancer symptoms, patients treated with pembrolizumab showed numerical improvements from baseline, while patients treated with docetaxel showed numerical worsening from baseline. Specifically, in all patients (TPS ≥ 1%) at week 12, alopecia (difference in mean change= -45.4, 95% CI, -49.9 to -41.1; p<0.0001), peripheral neuropathy (difference in mean change= -8.0, 95% CI, -12.4 to -3.61; p=0.0004) and sore mouth (difference in mean change= -7.5, 95% CI, -11.2 to -3.9; p<0.0001) were significantly improved with pembrolizumab 2mg/kg versus docetaxel. In the TPS ≥50% patient subgroup, dyspnea, hemoptysis, alopecia, and sore mouth were statistically significantly improved with pembrolizumab 2mg/kg versus docetaxel.

Compared to docetaxel, pembrolizumab 2mg/kg increased the time-to-true deterioration (defined as time-to first-10-point or more decrease in score from baseline) in QLQ-LC13 composite endpoint of cough, dyspnea, and chest pain. In the TPS ≥50% patient subgroup, statistical significance was achieved for the 2mg/kg dose (HR=0.68; 95% CI, 0.48-0.96; p=0.03).

EQ-5D

EQ-5D questionnaires were administered to patients during treatment (cycles 1, 2, 3, 5, 9, and 13) and following treatment (discontinuation visit, and 30-day safety follow-up visit). Considering all treatment groups, EQ-5D scores generally increased over time, with similar scores observed among the treatment groups at weeks 3 and 6, and lower scores observed in the docetaxel group at weeks 12, 24 and 36 (Table 12). At most assessment periods the mean differences in index scores between pembrolizumab groups versus docetaxel were small (<0.04), except at week 36 where at both doses the difference exceeded the MCID of 0.06 (difference versus docetaxel for both doses=0.18, p=0.01). It should be noted, however, that the number of patients included in the analysis at week 36 included only 14% of trial patients, which limits interpretation of the findings.

Harms Outcomes

The analysis of adverse events was based on a safety population of 991 patients that included 339 patients in the 2mg/kg pembrolizumab group, 343 patients in the 10mg/kg group, and 309 patients in the docetaxel group. The trial summarized treatment-related adverse events (all grade and grade 3-5 occurring in ≥10% of patients), as well as events considered of special interest due to immune etiology (occurring in ≥ two patients regardless of relatedness with study drug). Adverse

event data from the KEYNOTE 010 trial are summarized in Table 10. No statistical comparisons of these data were presented.

Compared to docetaxel, pembrolizumab was associated with fewer all grade and grade 3-5 treatment-related adverse events; the percentage of patients experiencing grade 3-5 adverse events was 13%, 16%, and 35% in the 2mg/kg pembrolizumab, 10mg/kg pembrolizumab, and docetaxel groups, respectively. A higher percentage of patients receiving docetaxel had dosage modifications due to adverse events: 42% versus 29% and 30% in the 2mg and 10mg pembrolizumab treatment groups, respectively. The percentage of patients discontinuing treatment due to treatment-related adverse events was also higher among patients treated with docetaxel: 10% versus 4% and 5% of patients in the 2mg/kg and 10mg/kg groups, respectively. However, treatment interruptions due to adverse events were similar among the treatment groups (22% and 24% in the 2mg/kg and 10mg/kg pembrolizumab groups, respectively, versus 24% in the docetaxel group).

Immune-related events of special interest occurred in 20% (69 of 339 patients) of patients receiving pembrolizumab at a dose of 2mg/kg, and 19% (64 of 343 patients) of patients at a dose of 10mg/kg. The most frequent type of events, any grade (2mg versus 10mg dose), included hypothyroidism (8% at both doses), pneumonitis (5% versus 4%), and hyperthyroidism (4% versus 6%). Of these events, only pneumonitis and severe skin reactions occurred at a severity of grade 3 or higher in greater than 1% of patients.

Data on infusion reactions were not reported in the trial publication. The Submitter provided these data, which showed infusion reactions occurred in 0.7% of patients treated with pembrolizumab and 2.6% of patients treated with docetaxel. All infusion reactions were graded as 1 or 2.

The trial reported 11 deaths attributable to study treatment. There were three deaths (<1%) in the 2mg/kg pembrolizumab group (two cases of pneumonitis, one case of pneumonia), three deaths (<1%) in the 10mg/kg pembrolizumab group (one case each of myocardial infarction, pneumonia and pneumonitis), and 5 deaths (2%) in the docetaxel group (one case each of cardiac failure, dehydration, febrile neutropenia, interstitial lung disease, and respiratory infection).

Table 9: Key efficacy outcomes in the KEYNOTE 010 trial[2] comparing two different doses of pembrolizumab to docetaxel in patients with previously treated NSCLC with tumour PD-L1 expression of at least ≥1%.

Efficacy Outcomes	All Patients with PD-L1 TPS of ≥1%			Patients with PD-L1 TPS ≥50%		
	Pembro 2mg/kg (n=344)	Pembro 10mg/kg (n=346)	Docetaxel (n=343)	Pembro 2mg/kg (n=139)	Pembro 10mg/kg (n=151)	Docetaxel (n=152)
Median Follow-up in months (range): 13.1 (8.6 -17.7)[A]						
Primary Outcome: OS						
No. Deaths (%)	172 (50)	156 (45)	193 (56)	58 (42)	60 (40)	86 (57)
Median, months (95% CI)	10.4 (9.4-11.9)	12.7 (10-17.3)	8.5 (7.5-9.8)	14.9 (10.4-not reached)	17.3 (11.8-not reached)	8.2 (6.4-10.7)
HR[B] (95%CI)	0.71 (0.58-0.88)	0.61 (0.49-0.75)	-	0.54 (0.38-0.77)	0.50 (0.36-0.70)	-
p-value	p=0.0008	p<0.0001	-	p=0.0002	p<0.0001	-
OS at 1 year, %	43	52	35	NR	NR	NR
Primary Outcome: PFS						
No. PFS events (%)	266 (77)	254 (73)	256 (75)	89 (64)	97 (64)	118 (78)
Median, months (95% CI)	3.9 (3.1-4.1)	4.0 (2.7-4.3)	4.0 (3.1-4.2)	5.0 (4-6.5)	5.2 (4.1-8.1)	4.1 (3.6-4.3)
HR[B] (95%CI)	0.88 (0.74-1.05)	0.79 (0.66-0.94)	-	0.59 (0.44-0.78)	0.59 (0.45-0.78)	-
p-value	p=0.07[C]	p=0.004[C]	-	p=0.0001	p<0.0001	-
Secondary Outcome: Response						
No. responses (%)	62 (18)[D]	64 (18)[D]	32 (9)[D]	42 (30)[D]	44 (29)[D]	12 (8)[D]
p-value	p=0.0005	p=0.0002	-	p<0.0001	p<0.0001	-
Secondary Outcome: Duration of Response						
Median, months	Not reached	Not reached	6.0	Not reached	Not reached	8.0

Abbreviations: CI = confidence interval, HR = hazard ratio, NR - not reported; OS = overall survival; Pembro - pembrolizumab; PFS = progression-free survival; TPS - tumour proportion score; "-" docetaxel is the reference treatment group.

Notes:
[A] Data cut-off date is September 30, 2015.
[B] HR is for pembrolizumab versus docetaxel, where a HR < 1 favours pembrolizumab 2mg/kg or 10mg/kg.
[C] Result is not statistically significant because it did not meet the pre-specified criterion declaring statistical significance for PFS (p<0.001).
[D] All responses were partial responses.

Table 10: Adverse events in the KEYNOTE 010 trial[2] comparing two different doses of pembrolizumab to docetaxel in patients with previously treated NSCLC with tumour PD-L1 expression of at least ≥1%.

Adverse Events, n (%)	All Patients (PD-L1 TPS of ≥1%)					
	Pembro 2mg/kg (n=339)		Pembro 10mg/kg (n=343)		Docetaxel (n=309)	
	Any grade	Grade 3-5	Any grade	Grade 3-5	Any grade	Grade 3-5
Treatment-related, as determined by investigator:						
Any	215 (63)	43 (13)	226 (66)	55 (16)	251 (81)	109 (35)
Occurring in ≥10% of patients:						
Decreased appetite	46 (14)	3 (1)	33 (10)	1 (<1)	49 (16)	3 (1)
Fatigue	46 (14)	4 (1)	49 (14)	6 (2)	76 (25)	11 (4)
Nausea	37 (11)	1 (<1)	31 (9)	2 (1)	45 (15)	1 (<1)
Rash	29 (9)	1 (<1)	44 (13)	1 (<1)	14 (5)	0
Diarrhea	24 (7)	2 (1)	22 (6)	0	56 (18)	7 (2)
Asthenia	20 (6)	1 (<1)	19 (6)	2 (1)	35 (11)	6 (2)
Stomatitis	13 (4)	0	7 (2)	1 (<1)	43 (14)	3 (1)
Anemia	10 (3)	3 (1)	14 (4)	1 (<1)	40 (13)	5 (2)
Alopecia	3 (1)	0	2 (1)	0	101 (33)	2 (1)
Neutropenia	1 (<1)	0	1 (<1)	0	44 (14)	38 (12)
Of special interest, occurring in ≥2 of patients in pembrolizumab treatment groups irrespective of being related to study drug:						
Hypothyroidism	28 (8)	0	28 (8)	0	1 (<1)	0
Pneumonitus[A]	16 (5)	7 (2)	15 (4)	7 (2)	6 (2)	2 (1)
Hyperthyroidism	12 (4)	0	20 (6)	1 (<1)	3 (1)	0
Colitis	4 (1)	3 (1)	2 (1)	1 (<1)	0	0
Severe skin reactions	4 (1)	3 (1)	7 (2)	6 (2)	2 (1)	2 (1)
Pancreatitis[B]	3 (1)	2 (1)	0	0	0	0
Adrenal insufficiency	2 (1)	0	3 (1)	1 (<1)	0	0
Myositis	2 (1)	0	1 (<1)	0	1 (<1)	0
Thyroiditis	2 (1)	0	0	0	0	0
Autoimmune hepatitis	1 (<1)	1 (<1)	2 (1)	0	0	0
Hypophysitis	1 (<1)	1 (<1)	1 (<1)	1 (<1)	0	0
Type 1 diabetes	1 (<1)	1 (<1)	2 (1)	1 (<1)	0	0

Abbreviations: PD-L1 - programmed cell death-ligand 1; Pembro - pembrolizumab; TPS - tumour proportion score.

Notes:
[A] Incudes patients with interstitial lung disease; one patient in the pembrolizumab 2mg/kg group, and two each in the pembrolizumab 10mg/kg and docetaxel groups.
[B] Includes one patient with acute pancreatitis.

Table 11. Health-related QOL assessment in the KEYNOTE 010 trial as measured by the EORTC Quality of Life Questionnaire (QLQ-C30).

Treatment Group	Baseline N	Baseline Score Mean (SD)	Week 12 N	Week 12 Score Mean (SD)	N with Baseline and Week 12 scores	Change from Baseline at Week 12 LS Mean (95% CI)*	Difference vs. Docetaxel LS Mean (95% CI)	p-value
PD-L1 ≥ 1%								
Pembro 2mg/kg	312	62.4 (21.0)	222	65.3 (19.9)	212	-1.2 (-3.7 to 1.4)	2.7 (-1.1 to 6.4)	0.16
Pembro 10mg/kg	300	63.7 (22.0)	230	64.1 (20.8)	210	-2.5 (-5.1 to 0.0)	1.3 (-2.4 to 5.0)	0.49
Docetaxel	266	61.9 (21.3)	162	62.4 (18.7)	146	-3.8 (-6.7 to -0.9)	-	-
PD-L1 ≥50%								
Pembro 2mg/kg	126	61.9 (22.3)	94	67.0 (20.8)	90	1.5 (-2.5 to 5.5)	8.3 (2.4 to 14.3)	0.006
Pembro 10mg/kg	135	63.6 (22.2)	110	63.9 (21.6)	103	-3.0 (-6.8 to 0.7)	3.8 (-1.9 to 9.6)	0.19
Docetaxel	114	61.3 (21.8)	66	59.7 (19.4)	60	-6.9 (-11.5 to -2.2)	-	-
Abbreviations: CI - confidence interval; PD-L1 - programmed cell death-ligand 1; LS - least squares; Pembro - pembrolizumab; SD - standard deviation; "-" docetaxel is the reference treatment group; vs. - versus.								
Notes: *Calculated only for patients with scores at both baseline and week 12.								

Table 12: Summary of EuroQOL 5 Dimensions (EQ-5D) data from the KEYNOTE 010 trial.

Study visit	Treatment Group Score*		Change in Score* from Baseline		Mean Difference vs. Docetaxel	p-value
	n**	Mean (SE)	n**	Mean (SE)	LS Mean (95% CI)	
Pembrolizumab 2mg/kg (n=305)						
Baseline	290	0.75 (0.01)		-	-	
Week 3	285	0.73 (0.01)	277	-0.011 (0.01)	-0.03 (-0.06 to 0.00)	0.07
Week 6	263	0.75 (0.01)	250	-0.006 (0.01)	-0.04 (-0.07 to 0.00)	0.06
Week 12	199	0.79 (0.01)	191	0.008 (0.01)	0.01 (-0.04 to 0.05)	0.80
Week 24	115	0.80 (0.02)	111	0.024 (0.02)	0.04 (-0.04 to 0.11)	0.31
Week 36	54	0.85 (0.03)	52	0.042 (0.03)	0.18 (0.04 to 0.32)	0.01
Pembrolizumab 10mg/kg (n=310)						
Baseline	281	0.76 (0.01)		-	-	
Week 3	282	0.73 (0.01	262	-0.012 (0.01)	-0.03 (-0.06 to 0.00)	0.06
Week 6	252	0.75 (0.01)	231	-0.006 (0.01)	-0.04 (-0.07 to 0.00)	0.07
Week 12	200	0.77 (0.01)	186	0.001 (0.02)	-0.00 (-0.05 to 0.05)	0.98
Week 24	105	0.79 (0.02)	98	0.007 (0.02)	0.02 (-0.05 to 0.09)	0.57
Week 36	60	0.81 (0.03)	57	0.042 (0.03)	0.18 (0.04 to 0.32)	0.01
Docetaxel (n=225)						
Baseline	230	0.73 (0.01)		-		
Week 3	233	0.73 (0.01)	212	0.019 (0.01)	-	-
Week 6	198	0.75 (0.01)	179	0.029 (0.01)	-	-
Week 12	133	0.75 (0.02)	120	0.002 (0.02)	-	-
Week 24	58	0.74 (0.02)	51	-0.014 (0.03)	-	-
Week 36	12	0.67 (0.07)	12	-0.142 (0.06)	-	-

Abbreviations: CI - confidence interval; LS - least squares; SE - standard error; "-" docetaxel is the reference treatment group.

Notes:
*Utility scores were calculated based on US algorithm for US patients, UK algorithm for UK patients, EU algorithm for all other patients.
**Number of subjects with at least one non-missing value in full analysis set population.

6.4 Ongoing Trials

No ongoing trials were identified.

7 SUPPLEMENTAL QUESTIONS

The following supplemental questions were identified during the development of the review protocol as relevant to the pCODR review of pembrolizumab for NSCLC:

1. What is the accuracy of programmed death ligand 1 (PD-L1) diagnostic antibody assays?
2. What is the clinical utility of PD-L1 testing in patients with non-small cell lung cancer?
3. What is the effectiveness of programmed cell death protein 1 (PD-1)/PD-L1 checkpoint inhibitors for treating patients with non-small cell lung cancer with different levels of PD-L1 expression?

Topics considered in this section are provided as supporting information.

7.1 Accuracy, Utility and Effectiveness

7.1.1 Objective

The PAG had concerns on the timing of conducting the PD-L1 test, the turn-around times for the test results, and the accuracy of the test results as well as co-ordinating with facilities set up to conduct the test and the possible need for another biopsy. Therefore, PAG requested clarity on the benefits of PD-L1 testing compared to not conducting PD-L1 testing prior to treatment of NSCLC with pembrolizumab.

The objective of this supplemental issue is to identify the evidence (in the form of a reference list) on the accuracy of PD-L1 diagnostic antibody assays, the clinical utility of PD-L1 testing, and the effectiveness of PD-1/PD-L1 checkpoint inhibitors for treating patients with NSCLC with different levels of PD-L1 expression.

7.1.2 Methods, Selection Criteria and Results

METHODS

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials and non-randomized studies. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between Jan 1, 2011 and May 23, 2016. Internet links were provided, where available.

SELECTION CRITERIA

One reviewer screened citations and selected studies based on the inclusion criteria presented in Table 13.

Table 13: Selection Criteria	
Population	Q1: Patients with cancer Q2, Q3: Patients with non-small cell lung cancer
Intervention	Q1, Q2: PD-L1 testing Q3: PD-1/PD-L1 checkpoint inhibitors (nivolumab, pembrolizumab, atezolizumab

	[MPDL3280A], durvalumab [MEDI4736], and avelumab [MSB0010718C])
Comparator	Q1, Q2: Any Q3: Different PD-L1 expression levels
Outcomes	Diagnostic accuracy, clinical utility (benefits and harms of testing), overall survival, progression-free survival, quality of life, objective response rate, duration of response, and time to response
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies

RESULTS

Two health technology assessments (HTAs), five systematic reviews, three randomized controlled trials, and two non-randomized studies were identified regarding the effectiveness of PD-1/PD-L1 checkpoint inhibitors for treating patients with non-small cell lung cancer with different levels of PD-L1 expression. No relevant studies were identified regarding the accuracy of diagnostic antibody assays or clinical utility of PD-L1 testing. Below is the list of references identified in the search.[54]

Health Technology Assessments

1. Ludwig Boltzmann Institut fuer Health Technology Assessment (LBI-HTA). Nivolumab (Nivolumab BMS®) for the second-line therapy of metastatic squamous non-small cell lung cancer [Internet]. Vienna: Ludwig Boltzmann Institut fuer Health Technology Assessment (LBIHTA); 2015. [cited 2016 May 27]. (DSD: Horizon Scanning in Oncology no. 53). Available from: http://eprints.hta.lbg.ac.at/1068/1/DSD_HSO_Nr.53.pdf[55]

2. Baumann M, Groessmann N . Pembrolizumab (Keytruda®) in previously treated advanced non-small cell lung cancer (NSCLC) [Internet]. Vienna: Ludwig Boltzmann Institut fuer Health Technology Assessment (LBIHTA); 2016. [cited 2016 May 27]. (DSD: Horizon Scanning in Oncology no.58). Available from: http://eprints.hta.lbg.ac.at/1086/1/DSD_HSO_Nr.58.pdf[56]

Systematic Reviews and Meta-analyses

3. Abdel-Rahman O. Correlation between PD-L1 expression and outcome of NSCLC patients treated with anti-PD-1/PD-L1 agents: A meta-analysis. Crit Rev Oncol Hematol. 2016 May;101:75-85.[57]
PubMed: PM26969107

4. Gandini S, Massi D, Mandala M. PD-L1 expression in cancer patients receiving anti PD-1/PD-L1 antibodies: A systematic review and meta-analysis. Crit Rev Oncol Hematol. 2016 Apr;100:88-98.[58]
PubMed: PM26895815

5. Aguiar PN Jr, Santoro IL, Tadokoro H, de Lima Lopes G, Filardi BA, Oliveira P, et al. The role of PD-L1 expression as a predictive biomarker in advanced non-small-cell lung cancer: a network meta-analysis. Immunotherapy. 2016 Apr;8(4):479-88.[59]
PubMed: PM26973128

6. Zhu L, Jing S, Wang B, Wu K, Shenglin MA, Zhang S. Anti-PD-1/PD-L1 therapy as a promising option for non-small cell lung cancer: a single arm meta-analysis. Pathol Oncol Res. 2016 Apr;22(2):331-9.[60]
PubMed: PM26552662

7. Passiglia F, Bronte G, Bazan V, Natoli C, Rizzo S, Galvano A, et al. PD-L1 expression as predictive biomarker in patients with NSCLC: a pooled analysis. Oncotarget. 2016 Feb 22.[61]
PubMed: PM26918451

Randomized Controlled Trials
8. Herbst RS, Baas P, Kim DW, Felip E, Perez-Gracia JL, Han JY, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. Lancet. 2016 Apr 9;387(10027):1540-50.[2]
PubMed: PM26712084

9. Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, et al. Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer. N Engl J Med. 2015 Oct 22;373(17):1627-39.[44]
PubMed: PM26412456

10. Brahmer J, Reckamp KL, Baas P, Crino L, Eberhardt WE, Poddubskaya E, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. N Engl J Med. 2015 Jul 9;373(2):123-35.[45]
PubMed: PM26028407

Non-Randomized Studies
11. Antonia S, Goldberg SB, Balmanoukian A, Chaft JE, Sanborn RE, Gupta A, et al. Safety and antitumour activity of durvalumab plus tremelimumab in non-small cell lung cancer: a multicentre, phase 1b study. Lancet Oncol. 2016 Mar;17(3):299-308.[62]
PubMed: PM26858122

12. Garon EB, Rizvi NA, Hui R, Leighl N, Balmanoukian AS, Eder JP, et al. Pembrolizumab for the treatment of non-small-cell lung cancer. N Engl J Med [Internet]. 2015 May 21 [cited 2016 May 27];372(21):2018-28. Available from: http://www.nejm.org/doi/full/10.1056/NEJMoa1501824#t=article ga[43]
PubMed: PM25891174

Of note, separate from the reference list above, the submitter recently published a study on the sensitivity, specificity, repeatability, and reproducibility of the Dako PD-L1 22C3 pharmDx,[63] which is the immunohistochemistry assay used in KEYNOTE 010 trial.[2] Currently, however, there is no gold standard assay for PD-L1 testing, which makes interpretation of the 22C3 assay data difficult. For this reason, the study on the Dako PD-L1 22C3 pharmDx assay has not been reported on below. Efforts are underway by the BluePrint Consortium to actively compare several commercial PD-L1 assays but at this time peer-reviewed published results are not available.[64]

7.1.3 Summary and Interpretation

The limited literature search did not identify any evidence to inform on the accuracy of available PD-L1 diagnostic antibody assays (i.e., sensitivity, specificity, and detection rate), or the clinical utility of PD-L1 testing compared to no testing (i.e., clinical benefits and harms of testing) in patients with NSCLC. Seven reports, considered higher-quality evidence, were identified that addressed the effectiveness of PD-1/PD-L1 inhibitors in treating NSCLC patients with different levels of PD-L1 expression. Of these, two were HTAs that narratively summarized the evidence from individual randomized trials, and five were systematic reviews that included a meta-analysis of trials (randomized and non-randomized) that examined outcomes by PD-L1 expression. In the absence of evidence on the accuracy and clinical utility of PD-L1 testing, however, it is questionable whether combining trial data is actually appropriate and yields relevant, accurate and reliable findings. Therefore, the findings of these meta-analyses have not been summarized in this report. The results of individual randomized trials assessing the

effectiveness of PD-1/PD-L1 checkpoint inhibitors for treating patients with NSCLC with varying levels of PD-L1 expression are presented in Sections 6 and 8 of this report.

8 COMPARISON WITH OTHER LITERATURE

It was noted that PAG is seeking clarity on the benefits of PD-L1 testing compared to not conducting the PD-L1 testing prior to treatment of NSCLC with pembrolizumab, given that the testing is not required for treatment with nivolumab, another PD-1 inhibitor, and not required for the treatment of melanoma with pembrolizumab. As a result, details of the phase 1 KEYNOTE 001 trial evaluating pembrolizumab[43] and the phase 3 CheckMate trials[44,45] evaluating nivolumab in NSCLC are summarized below. The latter trials did not restrict inclusion criteria based on tumour PD-L1 expression. Of note, the KEYNOTE and CheckMate trials used different immunohistochemistry (ICH) assays; therefore any comparisons made across trials should take this into consideration.

KEYNOTE Trial 001 Evaluating Pembrolizumab in NSCLC

KEYNOTE 001 was a multicentre,[43] open-label, phase I trial that evaluated the efficacy and safety of single-agent pembrolizumab (at a dose of 2mg/kg every 3 weeks, or 10mg/kg every 2 or 3 weeks) in adult patients with advanced or metastatic NSCLC. The trial included patients with an ECOG performance status of 0 or 1 and adequate organ function, and excluded patients with a history of pneumonitis, systemic immunosuppressive therapy, or active immune disease. Patients with progressive disease were allowed to continue on study treatment until scheduled imaging confirmed progression of disease. As the trial progressed modifications were made to its design to include different subgroups of patients. Thus an additional objective of the trial was to define and validate a tumour PD-L1 expression level associated with greater clinical benefit from pembrolizumab. PD-L1 expression was measured and tested using the anti-PD-L1 anti-body clone 22C3 (Merck) and different versions of a prototype ICH assay (developed by Dako) were used at distinct stages of the trial: for determination of PD-L1 status for eligibility, establishment of a PD-L1 threshold for clinical benefit (training patient group), and validation of the selected threshold (validation patient group). PD-L1 positivity was defined as staining in at least 1% of tumour cells. A total of 495 patients received at least one dose of pembrolizumab and were assigned to either the training or validation patient groups. Characteristics of included patients were noted as typical of those with advanced/metastatic NSCLC. A majority of patients had non-squamous NSCLC (81%) versus squamous NSCLC histology (17%).

182 patients were assigned to the training group. Of those patients, 129 had measurable disease (RECIST) and had tumour samples that could be evaluated by the ICH assay (25 patients' samples were archival). After evaluating the performance of potential cut-off points, a PD-L1 TPS of at least 50% was selected as the cut-off threshold. At this cut-off, the overall response rate in the training patient group (according to RECIST and central review) was 36.6%. The prevalence of PD-L1 expression in the trial among the initial 824 patients screened for enrolment (with evaluable tumour samples) was the following: <1% (39.2%), 1-49% (38%), and ≥50% (23%). Similar TPS distributions were observed in previously treated [n=643, <1% (41%), 1-49% (36%), and ≥50% (23%)] and treatment naïve patients [n=181, <1% (32%), 1-49% (44%), and ≥50% (25%)].

The validation patient group included 313 patients, of whom 223 were previously treated and 90 were treatment naïve. A total of 220 patients met the trial requirements for PD-L1 testing and were evaluable for PD-L1 status and efficacy. Table 13 summarizes efficacy outcomes by PD-L1 expression in the validation patient group. At data cut-off, patients had been followed for a median of 9.2 months. For each outcome (except for duration of response, where median duration of response was not reached for any patient subgroup), increasing TPS correlated with greater clinical benefit; the TPS ≥50% patient subgroup was associated with a higher response rate, and longer PFS and OS compared to each lower TPS subgroup. The benefit was demonstrated in both treated and treatment naïve patients. In 2016 updated OS data were published in abstract form for both previously treated and treatment naïve patients;[65] after a median follow-up of 23.1

months, the median OS was 22.1 months and 10.6 months for these patient groups, respectively. Median OS increased by increasing TPS score within both patient groups.

CheckMate Trials Evaluating Nivolumab in NSCLC

At the time the PAG provided input on the pCODR submission for pembrolizumab, another immune checkpoint inhibitor, nivolumab, was under review for NSCLC. In anticipation that nivolumab may become funded and made available, PAG requested information comparing the two inhibitors. On June 3, 2016, the pCODR Expert Review Committee recommended funding of nivolumab for the treatment of patients with advanced or metastatic NSCLC who have progressed on or after platinum-based doublet chemotherapy. The funding recommendation was informed by two randomized trials: CheckMate 057 and CheckMate 017.[44,45] Below, these trials are compared to the KEYNOTE 010 trial of pembrolizumab,[2] in terms of eligible patient populations, drug dosing and schedules, adverse event profiles, and efficacy findings by PD-L1 expression.

Both CheckMate trials were open-label, and compared nivolumab to docetaxel in adult patients with either non-squamous (CheckMate 057)[45] or squamous (CheckMate 017)[44] NSCLC who had progressed during or after platinum-based doublet chemotherapy. Similar to KEYNOTE 010, both trials included patients with stage IIIB/IIV disease, an ECOG performance status of 0 or 1, required a tumour sample for biomarker analysis, and excluded patients with specific prior treatments (docetaxel, other checkpoint inhibitors), active brain metastases or suspected autoimmune diseases or syndromes requiring steroid medication. The percentage of patients in the KEYNOTE trial with non-squamous versus squamous tumour histology was 70% and 21%, respectively; the remaining 8% were other or unknown histology. Considering all patients in KEYNOTE 010 and Checkmate trials, the majority of patients had an ECOG performance status of 1, were current or former smokers, and were white. The CheckMate 017 trial limited eligibility to patients with only one line of previous treatment for advanced disease. In contrast, approximately one third of patients in the KEYNOTE trial had at least two lines of previous therapy. The distinguishing difference in patient eligibility between KEYNOTE 010 and the CheckMate trials, however, was the requirement that all patients in KEYNOTE had to be PD-L1 positive with a tumour expression score (TPS) of 1% or greater. Conversely, in the CheckMate trials, the TPS of included patients was determined retrospectively, and thus not available for all patients. This limitation should be considered when interpreting the efficacy results summarized below. Further, the retrospective nature of collecting PD-L1 status meant the trials also included PD-L1-negative patients.

In both CheckMate trials, nivolumab was administered intravenously at a dose of 3mg/kg every two weeks until unacceptable toxicity or disease progression; however, the protocol permitted continued treatment with nivolumab beyond initial disease progression at the discretion of the investigator (24% and 21% of patients in CheckMate 057 and 017, respectively) so long as the patient displayed clinical benefit without unacceptable side effects and met other protocol-specified criteria. The median duration of nivolumab treatment after initial progression was 1.2 months (range, 0 - 20.5) in CheckMate 057, and 1.3 months (range, 0-16.3) in CheckMate 017. Neither trial permitted dose modifications of nivolumab. In KEYNOTE 010, pembrolizumab was administered intravenously at a dose of 2mg/kg or 10mg/kg, over 30 minutes every three weeks until disease progression or unacceptable toxicity. Patients with investigator-assessed progression could continue pembrolizumab until the next scheduled CT scan, which occurred approximately 4-6 weeks later. The median duration of treatment was 3.5 months for both pembrolizumab doses, and dose modifications were allowed. Docetaxel, at a dose of 75mg/m^2, was the comparator regimen used in all three trials, administered intravenously over one hour every three weeks. Docetaxel was not given beyond disease progression in the CheckMate trials, and patients in this arm of both trials were permitted to crossover to receive nivolumab after study treatment. No crossover to pembrolizumab from the docetaxel arm was permitted in KEYNOTE 010.

The frequency of treatment-related grade 3-4 adverse events was significantly lower in patients treated with nivolumab compared to docetaxel in both CheckMate trials (CheckMate 057: 10% versus 54%; CheckMate 017: 7% versus 55%). Considering both trials, the most frequent treatment-related adverse events, of any grade, that occurred in patients treated with nivolumab included fatigue (16%), nausea (9-12%), decreased appetite (10-11%), and asthenia (10%). Adverse events leading to treatment discontinuation also occurred less frequently with nivolumab treatment compared to docetaxel (CheckMate 057: 5% versus 15%; CheckMate 017: 3% versus 10%). In the KEYNOTE trial, the percentage of patients experiencing grade 3-5 adverse events ranged from 13% to 16% for either dose of pembrolizumab, was and 35% in the docetaxel group. The most frequent type of events, of any grade, that occurred in patients treated with either dose of pembrolizumab included hypothyroidism (8%), pneumonitis (4-5%), and hyperthyroidism (4-6%). The percentage of patients discontinuing treatment due to treatment-related adverse events was lower among patients treated with pembrolizumab: 4-5% of patients in the pembrolizumab groups, versus 10% of patients in the docetaxel group.

In KEYNOTE 010, efficacy analyses were performed for patients with a TPS ≥1% and for the subgroup of patients with a TPS ≥50%. In the CheckMate trials, PD-L1 positivity was categorized according to the following pre-specified TPS patient subgroups[c]: 1%, 5%, and 10%. Efficacy outcomes by level of PD-L1 expression are summarized in (Table 14). In both trials the primary outcome was overall survival (OS).

In CheckMate 057, 78% (455 of 582) of patients had quantifiable TPS, and the rates of expression were balanced between treatment groups. At the time of interim analysis, a test for interaction was performed and suggested a strong predictive association between PD-L1 expression and clinical outcome at all TPS levels and for all efficacy endpoints. After a minimum follow-up of 13.2 months, nivolumab was associated with longer OS, PFS, as well as a higher objective response rate, compared to docetaxel, at all PD-L1 expression levels (≥1%, ≥5%, and ≥10%).

In CheckMate 017, 83% (225 of 272) of patients had quantifiable TPS, and the rates of expression were balanced between treatment groups. Unlike CheckMate 057, however, a test for interaction showed no predictive association between PD-L1 expression and clinical outcome for OS, PFS and objective response rate. OS and PFS favoured treatment with nivolumab, but the treatment effect estimates were similar to those observed in the total population of patients in the trial, suggestive that treatment benefit was independent of PD-L1 expression.

Of interest to note, among patients with a TPS <1%, the following objective response rates were observed in the nivolumab group: 9% (10 of 108 patients) in CheckMate 057, and 17% (9 of 54 patients) in Checkmate 017. In CheckMate 057, the median OS time for patients with a TPS<1% treated with nivolumab was 10.5 months compared to 10.1 months for patients receiving docetaxel (HR=0.87, 95% CI, 0.63-1.19).

[c] In Checkmate 057 the pre-specified PD-L1 expression levels were ≥1%, ≥5%, and ≥10%.

Table 13: Efficacy outcomes by level of PD-L1 expression in the KEYNOTE 001 Trial[43] evaluating pembrolizumab in adult patients with advanced/metastatic NSCLC (Validation Patient Group).

Efficacy Outcome	TPS <1	TPS 1-49%	TPS ≥50%
n[A]	28	103	73
ORR, n (%)	3 (11)	17 (17)	33 (45)
Previously treated patients, n	22	77	57
ORR, n (%)	2 (9)	12 (16)	25 (44)*
Treatment naïve, n	6	26	16
ORR, n (%)	1 (17)	5 (19)	8 (50)**
n	30	112	78
Median DOR, in months	Not reached	Not reached	Not reached
Median PFS[B], in months (95% CI)	4.0 (2.1-6.2)	4.1 (2.3-4.4)	6.4 (4.2-not reached)
Previously treated patients, n	68	127	99
Median PFS, in months (95% CI)	NR	NR	6.1 (2.1-12.5)
Treatment naïve, n	8	34	20
Median PFS, in months (95% CI)	NR	NR	12.5 (2.4-12.5)***
Median OS[B], in months (95% CI)	10.4 (5.8-not reached)	10.6 (7.3-not reached)	Not reached
Previously treated patients, n	68	127	99
Median OS, in months (95% CI)	NR	NR	Not reached
Treatment naïve, n	8	34	20
Median OS, in months (95% CI)	NR	NR	Not reached

Abbreviations: CI - confidence interval; DOR - duration of response; n - number of evaluable patients; NR - not reported; NSCLC - non-small cell lung cancer; ORR - objective response rate; OS - overall survival; PFS - progression-free survival; TPS - PD-L1 tumour proportion score.

Notes:
[A] Includes only patients with measurable disease per central review at baseline; median duration of follow-up was 9.2 months.
[B] Includes patients from the training patient group.
*Difference in ORR (TPS ≥50% versus TPS <1; and TPS ≥50% versus TPS 1-49%) is statistically significant (p<0.001).
** Difference in ORR (TPS ≥50% versus TPS <1; and TPS ≥50% versus TPS 1-49%) is statistically significant (p=0.01).
***Upper limit of confidence interval may be incorrect, but this is the value that appears in the trial publication.

Table 14. Efficacy outcomes by level of PD-L1 expression in CheckMate Trials 057[44] and 017[45] comparing nivolumab to docetaxel in previously treated patients with advanced NSCLC.

Efficacy Outcomes	Overall Results		TPS <1%		TPS ≥1%		TPS ≥5%		TPS ≥10%	
	Nivolumab	Docetaxel	Nivolumab	Docetaxel	Nivolumab	Docetaxel	Nivolumab	Docetaxel	Nivolumab	Docetaxel
CheckMate 057(non-squamous NSCLC)[44]										
n	292	290	108	101	123	123	95	86	86	79
Median OS, in months	12.0	9.4	10.5	10.1	17.7	9.0	19.4	8.1	19.9	8.0
HR (95% CI)*	0.73 (0.59-0.89) p-value=0.002		0.87 (0.63-1.19)		0.58 (0.43-0.79)		0.43 (0.30-0.62)		0.40 (0.27-0.58)	
Median PFS, in months	2.3	4.2	2.1	3.6	4.2	4.5	5	3.8	5	3.7
HR (95% CI)*	0.92 (0.77-1.11) p-value=0.39		1.19 (0.88-1.61)		0.70 (0.53-0.94)		0.54 (0.39-0.76)		0.52 (0.37-0.75)	
ORR, n (%)	56 (19)	36 (12)	10 (9)	15 (15)	38 (31)	15 (12)	34 (36)	11 (13)	32 (37)	10 (13)
CheckMate 017 (squamous NSCLC)[45]										
n	135	137	54	52	63	56	42	39	36	33
Median OS, in months	9.2	6.0	NR	NR	NR	NR	NR	NR	NR	NR
HR (95% CI)*	0.59 (0.44-0.79) p-value<0.001		0.58 (0.37-0.92)		0.69 (0.45-1.05)		0.53 (0.31-0.89)		0.50 (0.28-0.89)	
Median PFS, in months	3.5	2.8	NR	NR	NR	NR	NR	NR	NR	NR
HR (95% CI)*	0.62 (0.47-0.81) p<0.001		0.66 (0.43-1.00)		0.67 (0.44-1.01)		0.54 (0.32-0.90)		0.58 (0.33-1.02)	
ORR, n (%)	27 (20)	12 (9)	9 (17)	5 (10)	11 (17)	6 (11)	9 (21)	3 (8)	7 (19)	3 (9)

Abbreviations: CI - confidence interval; HR = hazard ratio; NR = not reported; NSCLC - non-small cell lung cancer; ORR - objective response rate; OS - overall survival; PFS - progression-free survival; TPS - PD-L1 tumour proportion score.

Notes:
*HR <1 favour nivolumab versus docetaxel. In CheckMate 057, HRs are not stratified.
**Confirmed complete and partial responses.

9 ABOUT THIS DOCUMENT

This Clinical Guidance Report was prepared by the pCODR Lung 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 NSCLC 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. Note that no revision was made in between posting of the Initial and Final Clinical Guidance Reports.

The Lung 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

See Appendix B for more details on literature search methods.

1. Literature search via OVID platform

Database(s): **EBM Reviews - Cochrane Central Register of Controlled Trials** March 2016, **Embase** 1974 to 2016 April 27, **Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)** 1946 to Present

Search Strategy:

line #	Searches	Results
1	(pembrolizumab* or lambrolizumab* or keytruda* or MK-3475 or MK3475 or Merck3475 or Merck-3475 or Sch-900475 or Sch900475 or 1374853-91-4 or DPT0O3T46P).ti,ab,ot,kf,hw,rn,nm.	1611
2	Carcinoma, Non-Small-Cell Lung/	41271
3	NSCLC.ti,ab,kf.	74344
4	exp Adenocarcinoma/	406081
5	Carcinoma, Large Cell/	5038
6	exp Carcinoma, Squamous Cell/	225296
7	Carcinoma, Adenosquamous/	5797
8	Carcinoma/	135270
9	or/4-8	711248
10	(lung* or pulmonary or bronchial).ti,ab,kf.	2082820
11	and/9-10	83050

12	((non-small cell or nonsmall cell or large cell or squamous or bronchoalveolar or bronchioloalveolar or bronchiolo-alveolar) and (neoplasm* or cancer* or carcinoma* or tumor* or tumour* or adenocarcinoma* or malignan*) and (lung* or pulmonary or bronchial)).ti,ab,kf.	150371
13	or/2-3,11-12	213454
14	and/1,13	295
15	14 use pmez,cctr	67
16	*pembrolizumab/	290
17	(pembrolizumab* or lambrolizumab* or keytruda* or MK-3475 or MK3475 or Merck3475 or Merck-3475 or Sch-900475 or Sch900475).ti,ab,kw.	821
18	or/16-17	852
19	exp Non small cell lung cancer/	74848
20	NSCLC.ti,ab,kw.	75135
21	exp Adenocarcinoma/	406081
22	Large cell carcinoma/	5828
23	exp Squamous cell carcinoma/	225296
24	Carcinoma/	135270
25	or/21-24	708746
26	(lung* or pulmonary or bronchial).ti,ab,kw.	2083052
27	and/25-26	82853
28	((non-small cell or nonsmall cell or large cell or squamous or bronchoalveolar or bronchioloalveolar or bronchiolo-alveolar) and (neoplasm* or cancer* or carcinoma* or tumor* or tumour* or adenocarcinoma* or malignan*) and (lung* or pulmonary or bronchial)).ti,ab,kw.	151497

29	or/19-20,27-28	228297
30	and/18,29	223
31	30 use oemezd	158
32	or/15,31	225
33	limit 32 to english language	222
34	remove duplicates from 33	181

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

Search	Query	Items found
#17	Search **#15 AND #16**	11
#16	Search **publisher[sb] OR 2016/04/26:2016/04/28[edat]**	496870
#15	Search **#2 AND #14**	67
#14	Search **#3 OR #5 OR #6 OR #13**	99451
#13	Search **(non-small cell[tiab] OR nonsmall cell[tiab] OR large cell[tiab] OR squamous[tiab] OR bronchoalveolar[tiab] OR bronchiolo-alveolar[tiab] OR bronchioloalveolar[tiab]) AND (neoplasm*[tiab] OR cancer*[tiab] OR carcinoma*[tiab] OR adenocarcinoma*[tiab] OR tumor*[tiab] OR tumour*[tiab] OR malignan*[tiab]) AND (lung*[tiab] OR pulmonary[tiab] OR bronchial[tiab])**	59049
#6	Search **(Adenocarcinoma[mh] OR Carcinoma, Large Cell[mh] OR Carcinoma, Squamous Cell[mh] OR Carcinoma, Adenosquamous[mh] OR Carcinoma[mh:noexp]) AND (lung*[tiab] OR pulmonary[tiab] OR bronchial[tiab])**	47734
#5	Search **NSCLC[tiab]**	25891
#3	Search **Carcinoma, Non-Small-Cell Lung[mh]**	36955
#2	Search **pembrolizumab [Supplementary Concept] OR 1374853-91-4[rn] OR DPT0O3T46P[rn] OR pembrolizumab*[tiab] OR lambrolizumab*[tiab] OR keytruda*[tiab] OR MK-3475[tiab] OR MK3475[tiab] OR Merck-3475[tiab] OR Merck3475[tiab] OR Sch-900475[tiab] OR Sch900475[tiab]**	324

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 terms: pembrolizumab*, lambrolizumab*, keytruda*, MK-3475, MK3475, Merck3475, Merck-3475, Sch-900475, Sch900475

Select international agencies including:

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

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

Search terms: pembrolizumab, lambrolizumab, keytruda, MK-3475, MK4575, Merck4575, Merck-4575

Conference abstracts:

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

European Society for Medical Oncology (ESMO)
http://www.esmo.org/

Search terms: pembrolizumab, lambrolizumab, keytruda, MK-3475, MK4575, Merck4575, Merck-4575 - last 5 years

APPENDIX B: DETAILED METHOLODGY OF LITERATURE REVIEW

Literature Search Methods

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

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-) with in-process records & daily updates via Ovid; Embase (1974-) via Ovid; The Cochrane Central Register of Controlled Trials (April 2016) via Ovid; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were pembrolizumab (Keytruda) and non-small cell lung cancer (NSCLC).

No filters were applied to limit retrieval by study type. The search was also limited to English-language documents, but not limited by publication year. The search is considered up to date as of August 4, 2016.

Grey literature (literature that is not commercially published) was identified by searching the websites of regulatory agencies (Food and Drug Administration and European Medicines Agency), clinical trial registries (U.S. National Institutes of Health – clinicaltrials.gov and Canadian Partnership Against Cancer Corporation - Canadian Cancer Trials), and relevant conference abstracts. Searches of conference abstracts of the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) were limited to the last five years. Searches were supplemented by reviewing the bibliographies of key papers and through contacts with the Clinical Guidance Panel. In addition, the manufacturer of the drug was contacted for additional information as required by the pCODR Review Team.

Study Selection

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

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

Quality Assessment

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

Data Analysis

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

Writing of the Review Report

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

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

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