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pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Pembrolizumab (Keytruda) for Non-Small Cell Lung Cancer

August 23, 2017

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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 non-small cell lung cancer (NSCLC). 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 NSCLC 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 for NSCLC, a summary of submitted Provincial Advisory Group Input on pembrolizumab for NSCLC, and a summary of submitted Registered Clinician Input on pembrolizumab for NSCLC, and are provided in Sections 2, 3, 4, and 5 respectively.

1.1 Introduction

The objective of the systematic review is to evaluate the efficacy and safety of pembrolizumab compared to standard therapy for previously untreated patients with metastatic NSCLC whose tumours express PD-L1 (Tumour Proportion Score (TPS) ≥50%) and who do not harbor a sensitizing epidermal growth factor receptor (EGFR) mutation or anaplastic lymphoma kinase (ALK) translocation.

The appropriate comparator for pembrolizumab in the first line setting is platinum-based doublet chemotherapy with or without maintenance therapy for patients with metastatic NSCLC. Health Canada issued a Notice of Compliance with conditions (NOC/c) for pembrolizumab (Keytruda) as indicated for the treatment of metastatic non-small cell lung carcinoma (NSCLC) in adults whose tumours have high PD-L1 expression [Tumour Proportion Score (TPS) ≥50%] as determined by a validated test, with no EGFR or ALK genomic tumour aberrations, and no prior systemic chemotherapy treatment for metastatic NSCLC on July 12 2017. The funding request is for the treatment of patients with previously untreated metastatic NSCLC whose tumours express PD-L1 (as determined by a validated test) and who do not harbor a sensitizing EGFR mutation or ALK translocation. Pembrolizumab is a potent and highly selective humanized monoclonal anti-PD-1 antibody of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands PD-L1 and PD-L2. This blockade enhances functional activity of the target lymphocytes to facilitate tumour regression and ultimately immune rejection. The recommended dose of pembrolizumab is 200 mg administered intravenously over 30 minutes every 3 weeks. Pembrolizumab is available as powder for solution for infusion 50 mg. It is unknown when the solution for infusion 100 mg/4 mL vial will be available.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

Trials

The pCODR systematic review identified one randomized controlled trial that met the selection criteria of this review.[1] KEYNOTE-024 was an open-label, randomized phase 3 trial comparing pembrolizumab 200 mg IV every 3 weeks to a maximum of 35 cycles to one of the following five platinum based chemotherapy regimens for 4 to 6 cycles based on the

investigator's choice: carboplatin plus pemetrexed, cisplatin plus pemetrexed, carboplatin plus gemcitabine, cisplatin plus gemcitabine, or carboplatin plus paclitaxel. For entry to the trial, patients had to have previously untreated stage IV NSCLC with evidence of strong expression of PD-L1 (TPS of ≥50%) and without an epidermal growth factor receptor (EGFR) sensitizing mutation or anaplastic lymphoma kinase (ALK) translocation. The primary endpoint of the trial was progression-free survival (PFS). The secondary endpoints of the trial included overall survival (OS), and objective response rate (complete and partial). The exploratory end points included duration of response, and patient reported outcomes. Patients were evaluated every 9 weeks with radiographic imaging to assess response to treatment. For efficacy analyses, the assessment of PFS and tumour response was carried out by an independent blinded central review panel of radiologists.

Of the 305 patients randomized in the trial, 154 patients were allocated to the pembrolizumab group, and 151 were allocated to the chemotherapy group. Overall, the treatment groups were balanced for baseline characteristics except for smoking status, where more patients in the chemotherapy group than in the pembrolizumab group had never smoked (12.6% vs. 3.2%), and brain metastases where more patients in the pembrolizumab group than in the chemotherapy group had brain metastases (11.7% vs. 6.6%). The median age of patients in the pembrolizumab group was 64.5 years and in the chemotherapy group was 66.0 years. Most patients were white (82%), former or current smokers (92%), had non-squamous histology (82%), and an ECOG performance status of 1 (65%).

At the data cut-off (second interim analysis) 52% and 70% of patients had discontinued treatment on the pembrolizumab and the chemotherapy arms, respectively. Only 10% of patients in the chemotherapy treatment group were still receiving the assigned treatment at the data cut-off date versus 48% in the pembrolizumab treatment group. Progressive disease was indicated as the primary reason for treatment discontinuation in both treatment groups.

Overall, the KEYNOTE-024 trial[1] was well conducted owing to the use of appropriate methods to randomize patients, clear explanation of the disposition of patients throughout the trial, the use of an independent central review for the assessment of key efficacy outcomes, and the conduct of all efficacy analyses by assigned treatment. However, the trial did have some limitations, which are summarized below:

1. The trial was open-label, and as such, patients, investigators and sponsor personnel involved in the trial were aware of treatment assignment. This open label design may introduce moderate-high risk of bias in the assessment of measures such as patient-reported outcomes, and reporting of adverse events. The potential for bias was minimized in KEYNOTE-024 through the use of an independent central review of key efficacy outcomes progression-free survival (PFS) and objective response rate (ORR). Overall survival is unlikely to be influenced by subjective bias.
2. Although patient subgroup efficacy analyses were pre-specified, none of the subgroups was adequately powered, and results from any of these analyses may be difficult to interpret. In addition, some groups (patients with brain metastases at baseline and patients who were never smokers) included a smaller number of patients, which can have an influence on the treatment effects observed. The results of these analyses require further validation.
3. After disease progression, 66 patients (43.7%) in the chemotherapy group crossed over to receive pembrolizumab. Despite the crossover of patients to receive pembrolizumab, which one would expect to confound the observed treatment effect towards no effect, the OS remained statistically significantly

improved on the pembrolizumab arm of the trial. An attempt to adjust for the crossover were made by the manufacturer, but found to be inappropriate.

4. QOL data were assessed in the KEYNOTE-024 trial but the open-label design of the trial increases the risk of bias which makes interpretation of the QOL data difficult, thus increasing the uncertainty in these results.

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 the assigned treatment. Patient-reported QOL 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). For the QLQ-C30, a mean change from baseline of 10 points or greater was considered the minimum clinically important difference (MCID), with lower scores indicative of improvement in symptoms and side effects.

[Table 1]: Highlights of Key Outcomes

KEYNOTE-024[1,2]	Pembrolizumab Group (N = 154)	Chemotherapy Group (N = 151)
Key Efficacy Outcomes[a]		
As of May 9, 2016 the median duration of follow-up in months (range)	11.2 (6.3-19.7)	
Primary Outcomes: PFS		
Number of PFS events (%)	73 (47.4)	116 (76.8)
Median, months (95% CI)	10.3 (6.7, not reached)	6.0 (4.2, 6.2)
HR[b] (95% CI)	0 .50 (0.37, 0.68)	
p-value	< 0.001	
Secondary Outcome: OS		
Number of deaths (%)	44 (28.6)	64 (42.4)
Median, months (95% CI)	Not reached	Not reached
HR[b] (95% CI)	0.60 (0.41, 0.89)	
p-value	0.005	
Secondary Outcome: ORR		
Number of objective responses	69	42
CR, n (%)	6 (3.9)	1 (0.7)
PR, n (%)	63 (40.9)	41 (27.2)
Objective Response Rate % (95% CI)	44.8 (36.8,53.0)	27.8 (20.8,35.7)
Estimated difference (95% CI)	16.6 (6.0, 27.0)	
HRQoL		
QLQ-C30 Functional Scale/Global Health Status/QoL	n=150	n=147
LS Mean Change from Baseline at Week 15 (95% CI)	6.94 (3.29, 10.58)	-0.88 (-4.78, 3.02)
LS Mean Difference[c] (95% CI); p-value	7.82 (2.85, 12.79); p=0.002	
EQ-5D utility score	n=150	n=147
LS Mean Change from Baseline at Week 15 (95% CI)	0.05 (0.01, 0.09)	-0.00 (-0.04, 0.04)
LS Mean Difference[c] (95% CI); p-value	0.06 (0.00, 0.11); p=0.036	
EQ-5D VAS	n=150	n=147
LS Mean Change from Baseline at Week 15 (95% CI)	4.25 (0.72, 7.77)	0.39 (-3.33, 4.11)
LS Mean Difference[c] (95% CI); p-value	3.85 (-0.72, 8.42); p=0.098	
Harms Outcome, n (%)	**Pembrolizumab Group (N = 154)**	**Chemotherapy Group (N = 150)**
Grade ≥3	41 (26.6)	80 (53.3)
TRAE (any grade)	113 (73.4)	135 (90.0)
WDAE (any grade)	11 (7.1)	16 (10.7)
Abbreviation: AE = adverse event, CI = confidence interval, CR = complete response, HR = hazard ratio, HRQoL = health-related quality of life, LS = Least squares; NR = not reported, ORR = objective		

response rate; OS = overall survival, PFS = progression-free survival, PR = partial response, SD = standard deviation, TRAE = treatment-related adverse event, WDAE = withdrawal due to adverse event

Notes:
[a] Median follow-up - Data cut-off date is May 9, 2016
[b] HR is for Pembrolizumab versus chemotherapy, where HR < 1 favours Pembrolizumab
[c] pembrolizumab treatment group versus chemotherapy

Efficacy

The second interim analysis was conducted after 189 events of PFS, and 108 deaths had occurred. After reviewing the results from the IA2, the external data and safety monitoring committee recommended that the trial be stopped early to give the patients who were receiving chemotherapy the opportunity to receive pembrolizumab. All data reported below are based on the second interim analysis.

At the second interim analysis on May 9, 2016, after a median follow-up time of 11.2 months (range, 6.3-19.7), a total of 108 patients had died: 44 (28.6%) in the pembrolizumab group, and 64 (42.4%) in the chemotherapy treatment group.

The median OS was not reached in either treatment group. The 6-month OS rates were 80.2% and 72.4% for the pembrolizumab and chemotherapy treatment groups, respectively. The 12-month OS rates were 69.9% and 54.2% for the pembrolizumab and chemotherapy treatment groups, respectively. Overall survival was statistically significantly longer in the pembrolizumab treatment group than in the chemotherapy treatment group (HR = 0.60; 95% CI, 0.41 to 0.89; P = 0.005).

At the second interim analysis on May 9, 2016, a total of 189 PFS events were observed: 73 (47.4%) in the pembrolizumab treatment group and 116 (76.8%) in the chemotherapy treatment group.

The median PFS was 10.3 months for those treated with pembrolizumab and 6.0 months for those on the chemotherapy arm of the trial. The estimated percentage of patients who were alive and had no disease progression at 6 months was 62.1% and 50.3% for pembrolizumab and chemotherapy treatment groups, respectively, while the PFS rates at 12 months were 47.7% and 15.0% for pembrolizumab and chemotherapy treatment groups, respectively. Progression- free survival was statistically significantly longer in the pembrolizumab treatment group than in the chemotherapy treatment group (HR = 0.50; 95% CI, 0.37 to 0.68; P < 0.001).

The response rate, which was defined as the percentage of patients with a complete or partial response was significantly higher in the pembrolizumab treatment group compared to the chemotherapy treatment group (44.8% versus 27.8%, respectively).

Health-related Quality of Life (EORTC-QLQ,-C30, E0RTC-QLQ,-LC13 and EQ,-5D)

Differences in the mean change from baseline on the QLQ-C30 at week 15 showed numerical improvement (i.e., less deterioration) of the Global Health Status Score in patients treated with pembrolizumab but not in the chemotherapy group. The difference in mean change from baseline to week 15 reached statistical significance in the pembrolizumab treatment group compared to the chemotherapy group (difference in Least squares [LS] means = 7.82; 95% CI: 2.85, 12.79; p=0.002). This difference, however, did not reach the MCID of 10 points which is perceived as clinically meaningful for patients in NSCLC trials.

Compared to chemotherapy, pembrolizumab increased the time-to-true deterioration (defined as the time to the first onset of a 10-point or greater score decrease from baseline) in the QLQ-LC13 composite endpoint of cough (QLQ-LC13 question 1), chest pain

(QLQ-LC13 question 10), and dyspnea (QLQ-LC13 Q3 to question 5). Statistical significance was achieved in favor of pembrolizumab when compared to the chemotherapy group (HR=0.66; 95% CI: 0.44, 0.97; p=0.029).

Differences in the mean change from baseline on the EQ-5D utility scores at week 15 showed numerical improvements in patients treated with pembrolizumab but not in the chemotherapy group. The difference in mean change from baseline to week 15 reached statistical significance in the pembrolizumab treatment group compared to the chemotherapy group (difference in LS means = 0.06; 95% CI: 0.00-0.11; p=0.036).

EQ-5D VAS scores increased from baseline at week 15 in both treatment groups. The increase in scores in the pembrolizumab treatment group was higher than that in the chemotherapy group; however, the difference in mean change from baseline to week 15 was not statistically significant.

Harms

Compared to chemotherapy, 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 26.6%, and 53.3% in the pembrolizumab and chemotherapy treatment groups, respectively. The percentage of patients discontinuing treatment due to treatment-related adverse events was also higher among patients treated with chemotherapy compared with those on pembrolizumab (10.7% versus 7.1%).

Immune-related events of special interest occurred in 29.2% (45 of 154 patients) of patients receiving pembrolizumab versus 4.7% (7 of 150 patients) of patients in the chemotherapy group. The most frequent type of events of any grade (pembrolizumab versus chemotherapy), were hypothyroidism (9.1% versus 1.3%), hyperthyroidism (7.8% versus 1.3%), pneumonitis (5.8% versus 0.7%), infusion reaction (4.5% versus 1.3%), severe skin reaction (3.9% versus 0%), thyroiditis (2.6% versus 0%), colitis (1.9% versus 0%), and myositis (1.9% versus 0%). Of these events, only pneumonitis, severe skin reactions, and colitis occurred at a severity of grade 3 or higher in more than 1% of patients in the pembrolizumab treatment group. All infusion reactions were graded as 1 or 2.

The trial reported 4 deaths attributable to study treatment. There was one death (<1%) in the pembrolizumab group (sudden death of unknown cause on day 2), and 3 deaths (2%) in the chemotherapy group (one case each of pulmonary sepsis, pulmonary alveolar hemorrhage and unknown cause).

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 (Keytruda) for the treatment of patients with previously untreated metastatic NSCLC whose tumors express PD-L1 (TPS of ≥50%) and who do not harbor a sensitizing EGFR mutation or ALK translocation was provided by three patient advocacy groups: Lung Cancer Canada (LCC), British Columbia Lung Association (BCLA) and Ontario Lung Association (OLA).

From a patient perspective, lung cancer impacts many aspects of day-to-day life. It was reported by both patient and caregiver respondents that high symptom burden of lung cancer is difficult to

manage. LCC indicated that symptoms may include: loss of appetite, cough, pain, and shortness of breath. Moreover, one of the most common symptom burdens for lung cancer patients is fatigue or lack of energy. For the vast majority of this patient population, the current standard of care is 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.

Provincial Advisory Group (PAG) Input

Input was obtained from eight of nine provinces (ministries 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
- Sequencing of treatments after pembrolizumab
- The need for PD-L1 testing, timing of the testing and the accuracy of the test results

Economic factors:

- Implementation of PD-L1 testing in first-line setting
- Long duration of treatment of 35 cycles or until disease progression, whichever occurs first

Registered Clinician Input

The oncologists providing input identified that the key benefits of treatment with pembrolizumab in the first-line setting are the improved response rate, progression free survival, overall survival and durability of response. They identified that patients with PD-L1 expression less than 50% or patients with EGFR or ALK mutations or ECOG > 2 should not be recommended for first-line treatment with pembrolizumab at this time. They indicated that the availability of pembrolizumab for first-line treatment would shift the order of current treatments and recommend reflex testing of PD-L1 for all locally advanced and metastatic non-small cell lung cancer patients.

Summary of Supplemental Questions

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

1. What is the accuracy of 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?

The limited literature search did not identify any evidence to inform the question of 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 to be 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, 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. Two reports were identified that addressed the accuracy of available diagnostic antibody assays. One of the reports demonstrated that the Dako PD-L1 IHC 22C3 assay is a sensitive, specific, precise, and robust assay, which provides high value clinical utility to identify patients who will benefit from treatment with pembrolizumab. While the report on the Blueprint PD-L1 IHC Assay Comparison Project indicated that three other PD-L1 IHC assays (22C3, 28-8, and SP263) were aligned with regard to PD-L1 expression on tumour cells, one assay (SP142) consistently had fewer tumour cells expressing PD-L1. All the assays demonstrated IC staining but with greater variance than expression on tumour cells. By comparing assays and cutoffs, the study indicated that interchanging assays and cutoffs could lead to "misclassification" of PD-L1 status for some patients. The main limitation for this study was that it was based on small number of cases that used expert observers on single assays (n=39) using expert observers on single assays. A second limitation was that the sample was chosen to represent the range of levels of PD-L1 expression, rather than a representative cohort.

See section 7.1 for more information.

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 6.3.2.1a and 6.3.2.1b (regarding internal validity).

Table 2: Assessment of generalizability of evidence for pembrolizumab in patients with untreated metastatic NSCLC (First Line) [1]

Domain	Factor	Evidence (KEYNOTE-024trial)	Generalizability Question	CGP Assessment of Generalizability
Population	Performance Status	The trial limited eligibility to patients with an ECOG performance status of 0 or 1. ECOG 0: n=107 (35.1%) ECOG 1: n=197 (64.6%) Subgroup analyses were conducted (a priori) by performance status for 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 with an ECOG performance status of 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. The CGP agreed that they would be comfortable generalizing the evidence to patients with ECOG PS 2 if they are able to tolerate the treatment based on clinical judgement.
	Sex	The trial eligibility criteria included male and female patients. Pembrolizumab group female: n =62 (40.3%) Chemotherapy group female: n = 65 (37.1%) Subgroup analyses were conducted (a priori) by sex for PFS.	Do the results of the trial support the treatment of both genders?	The CGP noted that the HR for PFS in female patients was 0.75 compared to 0.39 for males suggesting there may be a less beneficial effect in females. The HR for OS in females was 0.95 and there was no difference in ORR in females between Pembrolizumab and SOC. This may relate to the short follow-up at the time of reporting and the better performance of the SOC arm for female patients. As the OS was significantly better in the ITT population and that PFS was better for females, the CGP concluded that female patients will likely benefit from treatment with pembrolizumab.

Domain	Factor	Evidence (KEYNOTE-024trial)	Generalizability Question	CGP Assessment of Generalizability
	Smoking status	The trial included patients who were current smokers, recent smokers and never smokers. <u>Smoking status in the Pembrolizumab group</u> Current: n=34 (22.1%) Former: n=115 (74.7%) Never: n=5 (3.2%) <u>Smoking status in the Chemotherapy group</u> Current: n=31 (20.5%) Former: n=101 (66.9%) Never: n=19 (12.6%) Subgroup analyses were conducted (a priori) by smoking status for PFS.	Do the results of the trial influence the decision about who should receive pembrolizumab based on smoking status?	The CGP noted that the 95% CI for the HR for OS crossed 1 (HR 1.69, 95% CI: 0.19-15.25) which could indicate that pembrolizumab is ineffective or even harmful to patients who are never smokers. However, the very small numbers of patients in the never smoker category who received pembrolizumab in the ITT population was only 5 which limits the CGP's ability to draw a definitive conclusion. Until further information becomes available, pembrolizumab should not be withheld from never smokers.
	Stage of disease	The trial limited eligibility to patients with histologically or cytologically confirmed diagnosis of stage IV NSCLC. 153 (99.4%) of patients in the pembrolizumab group were stage IV at screening and 1 (0.6%) patient was stage IIIB at screening. 150 (99.3%) of patients in the chemotherapy group were stage IV and 1(0.7%) patient was Stage IIIB at screening.	Does stage limit the interpretation of the trial results with respect to the target population (e.g., Canadian clinical practice, patients without the factor, etc.)?	Although virtually all of the patients in the KEYNOTE-024 trial had Stage IV disease, the CGP agreed that it is reasonable to generalize the evidence to patients with stage IIIB disease (locally advanced disease) who are not eligible for potentially curative concurrent chemoradiotherapy.
	Age	The trial eligibility criteria were	Does the age	There was no age restriction in the

Domain	Factor	Evidence (KEYNOTE-024trial)	Generalizability Question	CGP Assessment of Generalizability
		not limited by patient age. Median age of patients was 64.5 in the pembrolizumab treatment group and 66.0 in the Chemotherapy Group. 164/305 (53.8%) patients were ≥ 65 years. Subgroup analyses (< 65 and ≥ 65 years) were conducted a priori by age group for PFS.	restriction in the trial limit the interpretation of the trial results with respect to the target population?	trial. The CGP noted that the median age in the trial is somewhat higher than typically seen in clinical trials of NSCLC. From this, it can be inferred that pembrolizumab is tolerable in older patients.
	Organ dysfunction	The trial limited eligibility to patients with adequate organ function, including hematological, renal, hepatic, endocrine, and coagulation.	Does 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. Renal, hepatic and hematological dysfunction are not critical to the administration of pembrolizumab. Hepatic or renal impairment does not appear to increase toxicity of pembrolizumab. Pembrolizumab can be used with adequate monitoring in most settings of stable organ dysfunction. However, existing endocrine dysfunction may be aggravated by pembrolizumab (e.g. hypothyroidism, hypopituitarism, etc.) and caution must be exercised if the patient has an underlying immune-related disease.
	Metastatic Sites	The trial excluded patients with untreated central nervous system (CNS) metastases and/or carcinomatous meningitis, and included patients whose brain metastases have been treated	Did the exclusion of patients with certain sites of metastatic disease limit the interpretation of the trial results with	Patients with uncontrolled CNS metastases were excluded from the trial. Patients with stable CNS metastases were allowed in the trial. The CGP agree that patients with CNS metastases could be treated

Domain	Factor	Evidence (KEYNOTE-024trial)	Generalizability Question	CGP Assessment of Generalizability
		provided they show radiographic stability	respect to the target population (e.g., Canadian clinical practice, patients without the factor, etc.)?	with pembrolizumab if their brain or other CNS metastases have been managed according to usual standard of care.
	Ethnicity or Demographics	The trial was conducted in Canada and 15 other countries: Australia, Austria, Belgium, France, Germany, Hungary, Ireland, Israel, Italy, Japan, Netherlands, New Zealand, Spain, United Kingdom, and United States. East Asia: n=40 (13%) Not East Asia: n=265 (87%) White: n=251 (82%) Asian: n=46 (15%) Black: n=4 (1%) Other: n=2 (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 CGP is comfortable generalizing to other locations including developed countries with sophisticated health care systems. As such, the results of the trial are generalizable to the Canadian population. The CGP recognize that the number of Asians enrolled in the trial is low, and not reflective of the North American population; however, the CGP feels that the results of the trial are still generalizable to that population as well.
	Biomarkers	The trial enrolled patients who had a PD-L1 strong tumor as determined by IHC at a central laboratory. No specification on tumor proportion score (TPS) was provided in the study protocol, however in the published article on the study it indicated that TPS ≥ 50% was required for inclusion in the study.	Is the biomarker an effect modifier (i.e., differences in effect based on biomarker status)? Are the results of the trial applicable to all subgroups equally? Is there a substantial group of patients excluded from the trial to whom the results could be generalized?	The trial enrolled patients with tumour staining for PD-L1 protein. Patients in KEYNOTE-024 were required to have a tumor proportion score (TPS) of PD-L1 ≥50%. Patient tumours were screened for PD-L1 expression using the Dako immunochemistry assay with murine 22C3 anti-human PD-L1 antibody. Other antibodies - 28-8, SP263 and SP142 are also capable of detecting PD-L1 on tumour and immune cells. Preliminary studies suggest that the results of these various assays are closely aligned although SP142 may

Domain	Factor	Evidence (KEYNOTE-024trial)	Generalizability Question	CGP Assessment of Generalizability
				stain fewer tumour cells and may underestimate the percent positive cells.
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-024 study alone, the efficacy of pembrolizumab cannot be generalized beyond palliative intent therapy in previously untreated patients.
	Line of therapy	The trial was conducted in patients who have not received prior systemic chemotherapy treatment for their metastatic NSCLC.	Are the results of the trial generalizable to other lines of therapy	Pembrolizumab use should be confined to the first-line treatment of NSCLC (all histologic types) without a sensitizing mutation in EGFR or an ALK translocation.
	Administration of intervention	Pembrolizumab dose was 200 mg IV every 3 weeks	Are the results of the trial generalizable to a different dose or administration schedule?	PAG is seeking guidance on the use of 2mg/kg dose for first-line treatment, which is the dose for second-line treatment. Based on the opinion of the CGP, although the initial clinical trials of pembrolizumab in lung cancer used a dose of 2 mg/kg, the manufacturer is now promoting the use of a flat dose of 200 mg. There is no evidence to suggest that one dosing amount is superior to another but there is some evidence to suggest that the flat dose will result in a larger dose and cost for some patients. Therefore, the CGP suggests that it would be reasonable to employ the flat dose in situations where the total dose exceeds 2 mg/kg and otherwise to

Domain	Factor	Evidence (KEYNOTE-024trial)	Generalizability Question	CGP Assessment of Generalizability
				consider using a dose based on body weight.
	Appropriate treatments after progression on pembrolizumab	PAG is seeking guidance on the appropriate treatments after progression on pembrolizumab In the trial, there was no preplanned crossover from the pembrolizumab group to the chemotherapy group, and there were no guidelines regarding therapy after disease progression for patients in the pembrolizumab group.	What are the appropriate treatments after progression on pembrolizumab?	Treatment for NSCLC following progression on pembrolizumab should be with platinum-based chemotherapy for patients without a sensitizing mutation in EGFR or an ALK translocation. Following disease progression on pembrolizumab, there is no evidence to support the use of other PD-1/PD-L1 agents or combinations of PD-1/PD-L1 + anti- CTLA4 therapy at this time. Any use of a second line immunotherapy should only be used in the context of a clinical trial.
	Optimal Duration of Treatment and treatment discontinuation	PAG is seeking clarity on the duration of treatment and discontinuation. The trial was designed so that patient in the pembrolizumab treatment group would receive pembrolizumab 200 mg IV every 3 weeks for 35 cycles. It is not clear from the study design what patients would do after receiving 35 cycles. The median number of treatment cycles in the pembrolizumab group was 10.5 (range, 1 to 26); the median number in the chemotherapy group was 4 (range, 1 to 6). The median duration of treatment was 7.0 months (range, 1 day to	What is the optimal duration of treatment and treatment discontinuation	The CGP recommends pembrolizumab in the dose and schedule used in the trial and for the duration of treatment that was used in the trial, as this is the only currently available evidence.

Domain	Factor	Evidence (KEYNOTE-024trial)	Generalizability Question	CGP Assessment of Generalizability
		18.7 months) in the pembrolizumab group and 3.5 months (range, 1 day to 16.8 months) in the chemotherapy group.		
Comparator	Standard of Care	The comparators in the trial were platinum-based chemotherapy regimens which have been the standard of care for the first-line treatment of advanced NSCLC in Canada.	If the comparator is non-standard, are the results of the trial applicable in the Canadian setting?	Platinum-based chemotherapy is the standard of care for patients without EGFR mutations or an ALK-translocation and therefore is the appropriate comparator for pembrolizumab in the trial.
	Dose and Schedule	Doses used for the platinum-based chemotherapy are summarized in Table 4	If the dose and/or schedule is not standard, are the results of the trial relevant in the Canadian setting?	The doses and schedules used for the comparator chemotherapy regimens are relevant in the Canadian context.
Outcomes	Appropriateness of Primary and Secondary Outcomes	The primary outcome was PFS, and the secondary outcomes were OS and ORR of the trial are appropriate.		OS is the preferred clinical trial outcome; however, the CGP recognized that crossover contaminates the results of OS. PFS is also a reasonable primary outcome, supported by patient reported quality of life outcomes. Although ORR is an easy outcome to measure, it is not a reliable indicator of overall survival benefit in NSCLC. The CGP also noted there was only one planned analysis of ORR, which occurred at interim analysis 1. However, the results for the ORR at this analysis are not available, and results for the ORR that are available were from the second interim analysis which was not pre-specified and considered an exploratory analysis. Thus, the results of the ORR should be interpreted with caution.

Domain	Factor	Evidence (KEYNOTE-024trial)	Generalizability Question	CGP Assessment of Generalizability
	Assessment of Key Outcomes	Are the key outcomes assessed differently in the trial compared with clinical practice in Canada?	If the trial used a different method of assessment than that used in Canadian clinical practice, are the results of the trial applicable to the Canadian setting?	The outcomes in the trial outcomes were assessed in a fashion similar to usual Canadian practice.
Setting	Countries participating in the Trial	The trial was conducted in 15 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 countries and Canada? Differences in the patterns of care might impact the clinical outcomes or the resources used to achieve the outcomes.	The trial was conducted predominantly in developed countries with comparable health care systems to that of Canada.
	Location of the participating centres	Was the trial conducted in academic centres only or were community treatment facilities also involved?	If the trial was conducted only in academic centres are the results applicable in the community setting?	Most centres participating in the trial were academic institutions. Pembrolizumab could be administered in non-academic centres if the treating oncologist is familiar with the side effects of immune oncology agents and has access to specialists who can manage the toxicities that can occur with these agents
	Supportive medications, procedures, or care	All treatments that the investigator considers necessary for a patient's welfare were allowed to be administered at the discretion of the investigator in keeping with the community standards of medical care.	Are the results of the trial generalizable to a setting where different supportive medications, procedures, or care are used?	The supportive care agents used in the trial are similar to what would be used in Canada and would be considered standard of care.

Domain	Factor	Evidence (KEYNOTE-024trial)	Generalizability Question	CGP Assessment of Generalizability
		Palliative and supportive care was permitted during the course of the trial for underlying medical conditions and management of symptoms. Surgery for tumor control or symptom management was not permitted during the study. Patients were prohibited from receiving the following therapies: Immunotherapy not specified in the protocol, Chemotherapy not specified in the protocol, investigational agents other than pembrolizumab, Surgery for symptom management or tumor control, and Radiation therapy for tumor control. Glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest.		

1.2.4 Interpretation

Locally advanced and metastatic non-small cell lung cancer (NSCLC) continues to be a uniformly fatal disease despite some modest improvements in treatment over the past several decades. The standard of care for those without a sensitizing mutation for whom a targeted therapy exists, good performance status and willingness to receive treatment has been a cisplatin- based chemotherapy regimen. However, a substantial number of individuals are not candidates for treatment with the current best chemotherapy regimens because of poor performance status, comorbidities and advanced age. Despite advances in supportive care, most NSCLC patients find the toxicities of platinum-based chemotherapy difficult to endure. For those patients with a sensitizing mutation such as a mutation in the EGFR gene or a translocation of the ALK gene, molecular targeted therapies have become the first line standard of care. These agents are better tolerated than chemotherapy and increase survival. Nonetheless, resistance to these targeted therapies ultimately limits their effectiveness. As a result, there remains a large unmet need for more effective treatments for this very common cancer.

Pembrolizumab is a monoclonal antibody that binds to and blocks the programmed cell death 1 receptor (PD-1) located on lymphocytes. It has been evaluated in a randomized open label phase 3 trial, KEYNOTE-024, as a first-line therapy in 305 patients with advanced NSCLC compared to standard cisplatin- based chemotherapy regimens. Eligible patients had previously untreated stage IV NSCLC with an ECOG score of 0 or 1 and a PD-L1 tumour proportion score of 50% or greater. Patients received either pembrolizumab in a fixed dose of 200 mg every 3 weeks or standard chemotherapy consisting of one of five widely accepted platinum-based chemotherapy regimens. The baseline characteristics of the patients were balanced although more patients in the chemotherapy group had never smoked (12.6% vs 3.2%) and more patients in the pembrolizumab had brain metastases (11.7% vs 6.6%).

The primary endpoint of the trial was progression-free survival (PFS) and in the analysis of the intention-to-treat population, the median PFS was substantially longer for pembrolizumab (10.3 months) compared to 6.0 months for chemotherapy (hazard ratio [HR] for progression or death, 0.50; 95% CI, 0.37 to 0.68, p< 0.001). All patient subgroups appeared to benefit with pembrolizumab; however, the difference between treatment groups did not reach statistical significance in the following patient subgroups: female patients, patients who were current smokers, patients who had never been a smoker and patients with brain metastases at baseline. However, the study was not powered to detect a difference in these subgroups of patients.

For female patients, the HR for PFS was 0.75 compared to 0.39 for males suggesting that there may be a greater beneficial effect in males. The HR for OS in females was 0.95 and there was no difference in ORR in females between pembrolizumab and chemotherapy. This may relate to the short follow-up at the time of reporting and the better performance of the chemotherapy arm for female patients.

The HR ratio for individuals who were never smokers crossed 1, which could indicate that pembrolizumab is ineffective or even harmful to these patients. However, the number of

patients in the never smoker category who received pembrolizumab in the intention-to-treat population was only 5, which limits drawing a definitive conclusion.

At the planned second interim analysis, the median overall survival had not yet been reached in either arm but in multivariable modelling, overall survival was significantly longer in the pembrolizumab group than in the chemotherapy group (HR for death, 0.60; 95% CI, 0.41 to 0.89; p= 0.005). The objective response rate was also higher in patients on pembrolizumab compared to chemotherapy (44.8% vs 27.8%), as was the mean duration of response.

These positive findings have to be interpreted in the context of the impact of treatment on safety and quality of life. In this regard, treatment-related adverse events actually occur less commonly on pembrolizumab than on chemotherapy (73.4% versus 90.0%), and grade 3 to 5 treatment -related adverse events occurred in twice as many patients on chemotherapy as occurred on pembrolizumab (53.3% vs 26.6%). Although immune-mediated adverse events occurred in 29.2% of patients on pembrolizumab, grade 3 or 4 immune-mediated events occurred infrequently: severe skin reactions (3.9%), pneumonitis (2.6%) and colitis (1.3%).

Evidence of clinical efficacy on pembrolizumab against NSCLC was also observed in an earlier Phase 2/3 trial (KEYNOTE-010) in previously treated patients with PD-L1 expression on at least 1% of the tumour cells. Patients in this trial were randomly assigned to one of two doses of pembrolizumab based on body weight or to docetaxel 75 mg/m^2 every 3 weeks. Overall survival was significantly longer on pembrolizumab at 2 mg/kg versus docetaxel (HR 0.71, 95% CI 0.58-0.88; p= 0.0008) and at the 10 mg/kg dose (HR 0.61, CI 0.49-0.75; p<0.0001). Survival gains were greater among patients with at least 50% of tumour cells expressing PD-L1. Progression-free survival was also longer with both doses of pembrolizumab compared to docetaxel; response rates were higher and response durations were also longer on pembrolizumab compared with docetaxel.

Despite the compelling evidence of a clinically important improvement in progression-free survival when pembrolizumab is used as first-line therapy in NSCLC, the precise place of pembrolizumab in the treatment of stage IV NSCLC is not entirely clear. For those patients who do not have sensitizing mutations, the evidence strongly suggests that pembrolizumab should replace cisplatin-based chemotherapy as the first-line treatment in those patients who want treatment and who, in the opinion of their physicians, have a suitable performance status and no medical conditions that would preclude treatment. For patients with sensitizing mutations, it is unclear whether pembrolizumab should precede or follow molecular targeted therapies.

There is also uncertainty with regard to the amount of PD-L1 tumour staining necessary to identify patients for treatment with pembrolizumab and which specific platform and assay should be used. In the KEYNOTE- 024 trial, the assay used was the Dako 22C3 pharmDx assay. Other PD- L1 assays are available and it has been reported in a comparison study accepted for publication that the 28-8 and SP263 assays exhibit similar levels of tumour cell staining but that the SP 142 assay may stain fewer cells. A French study has also

demonstrated that 28-8, 22C3 and SP263 assays produce comparable results across the Dako and Ventana platforms. Currently, there is a Canadian validation study underway.

1.3 Conclusions

The Clinical Guidance Panel (CGP) concluded there is a net clinical benefit for patients with stage IV non-small cell lung cancer whose tumours display staining for PD-L1 in 50% of tumour cells and who do not harbor a sensitizing EGFR mutation or ALK translocation when treated with pembrolizumab. The CGP made this conclusion based on the results of the KEYNOTE- 024 randomized phase 3 trial which demonstrated a clinically meaningful and statistically significant improvement in progression free survival, a greater proportion of patients alive at 6 and 12 months and a higher objective response rate for pembrolizumab over conventional first-line platinum-based chemotherapy in the intention-to-treat analyses.

This recommendation takes into account:

- Overall survival data are relatively immature. At the time of the second interim analysis with a median duration of 11.2 months, the median OS was not reached in either treatment group; however, the 12 month OS rates were 69.9% and 54.2% for the pembrolizumab and chemotherapy treatment groups respectively. At the time of a later data cutoff, after a median follow-up time of 19.1 months, the median OS was not reached in the pembrolizumab group and it was 14.5 months in the chemotherapy arm. The 18-month OS rates were 61.2% and 43.0% for the pembrolizumab and chemotherapy treatment groups, respectively. Overall survival was statistically significantly longer in the pembrolizumab treatment group than in the chemotherapy treatment group (HR = 0.54; 95% CI, 0.40 to 0.72; P < 0.001). Whether there will be a long term survival benefit for lung cancer patients as seen in other tumour types treated with immune oncology drugs is uncertain.

- Cross-over was allowed in the KEYNOTE-024. 43.7% of patients in the chemotherapy treatment group crossed over to receive pembrolizumab, which confounds the interpretation of the survival data. The survival benefit may, in fact, be greater than reported.

- Female patients in the KEYNOTE-024 trial had a smaller treatment effect (PFS, OS, ORR) than the full trial population. However, as the sample sizes were small, the effect estimates would be sensitive to outliers. Therefore, more research is needed to better define the treatment effect size in females and males and to determine if sex is a treatment effect modifier. As the OS was significantly better in the ITT population and the PFS was better for females, the CGP concluded that female patients likely benefit from treatment with pembrolizumab.

- The number of never smokers in KEYNOTE- 024 was extremely small and although the HR for disease progression or death crossed 1 for this group of patients, the CGP felt that a definitive conclusion could not be reached. Future studies should be careful to assess the effects of immune oncology drugs in never smokers with lung cancer. Until further information becomes available, pembrolizumab should not be withheld from never smokers.

- 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 actual clinical

practice, patients with ECOG 2 performance status could be considered candidates for treatment as the assessment of performance status is subjective. The decision as to whether a patient is clinically fit to be treated with pembrolizumab should be left to the responsible treating physician.

- In addition to the improvements in survival, adverse events (grades 3-5) were less frequent with pembrolizumab compared with chemotherapy. As well, pembrolizumab delayed the time to deterioration in quality of life as measured by the Global Health Status Score and the QLQ-LC 13 composite endpoint of cough, chest pain and dyspnea.

- There is no evidence on the appropriate sequencing of therapy for those patients who are currently treated with first-line molecular targeted agents.

- There is also uncertainty as to the extent of tumour cell staining with PD-L1 required to select patients for treatment and whether assays other than the Dako 22C3 PharmaDx assay can be used to identify patients for pembrolizumab therapy. Until further evidence is available, the CGP recommends that pembrolizumab be used for the treatment of those NSCLC patients whose tumours have a tumour proportion score of 50% or greater with the Dako 22C3 pharmDx assay or an assay validated to have similar performance characteristics. Easy access to testing in clinical diagnostic laboratories will be essential to access pembrolizumab.

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 2015, it was estimated that 26,600 new cases of lung cancer would be diagnosed in Canada and 20,900 deaths from lung cancer would occur. In that year, the incidence and mortality rates for lung cancer were 51.9/100,000 and 40.2/100,000 respectively, underscoring the overall poor prognosis of lung cancer.[3] Non-small Cell Lung Cancer (NSCLC) is the most common type of lung cancer, comprising 85% of all lung cancers. During the past 25 years, the distribution of histologic types of NSCLC has changed. In North America, there has been a decline in the incidence of squamous cell carcinoma, which was formerly the predominant histological type, and an increase in adenocarcinomas in both genders. [4] Small cell lung cancer, the other major histological type of lung cancer has also been decreasing in incidence in many countries over the past several decades.

The median age of diagnosis of lung cancer is about 70 years and there are anticipated to be 16,300 new cases in the age group between 60 years and 79 years and 12,300 deaths.[3,5] A subset of patients with NSCLC presents a younger age (<40 years) but the incidence of this population has decreased in North America from the late 1970s to the present. [6]
The advanced age of the majority of patients, poor performance status and associated co-morbidities often associated with years of cigarette smoking, as well as an advanced stage of disease at presentation for the majority of patients means that many patients are not considered appropriate for any form of treatment. In Ontario, fully 29% of all newly diagnosed lung cancer patients receive no treatment. [7]

Tobacco smoking remains the main cause of lung cancer and the geographic and temporal patterns of the disease largely reflect tobacco consumption during prior decades. In countries with effective tobacco control measures, the incidence of lung cancer has begun to decline in men and is plateauing in women. [8-10] Besides tobacco, several other causes of lung cancer have been described including exposure to asbestos, arsenic, radon and non-tobacco-related polycyclic aromatic hydrocarbons. The incidence of lung cancer is higher in cities than in rural settings which may be due to outdoor air pollution. Indoor air pollution may also play a role in some countries where cooking fumes and fumes from coal-fuelled stoves may be responsible for the relatively high incidence of non-smoking related lung cancer in women in some countries.[11]There is also some evidence of a genetic predisposition to lung cancer with single nucleotide polymorphisms in genes in certain loci – 15q24-25, (CHRNA3, CHRNA5,CHRNAB4), 6p21.33, 5p15.23 – have an association with increased lung cancer risk. [12,13]

2.2 Accepted Clinical Practice

Introduction: The two main histological subtypes of NSCLC are squamous cell carcinoma and adenocarcinoma. Squamous cell carcinoma accounts for 30-40% of all NSCLC, and these tumors are more common in men than women.[14] Adenocarcinomas are the most common non-squamous cell carcinoma, and occur more frequently in women than men. Adenocarcinomas may be diagnosed in non-smokers with lung cancer. The principal goal of the treatment for patients with advanced stage NSCLC is palliative; namely, to prolong life while maintaining or improving quality of life. Factors that influence the choice of initial therapy include clinical condition (performance status, co-morbidities, etc.), 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 an actionable driver mutation: NSCLC tumours which do not have a targetable driver mutation are typically treated with platinum based doublet chemotherapy combinations. Platinum combinations can provide palliative benefit with a modest increase in median survival generally measured in months over the course of the last few decades.[15-18] 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 taxotere, have shown modest incremental gains over older regimens when paired with platinum agents.[18-20] Tumour histology has become important in the selection of treatment for NSCLC as pemetrexed combinations appears to preferentially benefit patients with non-squamous histologies. Alternatively, gemcitabine in combination with a platinum agent appears to be better in the first line treatment of squamous NSCLC.[21] This difference has been attributed to the lower levels of thymidylate synthase expression in adenocarcinomas compared with squamous cell cancers, as elevated levels of thymidylate synthase confers resistance.[22,23] The addition of maintenance pemetrexed therapy following first line therapy with a pemetrexed-platinum combination or the EGFR TKI, erlotinib, has demonstrated a modest incremental gain in survival.[24,25] Platinum doublets in combination with targeted therapy against Vascular Endothelial Growth Factor (VEGF) using bevacizumab has demonstrated a very modest improvement in progression free survival without consistently translating into an overall survival benefit in the first line setting. [26,27] While a meta-analysis showed 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 first-line chemotherapy. [28,29] Given the high cost of bevacizumab and its associated toxicities widespread adoption of this agent in the management of lung cancer has not occurred 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.[30,31] 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 both first- line and second- line, as well as maintenance therapy for patients with EGFR mutated tumors without demonstrating an advantage to overall survival, which may be attributable to the extensive cross over that occurred in these clinical trials. [32] However, a recent pooled analysis in patients with Exon 19 deletion subtype of EGFR mutation showed improved OS with first line afatinib compared to chemotherapy.[33]

In patients with the anaplastic lymphoma kinase (ALK) rearrangement, 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.[34,35] 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 can produce tumour regression and meaningful benefit in terms of progression free survival in both crizotinib resistant and crizotinib naive patients.[36-38] The exact sequencing of these agents in relation to chemotherapy has not yet been clearly established.[39] 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.

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 offer second line chemotherapy if they have maintained a good performance status and are willing

to receive additional chemotherapy. The use of single agent therapy with pemetrexed or docetaxel in this situation is based on a modest improvement in survival, as well as improved quality of life compared to best supportive care.[40,41] For those patients who receive biomarker driven therapy initially, second line systemic therapy typically consists of platinum-based chemotherapy and pemetrexed in third line for those who maintain a good performance status. Although erlotinib may be used in some patients in whom it is difficult to determine mutation status due to inaccessibility of tumour tissue for testing, it is less commonly used in clinical practice compared to docetaxel and pemetrexed as most patients are now assessed for mutation status before first line therapy is initiated and receive subsequent treatments based on their initial mutation status.

Third-line and subsequent systemic therapy: In this population, antineoplastic systemic therapy is typically dependent on patient performance status, as well as the patient's willingness to receive additional therapy. Gefitinib has demonstrated non-inferiority to docetaxel in the second or subsequent line of treatment.[42] Erlotinib has shown improved survival and symptom control in the second line or later line treatment when compared to best supportive care.[43] More recently, afatinib has been shown to provide greater benefit than erlotinib in the treatment of squamous cell cancers.[23] Supportive care therapy including palliative radiation and early referral to a 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.[44,45]

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 cisplatinum based combination chemotherapy as well as monotherapy [46]. 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.[47]

Patient population and attrition with subsequent lines of therapy: Retrospective analyses have suggested that there is a sharp decrease 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 less than 50% of patients who receive first line therapy will receive a second line therapy and fewer than 30% of those receiving first line therapy will proceed to third line regimens.[48,49] 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

Immunotherapy

Lung cancer has historically been considered to be poorly immunogenic, with no benefit from cytokine modulation or vaccines. Recently, however, the development of checkpoint inhibitors has provided a very promising new treatment strategy for lung cancer and many other cancers. Immune checkpoints are inhibitory pathways that maintain self-tolerance and protect body tissues by restricting the immune response. The two checkpoint targets that have been studied to the greatest extent to date in lung cancer are the cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and the programmed death 1 (PD-1) receptor. The PD-1 receptor on activated T cells interacts with ligands, PD-L1 and PD-L2, expressed

by tumor cells and infiltrating immune cells. Approximately 23-28% of patients with NSCLC have a high level of PD-L-1 expression defined as membranous PD-L-1 expression on at least 50% of tumour cells, regardless of staining intensity [1]. 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

Nivolumab is an IgG4 PD-1 immune checkpoint inhibitor and was the first immune checkpoint inhibitor to demonstrate substantial anti-tumour activity against NSCLC in a series of clinical trials. In a phase I trial, CheckMate 003, durable responses were noted in heavily pretreated patients with advanced NSCLC of all tumour histologies.[50] This observation led to two phase III randomized clinical trials, evaluating nivolumab in the second line setting for patients with advanced NSCLC. CheckMate 017 was a Phase III trial of nivolumab 3 mg/kg every 2 weeks in previously treated patients with squamous cell lung cancer compared to standard second-line docetaxel chemotherapy. It demonstrated a 3.2 month improvement in overall survival in favour of nivolumab. At data cut off, the median survival of patients on nivolumab was 9.2 months (95% CI: 7.3-13.3 months) on nivolumab compared to 6.0 months (95% CI: 5.1-7.3 months) on docetaxel with a 41% reduction in the risk of death on the nivolumab arm (HR 0.59, 95% CI 0.44 – 0.49; p<0.001). An updated follow-up reported an 18 month OS for nivolumab of 28% compared to 13% for docetaxel. The survival benefit was independent of PD-L1 expression. Nivolumab was also noted to be better tolerated than the second-line chemotherapy with a positive impact on quality of life and a longer time to symptom deterioration on nivolumab.

Similarly, CheckMate 057 evaluated nivolumab in comparison to docetaxel in non-squamous lung cancer. Again survival was longer on nivolumab (median OS 12.2 months on nivolumab vs 9.4 months on docetaxel, HR 0.73, 95% CI: 0.59-0.89; p=0.002) although there was a small, excess of early progression and/or deaths on the nivolumab arm compared to docetaxel. Response rates (19% vs 12%, p=0.021) and duration of response (17.2 vs 5.6 months) favoured nivolumab. There was a lower frequency of both serious adverse events (grade 3/4, 10% vs 54%) and adverse events leading to treatment discontinuation (4% vs 15%) with nivolumab. The most frequent AEs reported with nivolumab in both the CheckMate 017 and 057 trials were rash, pruritus, diarrhea, hypothyroidism, elevation of liver enzymes and pneumonitis.

A pre-planned exploratory analysis was strongly predictive of clinical benefit at all levels of expression of PD-L1 and for all efficacy end-points. Based on the results of these two trials the FDA and EMA granted approval for nivolumab as a second-line treatment in NSCLC.

Nivolumab has also been evaluated in the first-line setting in a Phase 1, multi-cohort trial, CheckMate 012. In this trial, 52 patients received nivolumab 3mg/kg intravenously every 2 weeks until progression or unacceptable toxicity. The overall response rate in patients with any degree of tumour PD-L-1 expression was 28% and 14% if there was no PD-L-1 expression. Median PFS was 3.6 months and the median OS was 19.4 months. The 1-year and 18 month OS rates were 73% and 57% respectively. In a subsequent Phase 3, open-label randomized trial (CheckMate 026) of nivolumab monotherapy patients with untreated, advanced NSCLC were randomized between nivolumab and standard chemotherapy in patients. Patients could have squamous or non-squamous histology and PD-L-1 expression of at least 1%. The trial randomized 542 patients either to nivolumab 3 mg/kg IV every 2 weeks or to investigator's choice of therapy (squamous NSCLC: gemcitabine + cisplatin, gemcitabine + carboplatin, paclitaxel + carboplatin and non-squamous: pemetrexed +

cisplatin, pemetrexed + carboplatin). Nivolumab failed to meet its primary endpoint of progression free survival. Even in those patients with >50% PD-L1 expression, no benefit was seen (HR for PFS, 1.06; HR for OS, 0.9).

Ongoing phase III trials include CheckMate -227 which is evaluating the combination of nivolumab plus ipilimumab for PD-L-1 positive patients and nivolumab + ipilimumab or nivolumab + chemotherapy in PD-L-1 negative patients [51].

Pembrolizumab

Pembrolizumab is a humanized IgG4 monoclonal antibody against PD-1 that has also been evaluated for the treatment of advanced NSCLC. In a large phase Ib trial of 550 patients, pembrolizumab was given in a dose of 2 mg/kg every 3 weeks (KEYNOTE-001). Patients could have any level of PD-L1 expression. This study showed impressive and durable responses in a subset of patients with high levels of PD-L1 expression.[52] In 2015, based on the results of this trial, the FDA granted accelerated approval for pembrolizumab I advanced NSCLC.

Subsequently, Pembrolizumab was evaluated in an open-label Phase 2/3 trial in 202 academic medical centres in 24 countries (KEYNOTE- 010)[53]. Previously treated patients with NSCLC and PD-L-1 expression on at least 1% of tumour cells were randomly assigned to pembrolizumab 2 mg/kg, or 10 mg/kg, or docetaxel 75 mg/m^2 every 3 weeks. The co-primary endpoints of the study were overall survival and progression free survival both in the total population and in patients with PD-L-1 expression on at least 50% of tumour cells. PD-L-1 expression was assessed at a central laboratory with an immunohistochemical test (Dako) with murine 22C3 anti-human PD-L-1 antibody (Merck; Kenilworth, USA).

Patients were included if they had tumour progression after two or more cycles of platinum-doublet chemotherapy, as well as appropriate tyrosine kinase inhibitor treatment for either EGFR-sensitizing mutations or ALK gene rearrangements, an ECOG performance status of 0 or 1. Patients with active brain metastases, active autoimmune disease requiring systemic steroids, interstitial lung disease or a history of pneumonitis requiring steroids were excluded. 1034 patients were enrolled: 345 were allocated to pembrolizumab 2 mg/kg, 346 to pembrolizumab 10 mg/kg and 343 to docetaxel. Pembrolizumab was administered intravenously over 30 minutes. For the total population, the median overall survival was 10.4 months with pembrolizumab 2 mg/kg, 12.7 months for pembrolizumab at 10 mg/kg and 8.5 months with docetaxel. Overall survival was significantly longer with pembrolizumab 2 mg/kg versus docetaxel (HR 0.71, 95% CI 0.58-0.88; p=0.0008) and for pembrolizumab 10 mg/kg (HR 0.61, CI 0.49-0.75; p<0.0001). Among patients with at least 50% of tumour cells expressing PD-L-1, overall survival was significantly longer with pembrolizumab 2 mg/kg than with docetaxel (median 14.9 months vs 8.2 months; HR 0.54, 95% CI 0.38-0.77; p=0.0002) and with pembrolizumab 10 mg/kg than with docetaxel (17.3 months vs 8.2 months; HR 0.50, 95% CI 0.36-0.70; p<0.0001). Progression free survival was also longer with both pembrolizumab 2 and 10 mg/kg compared with docetaxel: median 5.0 vs 5.2 vs 4.1 months respectively.

Among patients with a tumour proportion score of 50% or greater, responses occurred in 30% of 139 patients on pembrolizumab 2 mg/kg, 29% of 151 patients on pembrolizumab 10 mg/kg and 8% of 152 patients on docetaxel (P<0.0001 for each pembrolizumab group vs docetaxel). Median time to response was 9 weeks in each treatment arm. Responses were longer in the pembrolizumab groups than with docetaxel, with the median duration of response not reached for either pembrolizumab arm compared with 8 months for patients with a tumour proportion score of 50% or greater on the docetaxel arm.

The median duration of treatment was 3.5 months in both pembrolizumab groups and 2.0 months on docetaxel. Grade 3-5 adverse events attributable to the study drug occurred in 13% and 16% of patients on pembrolizumab 2 and 10 mg/kg respectively and 35% in patients on docetaxel.

Adverse events were as expected for docetaxel and pembrolizumab. AEs likely of an immune etiology were seen in 20% of those on pembrolizumab 2 mg/kg and 19% of those on the 10 mg/kg dose. The most common of these events were hypothyroidism, hyperthyroidism and pneumonitis.

The KEYNOTE-010 investigators concluded that pembrolizumab provided benefit to previously treated patients with both squamous and non-squamous NSCLC, although the difference for squamous was not statistically significant which was partly attributed to the small numbers of squamous cell cancers in the study. They noted that compared with the Checkmate trials where patients had received only one prior chemotherapy, two-thirds of patients in KEYNOTE-010 had received at least two lines of prior therapy. KEYNOTE-010 was also the first trial to demonstrate the utility of PD-L-1 as a biomarker although the best cutpoint to predict the effectiveness of pembrolizumab is as yet unknown.

KEYNOTE-024 has evaluated in a randomized open label trial, first line treatment with pembrolizumab in a fixed dose of 200 mg every 3 weeks compared to investigators' choice of first-line cytotoxic chemotherapy [1]. Patients had to have Stage IV NSCLC without sensitizing EGFR mutations or ALK translocations, no prior systemic therapy and ECOG performance status of 0,1 and a PD-L-1 tumour proportion score of 50% or greater. Patients were ineligible if they were receiving systemic corticosteroids for active autoimmune diseases, had active interstitial lung disease or a history of pneumonitis requiring treatment with glucocorticoids.

Patients were randomized to receive pembrolizumab 200 mg every 3 weeks for up to 35 doses or to the investigators' choice of one of 5 platinum-based chemotherapy regimens: carboplatin plus pemetrexed, cisplatin-pemetrexed, carboplatin-gemcitabine, cisplatin plus gemcitabine or carboplatin plus paclitaxel. Pemetrexed regimens were only permitted for patients with non-squamous histology and these patients could receive pemetrexed as maintenance therapy. Patients were randomized and stratified by performance status (0 vs 1), tumour histology (squamous vs non-squamous) and region of enrollment (East Asia vs non-East Asia).

The primary endpoint of the trial was progression free survival. Secondary endpoints included overall survival, objective response rate and safety. 1934 patients were screened for eligibility at 142 sites in 16 countries, including 1729 who submitted samples for PD-L-1 testing. Of the 1653 patients whose samples were evaluated for PD-L-1, 500 (30.2%) had a PD-L-1 tumour proportion score of 50% or greater. From these patients, 305 patients at 102 sites who met eligibility criteria were randomly assigned between September 2014 and October 2015 to either pembrolizumab (154 patients) or chemotherapy (151 patients). Baseline patient characteristics were well balanced although more patients in the chemotherapy group had never smoked (12.6% vs 3.2%) and more patients in the pembrolizumab group had brain metastases (11.7% vs 6.6%). These differences were not statistically significant.

At a median duration of follow-up of 11.2 months, 48.1% of patients on pembrolizumab and 10.0% of those on chemotherapy were still receiving the assigned treatment. The median duration of treatment was 7.0 months for pembrolizumab and 3.5 months for chemotherapy. The median number of pembrolizumab treatment cycles was 10.5 (range

1-26); the median for chemotherapy was 4 (range 1 to 6). 66 patients (44.7%) on chemotherapy crossed over to pembrolizumab after disease progression and 57.6% were still receiving pembrolizumab at the time of data cutoff.

In the intention to treat population, median progression free survival was 10.3 months for pembrolizumab and 6.0 months for chemotherapy. The estimated percentage of patients alive and progression free at 6 months was 62.1% in the pembrolizumab group and significantly longer than on chemotherapy (hazard ratio for progression or death, 0.50; 95% CI, 0.37 to 0.68, p<0.001) and the benefit was seen in all subgroups (age, gender, region of enrollment, ECOG performance status, histologic cell type, smoking status, brain metastases and chemotherapy with or without pemetrexed). However, the difference between treatment groups did not reach statistical significance in the following subgroups: female patients, patients who were current smokers, patients who had never been a smoker and patients with brain metastases at baseline.

At the time of a planned second interim analysis, the estimated percentage of patients alive at 6 months was 80.2% in the pembrolizumab arm and 72.4% in the chemotherapy arm; median overall survival had not been reached in either arm. Overall survival was significantly longer in the pembrolizumab group than in the chemotherapy group (HR for death, 0.60; 95% CI, 0.41 to 0.89; p=0.005.

Objective response rate was also higher on pembrolizumab compared to chemotherapy (44.8% vs 27.8%) as was the median duration of response (not reached in pembrolizumab arm; range, 1.9+ to 14.5+ months) vs 6.3 months on chemotherapy (range, 2.1+ to 12.6+ months).

Treatment related adverse events occurred in 73.4% of patients on pembrolizumab and in 90.0% of those on chemotherapy. Grade 3,4,5 treatment-related adverse events occurred in twice as many patients on chemotherapy as in the pembrolizumab treated group (53.3% vs 26.6%). Discontinuation of therapy occurred in 7.1% of pembrolizumab patients compared with 10.7% on chemotherapy. The most common treatment-related adverse events were diarrhea (14.3%), fatigue (10.4%) and pyrexia (10.4%) on pembrolizumab and anemia (44.0%), nausea (43.3%) and fatigue (28.7%) in the chemotherapy group. Immune-mediated adverse events occurred in 29.2% of patients on pembrolizumab and in 4.7% of chemotherapy patients. The only grade 3 or 4 immune-mediated events that occurred in 2 or more patients on pembrolizumab were severe skin reactions (3.9%), pneumonitis (2.6%) and colitis (1.3%) and there were no grade 5 immune-mediated events.

The investigators concluded that first-line treatment with pembrolizumab in patients with advanced NSCLC without a sensitizing EGFR mutation or an ALK translocation and with 50% or greater tumour cells staining for PD-L-1 produced a significantly longer progression-free and overall survival compared with standard first-line chemotherapy. The overall survival was longer despite the fact that a substantial percentage (43.7%) of chemotherapy patients crossed over to pembrolizumab. In addition, pembrolizumab had a higher response rate, a longer duration of response and a lower frequency of adverse events. KEYNOTE-024 used a cutoff for PD-L-1 staining or 50% or greater. KEYNOTE-042 is evaluating the benefit of pembrolizumab over chemotherapy in untreated patients who have a tumour proportion score of 1% or greater.

Other Trials

Recently, the OAK trial, a randomized, open label phase 3 trial of atezolizumab (an anti-programmed death-ligand 1 monoclonal antibody) versus docetaxel has been reported [54].

Eligible patients were previously treated with one or two cytotoxic chemotherapy regimens, had an ECOG performance status of 1 or 2, squamous or non-squamous histology and stage III or IV disease. 425 patients received atezolizumab and 425 patients received docetaxel. Overall survival was significantly longer with atezolizumab compared with docetaxel in the ITT population (median overall survival 13.8 months [95% CI 11.8 – 15.7] versus 9.6 months [95% CI 8.6 – 11.2]; hazard ratio 0.73, P= 0.0003). Survival benefit was greater in those with higher levels of PD –L1 staining tumour cells for tumour infiltrating immune cells but even in the PD–L1 undetectable subgroup, there was improved survival with atezolizumab compared with docetaxel (median OS, 12.6 months versus 8.9 months; HR 0.75). Survival improvement was similar in patients with squamous and non-squamous histology. The OAK study is the first randomized phase 3 study to report on the results of anti-PD– L1 targeted therapy and on the basis of this trial, the FDA approved atezolizumab on October 18, 2016 for the treatment of people with metastatic non-small cell lung cancer (NSCLC) "who have disease progression during or following platinum-containing chemotherapy, and have progressed on an appropriate FDA-approved targeted therapy if their tumor has EGFR or ALK gene abnormalities"[55].

Trials with other immune checkpoint inhibitors, including avelumab and durvalumab and combinations of immunotherapies with or without chemotherapy are ongoing, attesting to the increasingly significant role of immunotherapy in lung cancer.[5]

Biomarker: A reliable biomarker has not yet been elucidated for use with immunotherapies. While there is data from clinical trials that tumour expression of PD-L-1 is a biomarker for tumour response, diagnostic PD-L1 immunohistochemistry assays vary between pharmaceutical companies and thresholds for PD-L1 positivity have ranged 1 to 50 percent 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. Either fresh or archival tissue for PD-L1 testing can be used for testing in NSCLC.[53] Complicating decision-making is the fact that responses to PD-1 inhibition have been identified in patients reported to be PD-L1 negative across trials. Although PD-L-1 expression is predictive of response and the current best biomarker, the optimal test to determine responsiveness to immune checkpoint inhibition has not yet been 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 whose disease has progressed following ipilimumab therapy and, if BRAF V600 mutation positive, following a BRAF or MEK inhibitor. 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.[56]

Pembrolizumab has also received Health Canada approval for the treatment of patients with metastatic NSCLC whose tumour expresses PD-L1 (as determined by a validated test) and who have disease progression on or after platinum containing chemotherapy. Patients with EGFR mutations or ALK genomic rearrangements should have disease progression on approved therapy for these abnormalities prior to receiving pembrolizumab.

The U.S. FDA has also approved aezolizumab on May 18, 2016 for the treatment of bladder cancer.

Merck, the manufacturer of pembrolizumab currently lists 65 trials evaluating pembrolizumab alone or in combination with other immunotherapies or chemotherapy in a wide variety of tumours including recurrent squamous cell cancers of the head and neck, adenocarcinoma of the stomach and GE junction, renal cell and urothelial cancers, prostate, triple negative breast cancer and ovarian cancer, as well as hematological malignancies [57] [58]. The wide availability of these trials allows for a broad population of patients 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 previously untreated metastatic NSCLC whose tumors express PD-L1 (TPS of ≥50%) and who do not harbor a sensitizing EGFR mutation or ALK translocation was provided by three patient advocacy groups: Lung Cancer Canada (LCC), British Columbia Lung Association (BCLA) and Ontario Lung Association (OLA). Their input is summarized below.

BCLA conducted phone interviews with two Canadian patient respondents living with stage IV non-small cell lung cancer, as well as gathered information from on-line surveys developed through Fluid Survey and promoted through their website and membership databases. These surveys were completed by both patients and caregivers over the past 6 months. The responses from four caregiver respondents who completed the on-line survey were included in the patient input. Of the two patient respondents who were interviewed, only one patient had experience with pembrolizumab through a clinical trial in the second line setting after failure with chemotherapy and radiation.

OLA conducted two phone interview with patient respondents living with COPD and 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.

To gather information on patient experiences with second-line pembrolizumab experience, LCC had interviewed 4 patients and one caregiver. In addition to those, LCC interviewed 3 patients with first-line experience. LCC also conducted an environmental scan of online forums to gather patient and caregiver feedback regarding pembrolizumab. The comments from 16 patient and 13 caregiver respondents were included, of which 3 patients and 4 caregivers had first line pembrolizumab experience. LCC also provided an updated literature review from previous submissions. In summary, the perspectives of 23 patients and 14 caregivers, all with pembrolizumab experience, are captured in the LCC submission. Through both the focus groups and environmental scans LCC captured the voices of six patients and four caregivers who had experience with first line pembrolizumab.

From a patient perspective, lung cancer impacts many aspects of day-to-day life. 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 symptoms may include: loss of appetite, cough, pain, and shortness of breath. Moreover, one of the most common symptom burdens for lung cancer patients is fatigue or lack of energy. BCLA noted that symptoms are not fixed or consistent, but rather change frequently, which can be difficult to manage. 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. Respondents additionally indicated that they would value improved independence and requiring less assistance from others. 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. There was one patient who was taken off pembrolizumab due to pneumonitis. 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. Respondents wanted to address the importance of testing and qualifying for pembrolizumab and are concerned about potential wait times for accessing pembrolizumab. LCC indicated that patients are able to go to the infusion by themselves and feel well so that they can leave the hospital by themselves. One respondent was concerned with the stopping of pembrolizumab at two years since the respondent has been on the trial for 1.5 years and continues to experience tumour shrinkage.

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 Non-small Cell Lung Cancer

Both 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."

BCLA noted that by the time lung cancer is diagnosed, it is usually at an advanced stage. Most common symptoms include chronic cough, coughing up blood, chest pain, shortness of breath, repeated pneumonia or bronchitis, hoarseness of voice, loss of appetite or weight, and unusual or unexplained tiredness.

OLA also reported similar symptoms and problems that patients experience as a result of lung cancer, which include: pain (could be very intense at times), shortness of breath, cough, weakness, fatigue and being bed-ridden. Both 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.

3.1.2 Patients' Experiences with Current Therapy for 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!*"

Both BCLA and OLA conducted phone interviews with patients, two patients by each patient group respectively. The four patient respondents interviewed had undergone radiation and chemotherapy. The respondents from both groups 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, respectively 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 both 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 from the OLA input, 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*." The other OLA respondent indicated that whenever I try to swallow food, it feels like I am swallowing knives".

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.

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.

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

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.

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.

"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, 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. A patient who is in a first line pembrolizumab trial indicated that they are "very grateful that I did not have chemotherapy" "I would not be doing so well if I had chemotherapy first."

3.1.3 Impact of Non-small Cell Lung Cancer and Current Therapy on Caregivers

Both BCLA and OLA conducted surveys with caregiver respondents. BCLA conducted the survey with 4 caregivers and OLA conducted the survey with 8 caregivers. . 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 resulting in feeling helpless and suffering from depression and anxiety.

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 four additional caregivers with first-line pembrolizumab experience identified through a recent scan.

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

Both 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.

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.

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.

Patient Experiences with Pembrolizumab

None of the respondents from OLA had experience with pembrolizumab.

One patient respondent interviewed had experience with second-line pembrolizumab through a clinical trial. The respondent reported that it was "*Very easy infusion in a credible & accessible centre; however, the downside is the travel. I had to travel by ferry every time, and that my wife had to quit her job to take care of me*". The respondent also reported "*less shortness of breath, less tiredness and a lot more energy*".

According to LCC, 23 patients and 14 caregiver had experience with pembrolizumab. Six patients and four caregivers had experience with first-line pembrolizumab.

The majority of respondents interviewed and those from 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. This is consistent with the experiences of those that are on first-line pembrolizumab, with the exception of one patient respondent who was taken off pembrolizumab due to pneumonitis. Two of the patient respondents reported some fatigue that went away "with a nap during the day". At the beginning, one of the patient respondent had bloody stools that were managed through steroids. Three of the patient respondents reported rash that was managed through corticosteroids. One patient respondent said "compared to the side effects of chemotherapy, this is nothing!"

The patients that are on the first line trial for pembrolizumab felt "grateful". They are infused in the same unit as chemotherapy patients and see the side-effects. Others are refusing chemotherapy due to the side effects and are "trying to find a way to get access to immunotherapy."

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*."

A respondent also remarked that pembrolizumab relieved their symptoms of lung cancer. The respondent noted that he had a severe cough and had also lost weight, and 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*."

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.

One respondent reported that their tumour shrank 80% and importantly, she feels great. Another respondent reported that the tumour in his lungs and lymph node disappeared and the other tumour in his adrenal gland continues to shrink. According to LCC, the responses ranged from no change in tumour size but disease control to no evidence of disease.

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, patients on pembrolizumab are able to go to the infusions by themselves and importantly feel well so that they can leave the hospital by themselves. Caregivers are able to stay at work instead of taking time off work.

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.

LCC noted that the psychology of receiving an alternative first-line treatment to chemotherapy is significant. It has a large positive impact on hope and the outlook for their cancer. According to one patient, "you have lung cancer which means that you have an expiration date hanging over your head. This allows you the time to put your affairs in order." Patients, especially those that are younger feel this gives them extra time to get extra income for their family, help set things up and spend quality time creating precious memories. It allows patients to have quality in life.

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. They emphasize the need, especially in non-urban centres, to ensure that patients are not kept waiting for treatment.

Similarly, OLA also indicated that the biopsy, often required for an accurate diagnosis of lung cancer, was described as "incredibly painful". One patient respondent had to have this procedure done three times, as the technician was not skilled and had difficulty reaching the tumour. Training for general practitioners (GPs) was also mentioned as a need, as these patients felt their GPs needed to know more about lung diseases so there would not be unnecessary delays in diagnosis and treatment.

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.

4 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

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

Overall Summary

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

Clinical factors:

- Clarity of patients eligible
- Sequencing of treatments after pembrolizumab
- The need for PD-L1 testing, timing of the testing and the accuracy of the test results

Economic factors:

- Implementation of PD-L1 testing in first-line setting
- Long duration of treatment of 35 cycles or until disease progression, whichever occurs first

Please see below for more details.

4.1 Factors Related to Comparators

Platinum doublet therapies are the standard of care for first line treatment of advanced NSCLC. Pemetrexed in combination with platinum would be specific for non-squamous histology and may be continued as a single agent for maintenance therapy. PAG noted that the comparators in the KEYNOTE-024 were representative of therapies commonly used, including either cisplatin or carboplatin in combination with pemetrexed (non-squamous, maintenance allowed), gemcitabine or paclitaxel.

4.2 Factors Related to Patient Population

PAG identified that the funding request is for patients whose tumours have PD-L1 tumour proportion score of 50% or greater and not harboring EGFR mutations or ALK translocation. As a positive PD-L1 status of 50% or greater is required for use of pembrolizumab in the first line setting, PAG wished to note that there will be patients at time of first diagnosis, where either a tissue biopsy could not be obtained, or the biopsy was insufficient for testing, and they will remain unknown for PD-L1 status.

PAG is also seeking guidance on the appropriate treatments after progression on pembrolizumab, recognizing that evidence may not be available at this time and that follow-up information for patients from the clinical trial is limited.

PAG is seeking information on sequencing of all currently available treatments for non-small cell lung cancer, with and without mutations.

4.3 Factors Related to Dosing

PAG identified that with the flat dose of 200mg, there would be no drug wastage. In addition, the every three week administration schedule is similar to the current treatment schedule with cisplatin-pemetrexed. PAG noted that chemotherapy chair time with pembrolizumab will be less than with platinum-doublet chemotherapy.

PAG is seeking guidance on the following:

- duration of treatment – request clarity on whether treatment should be considered for up to a maximum of two years or 35 doses, or continued indefinitely until disease progression
- treatment discontinuation criteria – clinical progression versus pseudo-progression
- re-starting treatment with pembrolizumab if there are treatment interruptions for toxicity management without progression, but where disease progression occurs during the treatment break
- re-treatment with pembrolizumab in patients who have been initially treated with 35 cycles or less of pembrolizumab, but present with disease progression following a progression free time period.
- dosing for first-line treatment - whether the dose of 2 mg/kg that is used in second-line treatment can be used for first-line treatment. PAG noted the 2mg/kg dose for a 70kg patient would be 140mg (or three 50mg vials) at a cost of $6,600 per cycle. The flat dose of 200mg (or four 50mg vials) would cost $8,800 per cycle.

4.4 Factors Related to Implementation Costs

The high cost and large potential budget impact of pembrolizumab will be barriers to implementation. PAG noted that additional costs will be incurred on testing for PD-L1 in all patients at diagnosis and there may be system challenges in some jurisdictions to establish access to testing.

4.5 Factors Related to Health System

PAG noted that there will be a need to conduct EGFR, ALK and PD-L1 testing done at same time upon diagnosis to ensure patient access to the appropriate treatment in a timely manner.

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 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.

4.6 Factors Related to Manufacturer

PAG noted that treatment of small cell lung cancer is out of scope of the current review and there is an ongoing trial (KEYNOTE-028) for small cell lung cancer. PAG is interested in whether the manufacturer plans on making the submission of pembrolizumab for small cell lung cancer and when that may be.

5 SUMMARY OF REGISTERED CLINICIAN INPUT

One clinician input was provided from seven oncologists as a joint submission on the behalf of Lung Cancer Canada, Medical Advisory Committee.

The oncologists providing input identified that the key benefits of treatment with pembrolizumab in the first-line setting are the improved response rate, progression free survival, overall survival and durability of response. They identified that patients with PD-L1 expression less than 50% or patients with EGFR or ALK mutations or ECOG > 2 should not be recommended for first-line treatment with pembrolizumab at this time. They indicated that the availability of pembrolizumab for first-line treatment would shift the order of current treatments and recommend reflex testing of PD-L1 for all locally advanced and metastatic non-small cell lung cancer patients.

Please see below for details from the clinician input.

5.1 Current Treatment(s) for NSCLC

The oncologists providing input identified that the current treatment for NSCLC is platinum doublet chemotherapy (cisplatin or carboplatin with either gemcitabine, paclitaxel, docetaxel, vinorelbine or pemetrexed most commonly).

5.2 Eligible Patient Population

The oncologist providing input noted that there will not be a significant prevalent patient population. The incidence of non-small cell lung cancer in Canada is approximately 25,000 patients per year. Half of those have advanced or metastatic disease (~12,500) at diagnosis, although up to approximately 7,500 of those with earlier stage disease may relapse at a later time. Therefore overall about 80% patients will be diagnosed with, or develop, metastatic non-small cell lung cancer at some point in the course of their illness. Based on the studies published, only about 30% of the patients will have high PD-L1 expression, which is the most important criteria for receiving front line pembrolizumab (~5000). At most half of these patients currently do not receive any therapy at all due to co-morbidities, poor performance status, patient choice, etc.

They estimate that approximately 2500-3000 Canadians may be eligible to receive front line pembrolizumab.

5.3 Identify Key Benefits and Harms with Pembrolizumab

The benefits of pembrolizumab identified by the oncologists providing input are

- the improved response rate over chemotherapy (44.8% vs. 27.8%) and
- the improved progression free survival (10.3 vs 6 months).
- an overall survival benefit, despite cross-over (HR: 0.6, 95% CI: 0.41-0.89)
- significant superiority in patient reported outcomes for quality of life in comparison to chemotherapy.

They also noted that the durability of the response is also greater in the pembrolizumab arm (median duration not yet reached vs 6.3 months) and the benefits to survival are NOT at the cost of increased toxicity. Treatment-related adverse events of any grade were less frequent (occurring in 73.4% vs. 90.0% of patients), as were grade 3, 4, or 5 treatment-related adverse

events (26.6% vs. 53.3%) for the patients treated with pembrolizumab.

At this time, the oncologists providing input would NOT recommend pembrolizumab as first line therapy for patients with PD-L1 expression less than 50% or patients with EGFR or ALK mutations or ECOG > 2 as they were excluded from this trial.

They noted that the harms of these drugs come from the side effects. Fatigue is the most common adverse event. Many of the other side effects are related to the mechanism of action of the drug and are considered auto-immune phenomena such as hypothyroidism, pruritis / rash, diarrhea / colitis, pneumonitis, etc. The rate of side effects in general as well as severe side effects are less for pembrolizumab than platinum doublet chemotherapy (any grade: 73.4% vs. 90.0% of patients; grade 3, 4, or 5 treatment-related adverse events (26.6% vs. 53.3%).

5.4 Advantages of Pembrolizumab Over Current Treatments

For patients who have PD-L1 expression of 50% or greater on the tumour cells, pembrolizumab is superior to chemotherapy in the phase 3 trial for clinically important outcomes of survival and quality of life.

5.5 It is also important to note that clinically, we see patients who are refusing treatment for their lung cancer due to concern about the side effects and efficacy of chemotherapy. First line pembrolizumab will be a solution to those in this group that meet the criteria.

5.6 Sequencing and Priority of Treatments with Pembrolizumab

The oncologists providing input indicated that for patients who are PD-L1 50%, the sequence of treatment would be:

1. Pembrolizumab
2. Platinum doublet chemotherapy +/- maintenance if appropriate
3. Docetaxel
4. Erlotinib

They noted that this indication would shift the use of a PD-1 inhibitor from second line (after platinum doublet) to first line. This wouldn't replace a line of therapy, but rather switch the order. Both pembrolizumab and nivolumab have a positive pCODR recommendation in the second line setting, pending cost effectiveness is established.

5.7 Companion Diagnostic Testing

The oncologists providing input noted that companion diagnostic testing is required since patients must be PD-L1 positive for this therapy to be beneficial in the first line setting. They would recommend reflex testing for all locally advanced and metastatic non-small cell lung cancers. They noted that EGFR mutation and ALK translocation testing for the vast majority of this patient population are already done and this would add one additional immunohistochemical test to the reflex panel. They identified that this would be a change for the squamous lung cancer patients who currently do not get molecular testing.

5.8 Additional Information

No additional information was provided.

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the efficacy and safety of pembrolizumab (Keytruda) compared to standard therapy in previously untreated metastatic non-small cell lung carcinoma (NSCLC) patients whose tumors express programmed death-ligand 1 (PD-L1) (defined as a Tumour Proportion Score [TPS] ≥ 50%) and do not harbor a sensitizing epidermal growth factor receptor (EGFR) mutation or anaplastic lymphoma kinase (ALK) translocation.

Note: Supplemental Questions and Comparisons 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.

Potential Supplemental Questions:

1. What is the accuracy of 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 in previously untreated metastatic non-small cell lung carcinoma (NSCLC) patients.

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

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

Table 3. Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
RCTs	Adult patients (≥ 18 years) with previously untreated metastatic NSCLC whose PD-L1 tumor proportion score is ≥50% and does not harbor a sensitizing EGFR mutation or ALK translocation.	Pembrolizumab 200 mg as an IV infusion every 3 weeks	• Platinum doublet chemotherapy • Platinum doublet chemotherapy plus pemetrexed maintenance in patients with non-squamous histology	Primary efficacy outcomes: • **OS** • **QOL** Secondary efficacy outcomes: • **PFS** • ORR (CR, PR)

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
	Subgroups: • Histologic type (squamous versus non-squamous cell) • PD-L1 tumor percentage score • ECOG PS • Age • Sex • Weight • Smoking status • Brain metastases at baseline • Platinum-based chemotherapy regimen (included pemetrexed versus did not include pemetrexed)			• Duration of response • Time-to-response Safety: • AE o Endocrinopathies o Immune-related AE o 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; IV = intravenous; 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.				

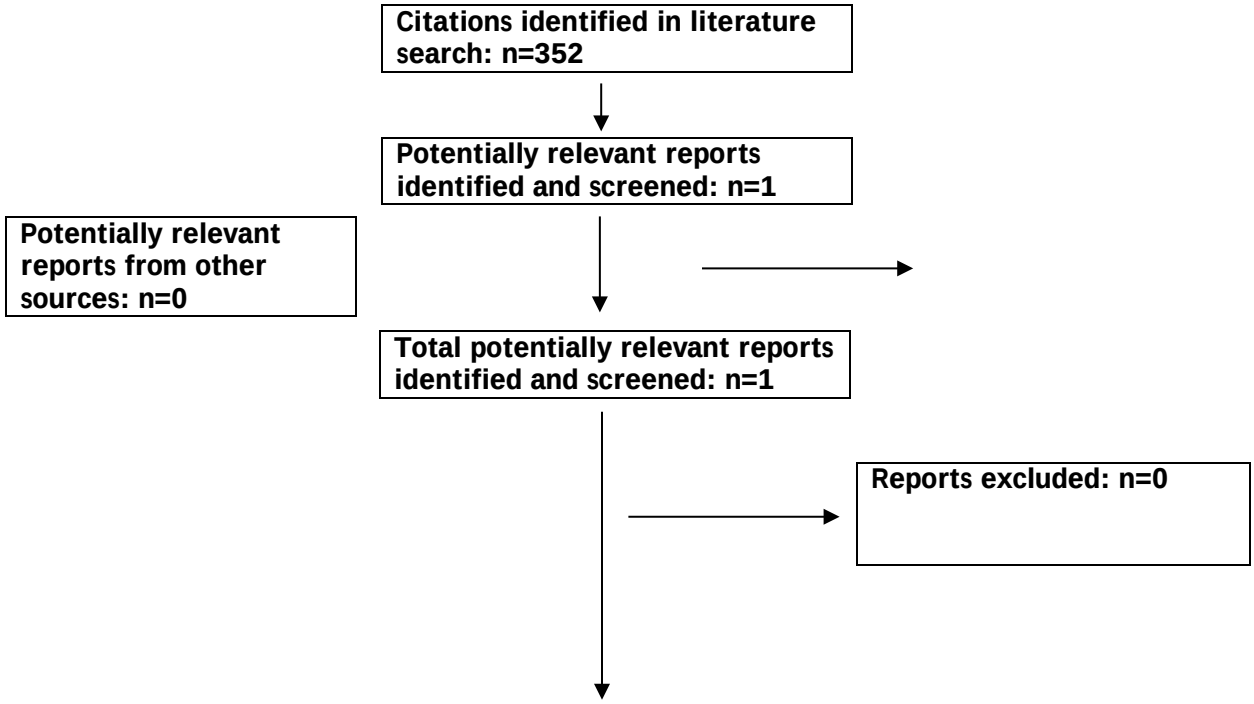
** Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions)*

6.3 Results

6.3.1 Literature Search Results

Of the potentially relevant reports identified, only one study was included in the pCODR systematic review[1].

QUOROM Flow Diagram for Inclusion and Exclusion of studies



1 report presenting data from the KEYNOTE-024 trial:
Reck 2016 (primary publication[1], along with supplementary Appendix and protocol[59])

4 reports were identified and included from other sources
Keytruda prescribing information[60]
Brahmer 2017 (abstract reporting quality of life results)[61]
Appraisal consultation document[2]
EMA Assessment report for Keytruda[62]

Additional references:
pCODR submission*[56]

**Note: Additional data related to the KEYNOTE-024 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.[1] KEYNOTE-024 is an open-label, randomized phase 3 trial comparing pembrolizumab 200 mg IV every 3 weeks to one of the following five platinum-

based chemotherapy regimens (carboplatin plus pemetrexed, cisplatin plus pemetrexed, carboplatin plus gemcitabine, cisplatin plus gemcitabine, or carboplatin plus paclitaxel) in patients with PD-L1 strong expressing tumor who had previously untreated stage IV NSCLC and did not have an epidermal growth factor receptor (EGFR) sensitizing mutation or anaplastic lymphoma kinase (ALK) translocation. Key characteristics of KEYNOTE-024 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-024 trial

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
KEYNOTE-024[1,59] Phase 3, open-label, RCT (1:1 ratio) Randomization was stratified by ECOG PS score (0 vs. 1), tumor histologic type (squamous vs. nonsquamous), and region of enrollment (East Asia vs. non-East Asia) N randomized = 305 ; N treated = 304 142 centres in 16 countries including Canada Patient Enrolment: September 19, 2014-October 29, 2015 Data cut-off date: May 9, 2016 (second interim analysis) Funded by Merck	<u>Key Inclusion Criteria:</u> • Age ≥18 years • ECOG PS 0 or 1 • Measurable disease using RECIST Version 1.1 • Histologically or cytologically confirmed diagnosis of stage IV NSCLC • Does not have an EGFR sensitizing (activating) mutation or ALK translocation[a] • Has not received prior systemic chemotherapy treatment for metastatic NSCLC • Has a life expectancy of at least 3 month • Has adequate organ function • No history of prior malignancy[b] • Provided a formalin fixed tumor tissue sample from a biopsy of a tumor lesion[c] • PD-L1 strong expressing tumor as determined by IHC at a central laboratory <u>Key Exclusion Criteria:</u> • Tumor specimen is not evaluable for PD-L1 expression by the central laboratory. • receiving systemic steroid therapy < 3 days prior to the first dose of trial treatment or receiving any other form of immunosuppressive medication	<u>Intervention</u> pembrolizumab 200 mg IV every 3 weeks for 35 cycles <u>Comparator</u> The investigator's choice of one of the following five platinum based chemotherapy regimens for 4 to 6 cycles: • Carboplatin (AUC 5 to 6)[f] + pemetrexed (500 mg/m^2)[fgh] • cisplatin (75 mg/m^2)[f] + pemetrexed (500 mg/m^2)[fgh] • carboplatin (AUC 5 to 6)[f] + gemcitabine (1250 mg/m^2)[i] • cisplatin (75 mg/m^2) + gemcitabine (1250 mg/m^2)[i] • carboplatin (AUC 5 to 6)[f] + paclitaxel (200 mg/m^2)[fj] Treatment was continued for the specified number of cycles or until the patient had radiologic disease progression, had treatment-related AE of unacceptable severity, or withdrew	<u>Primary:</u> PFS[k] <u>Secondary:</u> • OS[l] • ORR[m] • Safety <u>Exploratory:</u> • duration of response[n] • time to response • Patient reported outcomes (EORTC QLQ-C30, EORTC QLQ-LC13, EQ-5D-3L)

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
	• received thoracic radiation therapy of > 30 Gy within 6 months of the first dose of trial treatment • Has received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody • Active autoimmune disease, interstitial lung disease or history of pneumonitis requiring oral or IV steroids • Has untreated CNS metastases and/or carcinomatous meningitis[e]	consent or until the investigator decided to withdraw the patient, which-ever occurred first. Patients in the chemotherapy group who had disease progression, could cross over to receive pembrolizumab, if safety criteria were met. There was no preplanned crossover from the pembrolizumab group to the chemotherapy group	

Abbreviations: AE = adverse events; ALK = anaplastic lymphoma kinase; AUC = area under the curve; CNS = central nervous system; CTLA-4 = Cytotoxic T-lymphocyte-associated antigen-4; CR = complete response; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; EORTC= European Organization for Research and Treatment of Cancer; EQ-5D-3L = EuroQol-5 dimensions 3 level version; Gy = gray; IHC = immunohistochemistry; IV = intravenous; 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; QLQ = Quality of Life Questionnaire; QLQ-LC13 = Quality of Life Questionnaire and Lung Cancer Module; RCT = randomized controlled trial; RECIST = Response Evaluation Criteria in Solid Tumors; SAEs = serious adverse events.

Notes:
[a] EGFR sensitizing mutations were those mutations that are amenable to treatment with tyrosine kinase inhibitors including erlotinib, gefitinib, or afatanib.
[b] With the exception of basal cell carcinoma of the skin, superficial bladder cancer, squamous cell carcinoma of the skin, in situ cervical cancer; or has undergone potentially curative therapy with no evidence of that disease recurrence for 5 years since initiation of that therapy.
[c] The tumor tissue was provided either at the time of or after the diagnosis of metastatic disease has been made and from a site not previously irradiated to assess for PD-L1 status. Biopsies obtained prior to the administration of any systemic therapy administered for the treatment of a patient's tumor (such as neoadjuvant/adjuvant therapy) was not permitted for analysis. Needle or excisional biopsies, or resected tissue was required.
[d] Completion of treatment with chemotherapy and/or radiation as part of neoadjuvant/adjuvant therapy was allowed as long as therapy was completed at least 6 months prior to the diagnosis of metastatic disease.
[e] Patients whose brain metastases have been treated were eligible to participate provided that they show radiographic stability
[f] Frequency: Day 1 of each 21 day cycle
[g] Permitted for patients with non-squamous histology only.
[h] Followed by optional pemetrexed maintenance therapy given at a dose of 500 mg/m^2 every 3 weeks.
[i] Days 1 and 8 of every 3-week cycle
[j] Followed by optional pemetrexed maintenance therapy given at a dose of 500 mg/m^2 every 3 weeks (patients with non-squamous histology only).
[k] defined as time from randomization to documented progressive disease or death due to any cause, whichever occurs first (per RECIST 1.1) based on blinded independent radiologists' review
[l] defined as the time from randomization to death from any cause
[m] defined as the percentage of patients with a confirmed complete or partial response,

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
response were based upon blinded independent central radiologists' review per RECIST 1.1. [n] defined as the time from the first documentation of a complete or partial response to disease progression.			

Table 5: Select quality characteristics of the KEYNOTE-024 trial[1,59] comparing pembrolizumab to chemotherapy in patients who had previously untreated advanced NSCLC with PD-L1 strong expressing tumor (TPS of ≥50%)

Study	Treatment vs. Comparator	Primary outcome	Required sample size	Sample size	Randomization method	Allocation concealment	Blinding	ITT Analysis	Final analysis	Early termination	Ethics Approval
KEYNOTE-024[1,59]	pembrolizumab 200 mg vs. The investigator's choice of one of the following five platinum based chemotherapy[a] regimens: • Carboplatin (AUC 5 to 6) + pemetrexed (500 mg/m^2) • cisplatin (75 mg/m^2) + pemetrexed (500 mg/m^2) • carboplatin (AUC 5 to 6) + gemcitabine (1250 mg/m^2) • cisplatin (75 mg/m^2) + gemcitabine (1250 mg/m^2) • carboplatin (AUC 5 to 6) + paclitaxel (200 mg/m^2)	PFS	The study was event-driven and planned to randomize approximately 300 patients[b] The first interim analysis was conducted after the first 191 patients had a minimum of 6 months of follow up. This analysis was for ORR. This analysis had ~95% power to detect a 30% difference in ORR at alpha=0.005. The second interim analysis was to be performed after approximately 175 PFS events were observed between the pembrolizumab arm and control. With ~175 PFS events, the study had ~98%/97% power to detect a HR of 0.55 at alpha	305	Randomization occurred centrally using IVRS/IWRS[c] Randomization was stratified by region of enrollment (East Asia vs. non-East Asia), ECOG performance-status score (0 vs. 1), and tumor histologic type (squamous vs. nonsquamous)	No[d]	Outcome assessment[d]	Yes	Yes	Yes[e]	Yes

			= 0.025/0.02.								

Abbreviation: HR = hazard ratio; IVRS = interactive voice response system; IWRS = integrated web response system

[a] The specific chemotherapy platinum doublet as well as the dose to be administered were identified prior to randomization.

[b] The overall type I error rate for was strictly controlled at 2.5% (one-sided). There were one analysis planned for ORR, one analysis planned for PFS and two analyses planned for OS. The ORR analysis occurred when the first 191 randomized patients had a minimum of 6 months of follow up, and was tested at the 0.005 (one-sided) alpha level. PFS was tested only once at the planned PFS analysis after ~175 PFS events were observed, and was tested at the 0.025 (one-sided) level if ORR is positive or at the 0.02 (one-sided) level if ORR was negative. OS was tested only if PFS was positive and at the same level as PFS (i.e., step-down).

[c]The IVRS vendor generated the randomized allocation schedule(s) for study treatment assignment, and the randomization were implemented in IVRS. Access to the allocation schedule was restricted to an external unblinded statistician and, as needed, a scientific programmer performing the analysis, who had no other responsibilities associated with the study.

[d] PFS and ORR were assessed by independent central review for efficacy analysis. Treatment-level results of the planned ORR and PFS analyses were provided by an external unblinded statistician to the Data Monitoring Committee

[e] Because pembrolizumab was superior to chemotherapy with respect to overall survival, the external data and safety monitoring committee recommended that the trial be stopped early to give the patients who were receiving chemotherapy the opportunity to receive pembrolizumab. This study is still ongoing, but not recruiting participants.

a) Trials

KEYNOTE-024 was an open-label, randomized phase 3 trial conducted in 142 centres in 16 countries including Canada.[1] The trial's design placed importance on PD-L1 testing and had its primary endpoint, progression free survival.

Patient enrolment occurred between September 2014 and October 2015. The trial included patients with the following characteristics:

- ≥18 years of age
- Measurable disease using RECIST Version 1.1 as determined by the treating site
- Histologic or cytologic confirmation of stage IV NSCLC
- Absence of an EGFR sensitizing (activating) mutation or ALK translocation
- No received prior systemic chemotherapy for metastatic NSCLC
- An ECOG performance status of 0 or 1
- Tumour strongly expressing PD-L1 defined as PD-L1 expression on at least 50% of tumor cells, referred to as a tumour proportion score (TPS) ≥ 50%, by central laboratory .

Excluded from the trial were patients who had an EGFR sensitizing mutation and/or an ALK translocation, or who had received systemic therapy for the treatment of their stage IV NSCLC, or had previously been treated with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody, or had untreated central nervous system (CNS) metastases and/or carcinomatous meningitis, or active autoimmune disease, interstitial lung disease or history of pneumonitis requiring oral or IV steroids. Patients whose tumor specimen was not evaluable for PD-L1 expression were also excluded.

At the start of the trial, tumor tissue for biomarker analysis from a biopsy of a tumor lesion not previously irradiated was provided. Only biopsies obtained at the time of or after the diagnosis of metastatic disease were evaluated for PD-L1 expression. PD-L1 tumour expression testing was carried out at a central laboratory using the PD-L1 immunohistochemistry (IHC) 22C3 pharmDx assay (Dako North America). During patient enrolment, 1653 patients with assessable tumour samples were screened for PD-L1 assessable tumour samples with PD-L1 assay results. Of these patients, 500 (30%) had PD-L1 TPS ≥ 50%. A total of 305 patients met the eligibility criteria and were randomized into the trial.

Patients were randomized in a 1:1 ratio to one of the two treatment groups using central randomization methods. The randomization procedure was stratified by tumor histologic type (squamous vs. non-squamous), geographic site of enrollment (East Asia vs. non–East Asia), and ECOG performance status (0 versus 1). The trial was open label, and as such, patients, investigators and sponsor personnel involved with treatment or clinical evaluations were aware of treatment assignment.

Merck 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 8 of the 18 authors disclosed potential conflicts of interest related to the Sponsor.

The primary endpoints of the trial was progression-free survival (PFS), defined as the time from randomization to documented progressive disease or death due to any cause, whichever occurred first. The secondary endpoints of the trial included overall survival (OS) defined as the time from randomization to death from any cause, safety, and objective response rate (complete and partial). The exploratory

end points included duration of response, defined as the time from the first documentation of a complete or partial response to disease progression, and patient reported outcomes.

KEYNOTE-024 was event-driven and planned to randomize approximately 300 patients with 1:1 ratio into the pembrolizumab and chemotherapy arms.

There was one planned interim analysis for ORR (IA1), one planned analysis of PFS at Interim analysis 2 (IA2), and two planned analyses of OS one at interim OS analysis and a final OS analysis. Interim analysis 1 (IA1) occurred when the first 191 randomized patients had a minimum of 6 months of follow up and ORR was tested at the 0.005. (one-sided) alpha level. This analysis had approximately 95% power to detect a 30% difference in ORR at alpha=0.005. Progression free survival was tested at interim analysis 2 (IA2) after ~175 PFS events were observed. It was tested at the 0.025 (one-sided) level if ORR was positive at IA1 or 0.02 (one sided) if ORR was negative at IA1. OS was tested only if PFS was positive and at the same level as PFS (i.e., step-down). The trial had 97% power to detect a hazard ratio (HR) for PFS with pembrolizumab versus chemotherapy of 0.55. The interim OS analysis was to be conducted when approximately 110 OS events had occurred. At the time of the IA2, the trial had approximately 40% power to detect a HR for OS with pembrolizumab versus chemotherapy of approximately 0.65 at a one-sided alpha level of 0.0118. For OS, a Hwang-Shih-DeCani alpha-spending function with the gamma parameter -0.4 and beta-spending function with gamma -35 were constructed to implement group sequential boundaries that control the type I error rate as well as allow for non-binding futility analysis. The approach used for the alpha-spending function for the group sequential boundaries for the interim analyses was appropriate. The IA2 was conducted after 189 events of PFS, and 108 deaths had occurred. After reviewing the results from the IA2, the external data and safety monitoring committee recommended that the trial be stopped early to give the patients who were receiving chemotherapy the opportunity to receive pembrolizumab. All data reported in this report are based on the IA2.

Patients were evaluated every 9 weeks with radiographic imaging to assess response to treatment. For efficacy analyses, the assessment of PFS and response was carried out by an independent blinded central review panel of radiologists. However, the decision to continue treatment beyond disease progression was made by the investigator with the aid of immune related response criteria (irRC) assessments that were provided to the investigator.

b) Populations

Of the 305 patients randomized in the trial, 154 patients were allocated to the pembrolizumab group, and 151 were allocated to the chemotherapy group. Overall, the treatment groups were balanced for baseline characteristics except for smoking status where more patients in the chemotherapy group than in the pembrolizumab group had never smoked (12.6% vs. 3.2%) and brain metastases, where more patients in the pembrolizumab group than in the chemotherapy group had brain metastases (11.7% vs. 6.6%) (Table 6). The median age of patients in the pembrolizumab group was 64.5 years and in the chemotherapy group was 66.0 years. Most patients were white (82%), former or current smokers (92%), had non-squamous histology (82%), and an ECOG performance status of 1 (65%).

Table 6: Baseline characteristics of patients in the KEYNOTE-024 trial[1,62] comparing pembrolizumab to chemotherapy in patients who had previously untreated advanced NSCLC with PD-L1 strong expressing tumor (TPS of ≥50%)

Baseline Characteristic	Pembrolizumab Group (N = 154)	Chemotherapy Group (N = 151)
Age, median (range)	64.5 (33-90)	66.0 (38-85)
Male, n (%)	92 (59.7)	95 (62.9)
Race, n (%)		
White	125 (81.2)	126 (83.4)
Asian	25 (16.2)	21 (13.9)
Black	2 (1.3)	2 (1.3)
Other	0	2 (1.3)
Missing	2 (1.3)	0
Region, n (%)		
East Asia	21 (13.6)	19 (12.6)
Non-East Asia	133 (86.4)	132 (87.4)
ECOG PS, n (%)[a]		
0	54 (35.1)	53 (35.1)
1	99 (64.3)	98 (64.9)
Cancer Stage at Screening		
IIIB	1 (0.6)	1 (0.7)
IV	153 (99.4)	150 (99.3)
Smoking status, n (%)		
Current	34 (22.1)	31 (20.5)
Former	115 (74.7)	101 (66.9)
Never	5 (3.2)	19 (12.6)
Histology, n (%)		
Squamous	29 (18.8)	27 (17.9)
Nonsquamous	125 (81.2)	124 (82.1)
Brain metastases, n (%)	18 (11.7)	10 (6.6)
Previous systemic neoadjuvant therapy, n (%)	3 (1.9)	1 (0.7)
Previous systemic adjuvant therapy, n (%)	6 (3.9)	3 (2.0)

Abbreviation: ECOG = Eastern Cooperative Oncology Group; PS = performance-status
[a] One patient (0.6%), who was in the pembrolizumab group, had an ECOG performance-status score of 2.

c) *Interventions*

Patients allocated to the pembrolizumab treatment group received the drug intravenously over 30 minutes at a dose of 200 mg every 3 weeks for 35 cycles. Patients allocated to the chemotherapy treatment group received one of the following five platinum based chemotherapy regimens for 4 to 6 cycles based on the investigator's choice: cisplatin plus gemcitabine, cisplatin plus pemetrexed, carboplatin plus pemetrexed, carboplatin plus gemcitabine, or carboplatin plus paclitaxel. Only patients who had non-squamous tumors were permitted to received chemotherapy regimens that included pemetrexed; these patients could continue to receive pemetrexed as maintenance therapy after the completion of combination chemotherapy. The specific platinum doublet, with or without pemetrexed maintenance, as well as the dose was decided by the investigator prior to randomization.

Treatment was continued for the specified number of cycles or until the patient had radiologic disease progression, had treatment-related AEs of unacceptable severity, or withdrew consent or until the investigator decided to withdraw the patient, which-ever occurred first. Patients on chemotherapy who had disease progression, could crossover to receive pembrolizumab, if safety criteria were met. There was no preplanned crossover from the pembrolizumab group to the chemotherapy group. The decision to continue treatment beyond disease

progression was made by the investigator with the aid of immune related response criteria (irRC) assessments that were provided to the investigator.

One patient who was to receive carboplatin + pemetrexed followed by pemetrexed maintenance therapy withdrew consent before receiving the first dose of study treatment.

A total of 304 patients received at least one dose of study drug. The median duration of treatment was 7.0 months (range, 1 day to 18.7 months) in the pembrolizumab treatment group and was 3.5 months (range, 1 day to 16.8 months) in the chemotherapy treatment group. The median number of treatment cycles was 10.5 (range, 1 to 26) in the pembrolizumab group and was 4 (range, 1 to 6) in the chemotherapy group.

Sixty-six patients (43.7%) in the chemotherapy group, crossed over to receive pembrolizumab after disease progression. At the time of data cutoff, 57.6% of the patients who crossed over were still receiving pembrolizumab.

Table 7 below presents the number of patients who received any of the five platinum doublet.

Table 7: Therapy received in the chemotherapy group by tumor histology in the KEYNOTE-024 trial[1,59]

Regimen	27 patients with squamous histology	123 patients nonsquamous histology
Carboplatin + gemcitabine, n	15	5
Cisplatin + gemcitabine, n	7	4
Carboplatin + paclitaxel, n	5	12
Carboplatin + pemetrexed with pemetrexed maintenance, n	NA	28
Carboplatin + pemetrexed without pemetrexed maintenance, n	NA	38
Cisplatin + pemetrexed with pemetrexed maintenance, n	NA	18
Cisplatin + pemetrexed without pemetrexed maintenance, n	NA	18
Cycles received		
Median (range)	4 (1-6)	4 (1-6)
<4 cycles	11	42
4 cycles	3	47
5 cycles	0	7
6 cycles	13	27

NA = not applicable

d) Patient Disposition

The disposition of patients through the KEYNOTE-024 trial is summarized in Table 8. At the time of the data cut-off (second interim analysis) 52% and 70% of patients had discontinued treatment in the pembrolizumab and chemotherapy treatment groups, respectively. Of the 154 patients randomized to pembrolizumab, [redacted] ([redacted]%) continued the assigned treatment after progression of disease versus [redacted] ([redacted]%) of the 151 randomized patients continued chemotherapy treatment after progression of disease. (*Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by manufacturer that it can be publicly disclosed.*) Only

10% of patients in the chemotherapy treatment group were still receiving the assigned treatment at the data cut-off date versus 48% in the pembrolizumab treatment group. Progressive disease was indicated as the primary reason for treatment discontinuation in both treatment groups. The second reason for treatment discontinuation in the chemotherapy group was that patients completed treatment.

Table 8: Patient disposition in the KEYNOTE-024 trial[1,59] comparing pembrolizumab to chemotherapy in patients who had previously untreated advanced NSCLC with PD-L1 strong expressing tumor (TPS of ≥50%)

Patient disposition, n(%)	Pembrolizumab Group	Chemotherapy Group
Screened	1934	
With samples for PD-L1 assessment	1729	
With PD-L1 assay results	1653[ab]	
With PD-L1 TPS ≥50%	500	
Randomized	305[c]	
Allocated	154	151
Received treatment as assigned	154 (100)	150 (99.3)[de]
Discontinued randomized treatment	80 (51.9)	106 (70.2)[f]
Ongoing treatment	74 (48.1)	15 (9.9)
Completed treatment	0 (0)	29 (19.2)
ITT efficacy population	154 (100)	151 (100)
Safety population	154 (100)	150 (99.3)
Primary reason for discontinuation		
Progressive disease	51 (33.1)[g]	69 (45.7)[g]
Adverse events	17 (11)	16 (10.6)
Died	6 (3.9)	9 (6.0)
Patient withdrawal	4 (2.6)	5 (3.3)
Physician decision	1 (0.6)	7 (4.6)
Complete response	1 (0.6)	0
Completed treatment	0	29 (19.2)
Number (%) of patients who continued their assigned study treatment beyond disease progression[56]	[redacted]	[redacted]
Percentage of patients still receiving assigned treatment on May 9, 2016	74 (48.1)	15 (10.0)

Abbreviation: PD-L1 = programmed death ligand 1; TPS = tumor proportion score.

[a] Reasons for nonevaluable samples were insufficient tumor cells (n=62), excluded sample collection method or sample type (n=11), and sample contained bone that was at least partially decalcified (n=3).

[b] 500 patients with PD-L1 TPS ≥50%, and 1153 with PD-L1 TPS <50%

[c] Reasons for screen failure were untreated brain metastases (n=59); sensitizing EGFR mutation or ALK translocation (n=30); Eastern Cooperative Oncology Group performance status of 2 or 3 (n=27); inadequate organ function (n=19); intercurrent condition prohibited by protocol or that would prevent full study participation (n=16); no histological or cytological confirmation of non-small-cell lung cancer (n=13); written, informed consent not provided (n=11); life expectancy <3 months (n=6); previous malignancy other than basal cell carcinoma of the skin, superficial bladder cancer, squamous cell carcinoma of the skin, in situ cervical cancer, or underwent potentially curative therapy with no evidence of that disease recurrence for 5 years since initiation of that therapy (n=3); treatment with other systemic or localized antineoplastic therapy expected while on study (n=3); incorrect interpretation of PD-L1 results (n=2); lack of measurable disease per RECIST (n=2); previous systemic therapy for stage IV disease (n=2); previous systemic chemotherapy, biological therapy, or major surgery within 3 weeks or thoracic radiation >30 Gy within 6 months of first dose of study treatment (n=2); and participation within another clinical trial within 30 days of first dose of study treatment (n=1).

[d] One patient who was to receive carboplatin + pemetrexed followed by pemetrexed maintenance therapy withdrew consent before receiving the first dose of study treatment.
[e] 67 patients were to receive carboplatin + pemetrexed, 36 patients were to receive cisplatin + pemetrexed, 20 patients were to receive carboplatin + gemcitabine, 11 patients were to receive cisplatin + gemcitabine, and 17 patients were to receive carboplatin + paclitaxel. 28 (42.4%) patients who received carboplatin + pemetrexed and 18 (50.0%) who received cisplatin + pemetrexed received pemetrexed maintenance therapy.
[f] Includes 66 (43.7%) patients who crossed over to receive pembrolizumab after disease progression as part of the study
[g] Includes clinical progression.

(Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by manufacturer that it can be publicly disclosed.)

e) Limitations/Sources of Bias

Overall, the KEYNOTE-024 trial[1] was well conducted owing to the use of appropriate methods to randomize patients, clear explanation of the disposition of patients throughout the trial, the use of an independent central review for the assessment of key efficacy outcomes and the conduct of 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. This open label design may threaten the internal validity of the trial and introduce moderate-high risk of bias in the assessment of measures such as patient-reported outcomes, and reporting of adverse events. The potential for bias is minimized in KEYNOTE-024 through the use of an independent central review of key efficacy outcomes progression-free survival (PFS) and objective response rate (ORR). On the other hand, it seems that treatment-level results of the planned ORR and PFS analyses were provided by unblinded statisticians who were employed by Merck which might threaten the internal validity of the results. Overall survival is unlikely to be influenced by subjective bias.
2. There was only one planned analysis of ORR, which occurred at interim analysis 1 when the first 191 randomized patients had a minimum of 6 months of follow up and ORR was tested at the 0.005 (one-sided) alpha level. However, results for this ORR are not available and results for the ORR that are available were from the second interim analysis which was not pre-specified, hence results presented in this report for the ORR should be interpreted with caution.
3. Although patient subgroup efficacy analyses were pre-specified, none of the subgroups was adequately powered, and results from any of these analyses may be difficult to interpret. In addition, some groups (patients with brain metastases at baseline and patients who were never smokers) included a smaller number of patients, which can have an influence on the treatment effects observed. The results of these analyses require further validation.
4. After disease progression, 66 patients (43.7%) in the chemotherapy group crossed over to receive pembrolizumab. Despite the crossover of patients in the chemotherapy group to receive pembrolizumab, which one would expect to confound the observed treatment effect towards no effect, the OS remained statistically significantly improved on the pembrolizumab arm of the trial. An attempt to adjust for the crossover were made by the manufacturer, but found to be inappropriate.

5. The patients included in this study were limited to PS 0 and 1. Performance status is a well-established prognostic factor in NSCLC. Consequently, the beneficial effects of pembrolizumab may have been overestimated in a study population with a better survival probability than typically seen in practice. Therefore, whether the findings in this study could be generalizable to all previously untreated advanced NSCLC patients including PS greater than one is unclear.
6. QOL data were assessed in the KEYNOTE-024 trial but the open-label design of the trial increases the risk of bias which makes interpretation of the QOL data difficult, thus increasing the uncertainty in these results. On the other hand, the clinical guidance panel indicated that in clinical practice they noticed that immunotherapy is better tolerated than chemotherapy.
7. The data on survival are relatively immature with a median duration of follow-up of only 11.2 months
8. The RCT was funded by the manufacturer. The manufacturer in collaboration with the trial investigators designed the study, collected data and interpreted the results.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

In the KEYNOTE-024 trial,[1] efficacy analyses for OS, PFS and response rate were performed by intent-to-treat. For duration of response, all patients who had a complete or partial response were included in the analyses. The non-parametric Kaplan Meier method was used to generate survival curves for OS and PFS outcomes. Differences in OS and PFS between treatment groups were analyzed using the stratified log-rank test. Hazard ratios (HR) and 95% confidence intervals (CIs) were generated using the stratified Cox proportional hazards models with Efron's method of handling ties. The same stratification factors used for randomization were applied to both the stratified log-rank test and the stratified Cox model. Since patients in the chemotherapy arm were expected to discontinue from the study earlier compared to patients in the pembrolizumab arm because of earlier onset of progression disease and the opportunity to switch to the pembrolizumab treatment after the confirmed progression disease, the Rank Preserving Structural Failure Time (RPSFT) model was pre-specified to adjust for the effect of crossover on OS. RPSFT method is only valid if the effect of treatment with pembrolizumab is constant, irrespective of the point in time that the therapy was initiated (baseline or switch). When the validity of the common treatment effect was explored numerically, it was found the post-progression treatment estimate of pembrolizumab (acceleration factor of 4.05, [95% CI 1.39 to 16.44]) while the overall effect of pembrolizumab adjusted for switching (acceleration factor of 2.11, [95% CI 1.49 to 2.99]).[2] Hence the assumption of a common treatment effect does not hold given that the post-progression estimate of pembrolizumab (without switching) and the treatment effect of pembrolizumab adjusted for switching are not the same, therefore, it was not appropriate to use the RPSFT method to adjust for the effect of crossover. So the results reported for OS are for the ITT population without adjustment.

The National Institute for Clinical Excellence (NICE) in the Evidence Review Group (ERG) report for Pembrolizumab for untreated PD-L1 positive metastatic non-small-cell lung cancer explored the methods used by the manufacturer to adjust for crossover. Methods reported were the RPSFT method, the IPCW method, and the 2-stage method. It was reported that all three methods are unreliable.[2]

The statistical plan accounted for one primary endpoint PFS and two secondary endpoints OS and ORR. There was one planned analysis of ORR at interim analysis 1 (IA1), one planned analysis of PFS at interim analysis 2 (IA2), and two planned analyses of OS, one at interim OS analysis and a final OS analysis. The one-sided p-value used for declaring statistical significance for ORR at IA1 was p=0.005. The one-sided p-value used for declaring statistical significance for PFS at IA2 was p=0.025 if ORR was positive at IA1 or was p=0.02 (one sided) if ORR was negative at IA1. OS was tested only if PFS is positive and at the same level as PFS (i.e., step-down). Results reported in the article for PFS and OS were pre-specified; however, the results reported for ORR at the second interim analysis was not pre-specified and hence results should be interpreted with caution. Subgroup analyses for PFS were also planned a priori, and included age, sex, ECOG performance status, histology, smoking status, brain metastasis status, and investigators' choice of standard of care chemotherapy. For the analysis of PFS, data for patients who were alive and had no disease progression or who were lost to follow-up were censored at the time of the last tumor assessment. For the analysis of OS, data for patients who were alive or who were lost to follow-up were censored at the time of the last contact. The data cut-off date was that of the second interim analysis of May 9, 2016 when the external data and safety monitoring committee recommended that the trial be stopped early in order to give the patients who were receiving chemotherapy the opportunity to receive pembrolizumab. It was reported that data was analyzed by unblinded statisticians employed by Merck.

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-024 trial have not been published in an article; an abstract and a report with results for the change from baseline to week 15 in the QLQ-C30 global health status/QoL score and time to deterioration in the QLQ-LC13 composite of cough, chest pain, and dyspnea was identified [2,61] and are presented in this report. Results for the change from baseline to week 15 in EQ-5D utility score (Using European Algorithm) and visual analog scale (VAS) were reported in the Committee papers of the Single technology appraisal of pembrolizumab published by NICE.[2]

The QLQ-C30 measures overall QOL and different aspects of patient functioning. It comprises five functional 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 15. 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. Across treatment groups, compliance rates over 90% were reported at baseline and rates were approximately 80% at week 15. Compliance was slightly lower in the chemotherapy treatment group than the pembrolizumab treatment group.

The EQ-5D was used to measure overall health status during treatment and follow-up phases of the KEYNOTE-024 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 European algorithm. A change in score of greater than 0.06 has been established as the MCID in US cancer patients. Considering all treatment groups, compliance rates were over 90% at baseline, and were around 66% by week 15. Compliance was slightly lower in the chemotherapy treatment group than the pembrolizumab treatment group.

Patient-reported outcomes were analyzed using the full analysis set (FAS), which consisted of all randomized patients who received at least one dose of study medication and completed at least one PRO instrument. At week 15, the treatment effect on PRO score change from baseline was evaluated using constrained longitudinal data analysis.[2]

The as-treated population was used for the analysis of safety data, which included all patients who received at least one dose of assigned trial medication.

Efficacy Outcomes

The key efficacy outcomes of the KEYNOTE-024 trial [1] are summarized in Table 9.

Overall Survival

At the time of interim analysis (IA2) on May 9, 2016, after a median follow-up time of 11.2 months (range, 6.3-19.7), a total of 108 patients had died: 44 (28.6%) in the pembrolizumab group, and 64 (42.4%) in the chemotherapy treatment group.

The median OS was not reached in either treatment group. The 6-month OS rates were 80.2% and 72.4% for pembrolizumab and chemotherapy treatment groups, respectively. The 12-month OS rates were 69.9% and 54.2% for the pembrolizumab and chemotherapy treatment groups, respectively. Overall survival was statistically significantly longer in the pembrolizumab treatment group than in the chemotherapy treatment group (HR = 0.60; 95% CI, 0.41 to 0.89; P = 0.005).

Figure 1 presents the Kaplan-Meier estimates of overall survival in the KEYNOTE-024 trial at the 2nd interim analysis, this figure indicates that there has been a large amount of censoring and that after 9 months there are only a small number of patients at risk. Hence, results from this analysis should be interpreted with caution because the median OS has not been reached for either treatment group. Also it is worth noting that there was a high level of crossover. At the time of IA2, 43.7% of patients in the chemotherapy treatment group had crossed over to pembrolizumab, which limits the reliability of the survival data collected in KEYNOTE-024.

The treatment benefit was also evident in many of the patient subgroups examined; however, the difference between treatment groups did not reach statistical significance in the following patients subgroups: age ≥ 65, female patients, non-white patients, patients with ECOG PS of 0, patients with squamous histology, patients who were current smokers, patients who are never smokers, patients with brain metastases at baseline, and patients who in the chemotherapy treatment group received pemetrexed. However, only a small number of events occurred in some subgroups (for example, never smoking, 7 events and presence of brain metastases at baseline, 10 events), which would result in wide confidence intervals (CIs), which preclude definitive interpretation of the treatment effect.

Progression-free Survival

At the time of IA2 on May 9, 2016, a total of 189 PFS events were observed: 73 (47.4%) in the pembrolizumab treatment group and 116 (76.8%) in the chemotherapy treatment group.

The median PFS was 10.3 months in the pembrolizumab treatment group and 6.0 months in the chemotherapy treatment group. The estimated percentage of patients who were alive and had no disease progression at 6 months was 62.1% and 50.3% for pembrolizumab and chemotherapy treatment groups, respectively, while the PFS rates at 12 months were 47.7% and 15.0% for pembrolizumab and chemotherapy, respectively. Progression- free survival was statistically significantly longer on the pembrolizumab than in the chemotherapy treatment group (HR = 0.50; 95% CI, 0.37 to 0.68; P < 0.001).

The treatment benefit was also evident in all patient subgroups examined, however, the difference between treatment groups did not reach statistical significance in the following patients subgroups: female patients, patients who are current smoker, patients were smokers, and patients with brain metastases at baseline. However, only a small number of events occurred in some subgroups (for example, never smoking, 12 events and presence of brain metastases at baseline, 17 events), which would result in a wide CI, which precludes an accurate interpretation of the treatment effect.

An exploratory analysis of PFS based on investigator assessment indicated that the PFS results for patients on chemotherapy were similar, irrespective of method of assessment (5.5 months when assessed by the Blinded independent central review, and 6 months when investigator assessed). However, for patients on pembrolizumab, there appears to be a difference of 3.1 months in median PFS between the results of the blinded independent central review and the investigator-assessed results (10.3 months when assessed by the blinded independent central review and 7.2 months when investigator assessed). It is unclear why there would be this magnitude of difference between these two assessment methods.[2]

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 the pembrolizumab treatment group compared to the chemotherapy treatment group (44.8% in the pembrolizumab group versus 27.8% on chemotherapy). However, results of this analysis should be interpreted with caution as it was not pre-specified. More than 90% of the observed responses were partial responses (Table 9). Median time-to-response was 2.2 months in each treatment group.

The median duration of response was not reached for the pembrolizumab treatment group and was 6.3 months in the chemotherapy treatment group.

Updated Overall Survival and Progression-free Survival after the next line of therapy results

Updated OS results and results for progression after the next line of therapy (PFS2) were presented on June 6, 2017 at the American Society of Clinical Oncology (ASCO).[63] PFS2 was defined as time from randomization to disease progression per investigator review (RECIST v1.1) after the start of second line therapy or death whichever occurs first. Patients were censored if they were alive without disease

progression at time of last known survival without disease progression. Patients who dies with disease progression and patients who discontinued the second line therapy were counted as events.[64]

Data cutoff date for the result present was January 5, 2017, after a median follow-up time of 19.1 months (range, 14.3-27.6).[64]

At the time of this data cutoff, 107 (69.4%) patients had discontinued pembrolizumab of which 48 (44.9%) were receiving subsequent therapy with a median (range) duration of second-line therapy was 3.6 months (range 1 d to 10.7 plus months). Of the 48 patients who discontinued pembrolizumab and received second-line therapy forty-two (87.5%) of them received platinum double, and 6 (12.5%) patients received other treatments.[64]

At the time of this data cutoff, 120 (79.5%) patients had discontinued chemotherapy of which 97 (80.8%) were receiving subsequent therapy with a median (range) duration of second-line therapy was 3.5 months (range 1 d to 20.3 plus months). Of the 97 patients who discontinued chemotherapy and received second-line therapy 79 (81.4%) of them crossed-over to pembrolizumab, 12 (12.4%) received Anti-PD1 outside of crossover, and 6(6.2%) received other treatments.[64]

At the time of the data cutoff on January 5, 2017, after a median follow-up time of 19.1 months (range, 14.3-27.6), a total of 147 patients had died: 63 (40.9%) in the pembrolizumab group, and 84 (55.6%) in the chemotherapy treatment group. The median OS was not reached in the pembrolizumab group and it was 14.5 month (range, 9.8-19.6) in the chemotherapy arm. The 18-month OS rates were 61.2% and 43.0% for the pembrolizumab and chemotherapy treatment groups, respectively. Overall survival was statistically significantly longer in the pembrolizumab treatment group than in the chemotherapy treatment group (HR = 0.54; 95% CI, 0.40 to 0.72; P < 0.001).[64]

At the time of this data cutoff on January 5, 2017, a total of 184 PFS2 events were observed: 74 (48.0%) in the pembrolizumab treatment group and 110 (72.8%) in the chemotherapy treatment group. The median PFS was 18.3 months in the pembrolizumab treatment group and 8.4 months in the chemotherapy treatment group. The estimated percentage of patients who were alive and had no PFS2 at 18 months was 51.0% and 24.6% for pembrolizumab and chemotherapy treatment groups, respectively. Progression- free survival was statistically significantly longer for patients on pembrolizumab than those on (HR = 0.54; 95% CI, 0.40 to 0.72; P < 0.001).[64]

These updated OS and PFS2 results suffer from many major limitations listed below:

- It is poster presentation, so it might be selective reporting
- It is not possible to critically appraise presented data appropriately due to incomplete information or incomplete data
- Any statistical significance results should be interpreted with caution due to the type of the analysis which were not pre-planned.
- After discontinuing study treatment, 145 patients (47.5%) received subsequent anti-cancer therapy. The OS results of the trial are likely confounded by these treatments.
- The criteria of how subsequent therapy was chosen for patient who were on pembrolizumab were not reported, and it is not clear why patients who were on pembrolizumab had to use subsequent therapy.

- At the second interim analysis, the external data and safety monitoring committee recommended that the trial be stopped early to give the patients who were receiving chemotherapy the opportunity to receive pembrolizumab. However, it does not seem that all patients who were on chemotherapy crossed over to pembrolizumab.

Table 9: Key efficacy outcomes in the KEYNOTE-024 trial [1,2,60,62] as of cut-off date of May 9, 2016

Efficacy Outcomes	Pembrolizumab Group (N = 154)	Chemotherapy Group (N = 151)
As of May 9, 2016 the median duration of follow-up in months (range)	11.2 (6.3-19.7)	
Primary Outcomes: PFS		
Number of PFS events (%)	73 (47.4)	116 (76.8)
Median, months (95% CI)	10.3 (6.7, NR)	6.0 (4.2, 6.2)
HR[a] (95% CI)	0 .50 (0.37, 0.68)	
p-value	< 0.001	
% of patients who were PFS at 6 months (95% CI)	62.1 (53.8, 69.4)	50.3 (41.9, 58.2)
% of patients who were PFS at 12 months	47.7%	15.0%
HR by subgroup (95% CI)		
Age <65 years	0.61 (0.40-0.92)	
Age ≥65 yr	0.45 (0.29-0.70)	
Male	0.39 (0.26-0.58)	
Female	0.75 (0.46-1.21)	
ECOG performance-status score 0	0.45 (0.26-0.77)	
ECOG performance-status score 1	0.51 (0.35-0.73)	
Histologic type Squamous	0.35 (0.17-0.71)	
Histologic type Nonsquamous	0.55 (0.39-0.76)	
Current smoker	0.68 (0.36-1.31)	
Former smoker	0.47 (0.33-0.67)	
Never been a smoker	0.90 (0.11-7.59)	
Brain metastases at baseline (Yes)	0.55 (0.20-1.56)	
Brain metastases at baseline (No)	0.50 (0.36-0.68)	
Platinum-based chemotherapy regimen Included pemetrexed	0.63 (0.44-0.91)	
Platinum-based chemotherapy regimen Did not include pemetrexed	0.29 (0.17-0.50)	
Exploratory analysis of PFS based on investigator assessment		
Number of PFS events (%)	86 (55.8)	123 (81.5)
Median, months (95% CI)	7.2 (6.0 to 10.2)	5.5 (4.2 to 6.2)
HR (95% CI)	0.55 (0.41 to 0.73)	
p-value	< 0.001	
% of patients who were PFS at 6 months	58.9%	48.6%
Secondary Outcome: OS		
Number of deaths (%)	44 (28.6)	64 (42.4)
Median, months (95% CI)	NR	NR
HR[a] (95% CI)	0.60 (0.41, 0.89)	
p-value	0.005	
OS rate at 6 month in % (95% CI)	80.2 (72.9, 85.7)	72.4 (64.5, 78.9)
OS rate at 12 month	69.9%	54.2%
HR by subgroup (95% CI)		
Age <65 years	0.48 (0.27-0.86)	
Age ≥65 yr	0.71 (0.42-1.21)	
Male	0.47 (0.28-0.77)	
Female	0.95 (0.50-1.83)	

Efficacy Outcomes	Pembrolizumab Group (N = 154)	Chemotherapy Group (N = 151)
ECOG performance-status score 0	0.86 (0.37-2.04)	
ECOG performance-status score 1	0.54 (0.35-0.84)	
Histologic type Squamous	0.70 (0.31-1.61)	
Histologic type Nonsquamous	0.56 (0.36-0.87)	
Current smoker	0.85 (0.40-1.80)	
Former smoker	0.51 (0.32-0.82)	
Never been a smoker	1.69 (0.19-15.25)	
Brain metastases at baseline (Yes)	0.53 (0.13-2.15)	
Brain metastases at baseline (No)	0.61 (0.40-0.91)	
Platinum-based chemotherapy regimen Included pemetrexed	0.73 (0.45-1.17)	
Platinum-based chemotherapy regimen Did not include pemetrexed	0.42 (0.21-0.82)	
Secondary Outcome: ORR		
Number of objective responses	69	42
CR, n (%)	6 (3.9)	1 (0.7)
PR, n (%)	63 (40.9)	41 (27.2)
Objective Response Rate % (95% CI)	44.8 (36.8,53.0)	27.8 (20.8,35.7)
Estimated difference (95% CI)	16.6 (6.0, 27.0)	
Median time to response in month (range)[b]	2.2 (1.4 to 8.2)	2.2 (1.8 to 12.2)
Mean (SD) time to response in month	3.0 (1.4)	3.2 (2.2)
Median duration of response in months (range)[c]	NR (1.9+ to 14.5+)	6.3 (2.1+ to 12.6+)
Number of patients with response ≥ 2 months (%)	68 (100)	42 (100)
Number of patients with response ≥ 4 months (%)	59 (93.6)	33 (89.3)
Number of patients with response ≥ 6 months (%)	43 (88.0)	16 (59.4)
Number of patients with response ≥ 9 months (%)	15 (81.9)	4 (36.2)

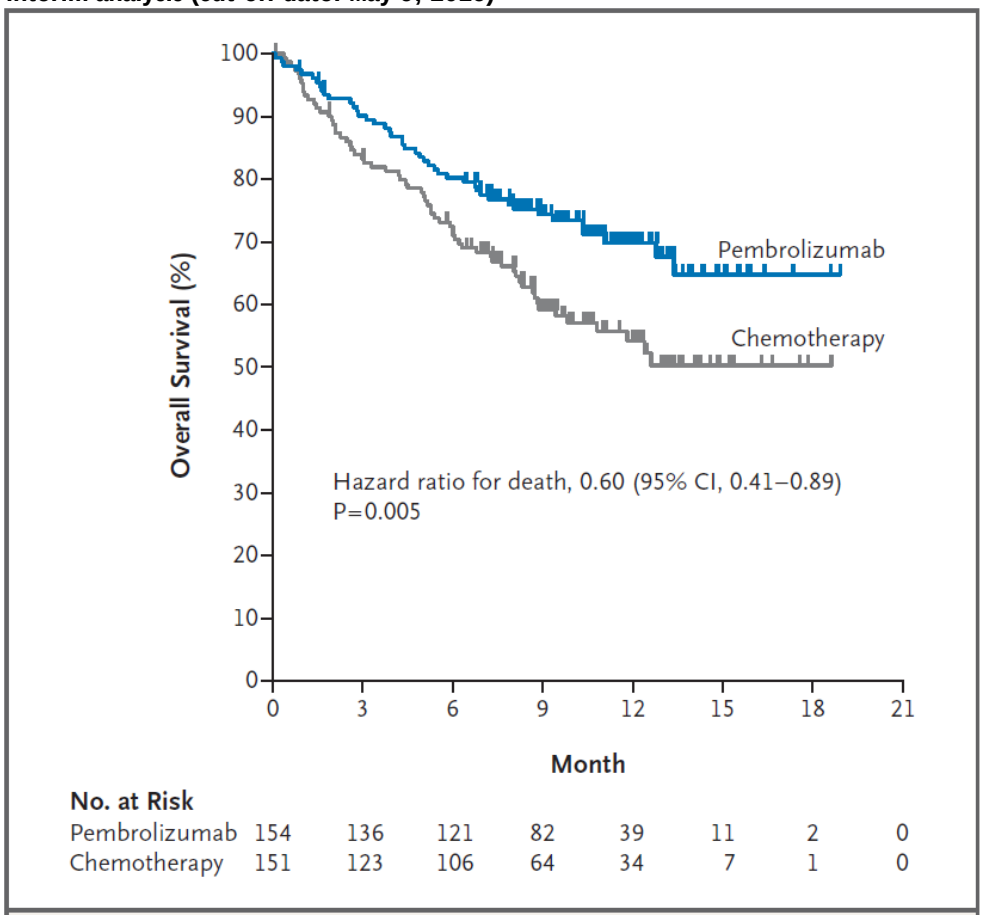
Abbreviation: CI = confidence interval; CR = complete response; HR = hazard ratio; NR = Not reached; OS = overall survival; PFS = progression-free survival; PR = partial response;

[a]HR is for Pembrolizumab versus chemotherapy, where HR < 1 favours Pembrolizumab

[b] Time to response and duration of response were evaluated in the patients who had an objective response (69 patients in the pembrolizumab group and 42 in the chemotherapy group).

[c] Duration of response was calculated with the use of the Kaplan-Meier method for censored data. Plus signs in the ranges indicate the response was ongoing at cutoff.

Figure 1: Kaplan-Meier estimates of overall survival in the KEYNOTE-024 trial at the 2nd interim analysis (cut-off date: May 9, 2016)[1]



Source: From the New England Journal of Medicine, Reck M, Rodriguez-Abreu D, Robinson AG, Hui R, Csoszi T, Fulop A, et al., pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer, 375(19),1823-33. Copyright ©2016 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

Quality of Life

EORTC QLQ-C30

Differences in the mean change from baseline on the QLQ-C30 at week 15 showed numerical improvements (i.e., less deterioration) of the Global Health Status Score in patients treated with pembrolizumab but not in the chemotherapy group (Table 10). The difference in mean change from baseline to week 15 reached statistical significance in the pembrolizumab treatment group compared to the chemotherapy group (difference in LS means = 7.82; 95% CI: 2.85, 12.79; p=0.002).[2] This difference, however, did not reach the MCID of 10 points which is perceived as clinically meaningful by patients in NSCLC trials.

Table 10: Change from Baseline for EORTC QLQ-C30 Functional Scale/Global Health Status/QoL at Week 15 (FAS Population)[2,61]

Treatment Group	Baseline		Week 15		Change from Baseline at Week 15	
	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)[a]
Pembrolizumab	145	62.24 (22.267)	109	70.95 (21.234)	150	6.94 (3.29, 10.58)
Chemotherapy	137	59.85 (22.306)	92	63.68 (20.546)	147	-0.88 (-4.78, 3.02)

Pairwise Comparison	Difference in LS Means (95% CI)	p-Value
Pembrolizumab vs. Chemotherapy	7.82 (2.85, 12.79)	0.002

EORTC QLC-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; FAS = Full Analysis Set; LS = Least squares; QoL = quality of life

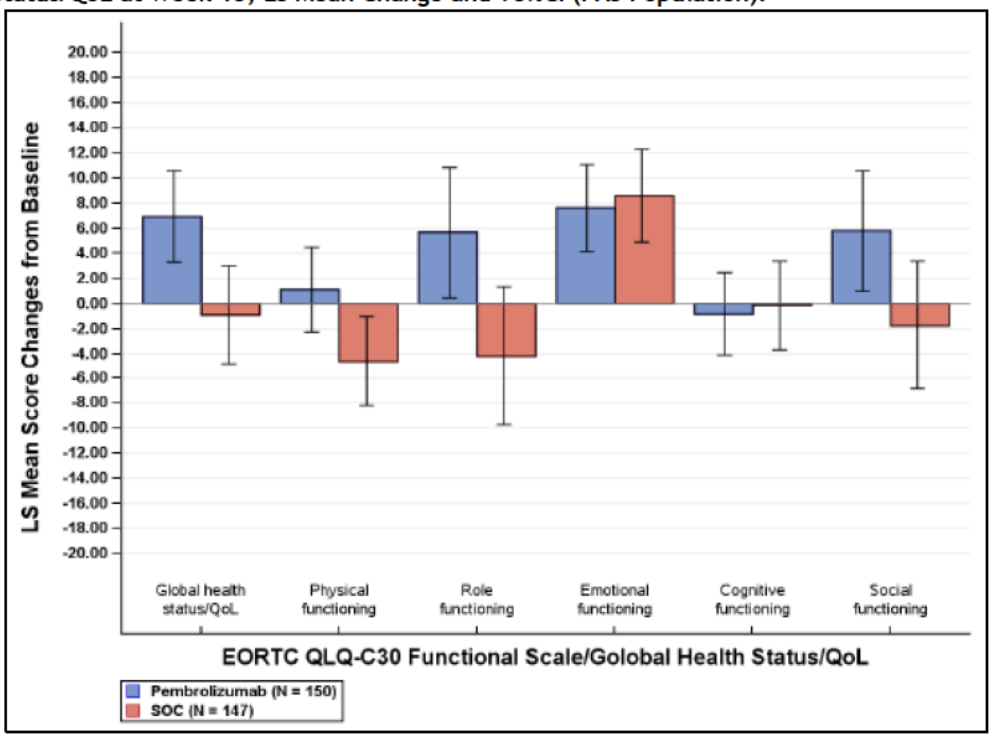
[a] Based on constrained longitudinal data analysis model with the PRO scores as the response variable, and treatment by study visit interaction, stratification factors (geographic region (East Asia vs. non-East Asia), ECOG PS (0 vs. 1) and histology (squamous vs. non-squamous)) as covariates.
For baseline and Week 15, N is the number of subjects in each treatment group with non-missing assessments at the specific time point;
For change from baseline, N is the number of subjects in the analysis population in each treatment group.

Minimal Important Difference = 10 points

Source: Single technology appraisal: pembrolizumab for untreated PD-L1 positive metastatic non-small-cell lung cancer [ID990]. NICE; 2017 [Table 26][2]

Figure 2 indicates that patients in the pembrolizumab arm had a significant improvement (i.e. 95% CI did not include zero) from baseline to Week 15 in Global Health Status/QoL, role functioning, emotional functioning, and social functioning. Patients in the chemotherapy treatment group had a significant improvement in a single EORTC functioning domain (i.e. emotional functioning); these patients also had a significant worsening in physical functioning.

Figure 2: Change from Baseline for EORTC QLQ-C30 Functional Scale/Global Health Status/QoL at Week 15, LS Mean Change and 95%CI (FAS Population).[62]



EORTC QLC-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; FAS = Full Analysis Set; QoL = quality of life

[a] For global health status quality of life score and all functional scales, a higher score denotes better HRQOL or function. N is the number of subjects, in the analysis population in each treatment group.

Source: Assessment report: Keytruda (pembrolizumab). European Medicine Agency; 2016 [Figure 16][62]

EORTC QLQ-LC13

Compared to chemotherapy, pembrolizumab increased the time-to-true deterioration (defined as the time to the first onset of a 10-point or greater score decrease from baseline) in QLQ-LC13 composite endpoint of cough (QLQ-LC13 question 1), chest pain (QLQ-LC13 question 10), and dyspnea (QLQ-LC13 Q3 to question 5). Statistical significance was achieved in favor of pembrolizumab when compared to the chemotherapy group (HR=0.66; 95% CI: 0.44, 0.97; p=0.029) (Table 11).[2]

Table 11: Time to Deterioration of EORTC QLQ-LC13 Composite Endpoint of Cough, Chest Pain, and Dyspnea (FAS Population)[2]

Treatment Group	N	Deterioration Events, n(%)	Pembrolizumab vs. Chemotherapy	
			Hazard Ratio (95% CI)[a]	p-Value[b]
Pembrolizumab	151	46 (30.5)		
Chemotherapy	148	58 (39.2)	0.66 (0.44, 0.97)	0.029

EORTC QLC-LC13 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer Module; FAS = Full Analysis Set

True deterioration was defined as the time to first onset of 10 or more decrease from baseline with confirmation under right-censoring rule (the last observation).

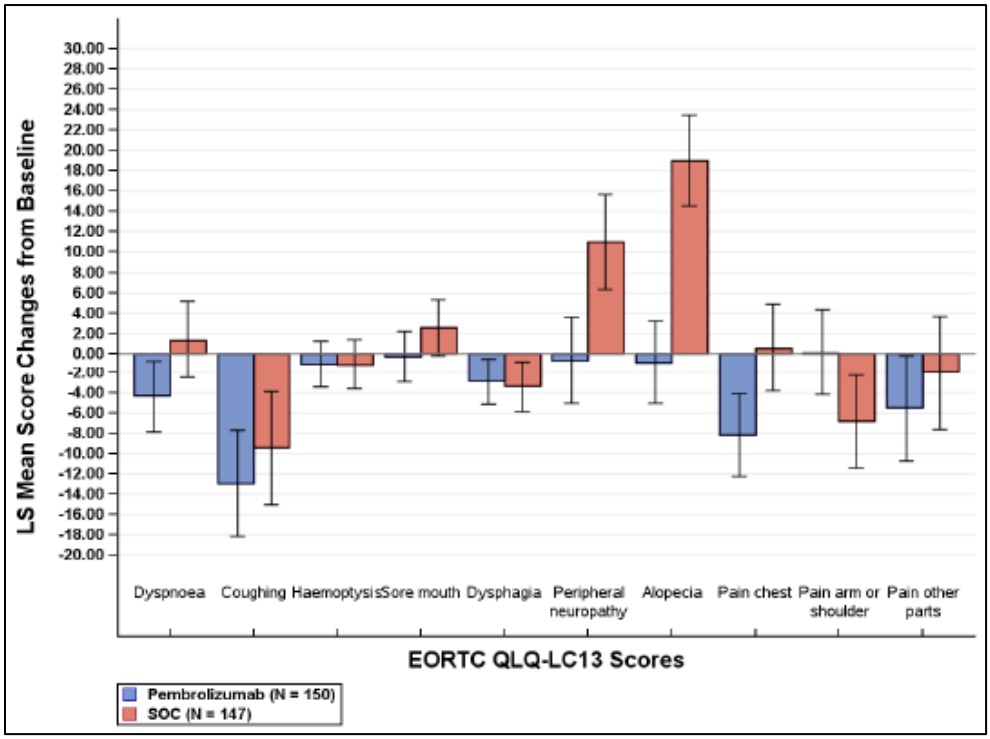
[a] Based on Cox regression model with treatment as a covariate stratified by geographic region (East Asia vs. non-East Asia), ECOG PS (0 vs. 1) and histology (squamous vs. non-squamous).

[b] Two-sided p-value based on log-rank test.

Source: Single technology appraisal: pembrolizumab for untreated PD-L1 positive metastatic non-small-cell lung cancer [ID990]. NICE; 2017 [Table 27][2]

Figure 3 indicates that patients in the pembrolizumab arm had a significant improvement from baseline to Week 15 in most EORTC symptom domains (i.e. 95% CI did not include zero). Patients in the chemotherapy treatment group had a significant improvement in a few symptom domains (coughing, dysphagia and shoulder pain) but numerical worsening in others. Peripheral neuropathy, alopecia and chest pain were significantly improved with pembrolizumab versus SOC (i.e., 95% CI did not overlap).

Figure 3: Change from Baseline for EORTC QLQ-LC13 Scores at Week 15, LS Mean Change and 95%CI (FAS Population).[62]



EORTC QLC-LC13 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer Module; FAS = Full Analysis Set

[a] For symptoms scales, a higher score denotes worse symptoms. N is the number of subjects in the analysis population in each treatment group.

Source: Assessment report: Keytruda (pembrolizumab). European Medicine Agency; 2016 [Figure 18][62]

EQ-5D

Differences in the mean change from baseline on the EQ-5D utility scores at week 15 showed numerical improvements in patients treated with pembrolizumab but not in the chemotherapy group (Table 12). The difference in mean change from baseline to week 15 reached statistical significance in the pembrolizumab treatment group compared to the chemotherapy group (difference in LS means = 0.06; 95% CI: 0.00, 0.11; p=0.036).[2] This difference met the MCID of 0.06.

EQ-5D VAS scores increased from baseline at week 15 in both treatment groups (Table 12). The increase in scores in the pembrolizumab treatment group was higher than that in the chemotherapy group; however, the difference in mean change from baseline to week 15 was not statistically significant.

Table 12: change from baseline in EQ-5D utility score (Using European Algorithm) and in visual analog scale (VAS) at week 15 (FAS Population)[2]

Treatment Group	Baseline		Week 15		Change from Baseline at Week 15	
	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)[a]
EQ-5D utility score						
Pembrolizumab	144	0.72 (0.242)	108	0.80 (0.224)	150	0.05 (0.01, 0.09)
Chemotherapy	137	0.71 (0.214)	92	0.76 (0.184)	147	-0.00 (-0.04, 0.04)
Pairwise Comparison					Difference in LS Means (95% CI)	p-Value
Pembrolizumab vs. Chemotherapy					0.06 (0.00, 0.11)	0.036
EQ-5D VAS						
Pembrolizumab	144	68.72 (21.099)	108	75.52 (17.166)	150	4.25 (0.72, 7.77)
Chemotherapy	137	69.71 (19.279)	92	72.73 (17.123)	147	0.39 (-3.33, 4.11)
Pairwise Comparison					Difference in LS Means (95% CI)	p-Value
Pembrolizumab vs. Chemotherapy					3.85 (-0.72, 8.42)	0.098

FAS = Full Analysis Set; LS = Least squares

[a] Based on constrained longitudinal data analysis model with the PRO scores as the response variable, and treatment by study visit interaction, stratification factors (geographic region (East Asia vs. non-East Asia), ECOG PS (0 vs. 1) and histology (squamous vs. non-squamous)) as covariates.
For baseline and Week 15, N is the number of subjects in each treatment group with non-missing assessments at the specific time point;
For change from baseline, N is the number of subjects in the analysis population in each treatment group.

Source: Single technology appraisal: pembrolizumab for untreated PD-L1 positive metastatic non-small-cell lung cancer [ID990]. NICE; 2017 [Tables 28 & 29][2]

Harms Outcomes

The analysis of adverse events was based on a safety population of 304 patients that included 154 patients in the pembrolizumab treatment group and 150 patients in the chemotherapy 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. Adverse event data from the KEYNOTE-024 trial are summarized in Table 13.

Compared to chemotherapy, 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 26.6% and 53.3% in the pembrolizumab, and chemotherapy treatment groups, respectively. The percentage of patients discontinuing treatment due to any grade treatment-related adverse events was also higher among patients treated with chemotherapy 10.7% compared with 7.1% of patients in the pembrolizumab treatment group.

Immune-related events of special interest occurred in 29.2% (45 of 154 patients) of patients receiving pembrolizumab versus 4.7% (7 of 150 patients) of patients in the chemotherapy group. The most frequent types of events, any grade (pembrolizumab versus chemotherapy), included hypothyroidism (9.1% versus 1.3%), hyperthyroidism (7.8% versus 1.3%), pneumonitis (5.8% versus 0.7%), infusion

reaction (4.5% versus 1.3%), severe skin reaction (3.9% versus 0%), thyroiditis (2.6% versus 0%), colitis (1.9% versus 0%), and myositis (1.9% versus 0%). Of these events, only pneumonitis, severe skin reactions, and colitis occurred at a severity of grade 3 or higher in greater than 1% of patients in the pembrolizumab treatment group. All infusion reactions were graded as 1 or 2.

The trial reported 4 deaths attributable to study treatment. There was one death (<1%) in the pembrolizumab group (sudden death of unknown cause on day 2), and 3 deaths (2%) in the chemotherapy group (one case each of pulmonary sepsis, pulmonary alveolar hemorrhage, and unknown cause).

Table 13: Adverse events in the KEYNOTE-024 trial[1]

Adverse Events in the As-Treated Population, n(%)[a]	Pembrolizumab Group (N = 154)		Chemotherapy Group (N = 150)	
	Any Grade	Grade 3-5	Any Grade	Grade 3-5
	number of patients (percent)			
Treatment-related[b]:				
Any	113 (73.4)	41 (26.6)	135 (90.0)	80 (53.3)
Serious	33 (21.4)	29 (18.8)	31 (20.7)	29 (19.3)
Led to discontinuation	11 (7.1)	8 (5.2)	16 (10.7)	9 (6.0)
Led to death	1 (0.6)	1 (0.6)	3 (2.0)	3 (2.0)
Occurred in ≥ 10% of patients in either group[c]:				
Nausea	15 (9.7)	0	65 (43.3)	3 (2.0)
Anemia	8 (5.2)	3 (1.9)	66 (44.0)	29 (19.3)
Fatigue	16 (10.4)	2 (1.3)	43 (28.7)	5 (3.3)
Decreased appetite	14 (9.1)	0	39 (26.0)	4 (2.7)
Diarrhea	22 (14.3)	6 (3.9)	20 (13.3)	2 (1.3)
Neutropenia	1 (0.6)	0	34 (22.7)	20 (13.3)
Vomiting	4 (2.6)	1 (0.6)	30 (20.0)	1 (0.7)
Pyrexia	16 (10.4)	0	8 (5.3)	0
Constipation	6 (3.9)	0	17 (11.3)	0
Stomatitis	4 (2.6)	0	18 (12.0)	2 (1.3)
Decreased neutrophil count	0	0	20 (13.3)	6(4.0)
Increased blood creatinine level	3 (1.9)	0	15 (10.0)	1 (0.7)
Decreased platelet count	0	0	18 (12.0)	9 (6.0)
Thrombocytopenia	0	0	17 (11.3)	8 (5.3)
Decreased white-cell count	1 (0.6)	0	16 (10.7)	3 (2.0)
Dysgeusia	1 (0.6)	0	15 (10.0)	0
Immune-mediated[d]:				
Any	45 (29.2)	15 (9.7)	7 (4.7)	1 (0.7)
Hypothyroidism	14 (9.1)	0	2 (1.3)	0
Hyperthyroidism	12 (7.8)	0	2(1.3)	0
Pneumonitis	9 (5.8)	4 (2.6)	1 (0.7)	1 (0.7)
Infusion reaction	7 (4.5)	0	2(1.3)	0
Severe skin reaction	6 (3.9)	6 (3.9)	0	0
Thyroiditis	4 (2.6)	0	0	0
Colitis	3 (1.9)	2 (1.3)	0	0
Myositis	3 (1.9)	0	0	0
Hypophysitis	1 (0.6)	1 (0.6)	0	0
Nephritis	1 (0.6)	1 (0.6)	0	0
Pancreatitis	1 (0.6)	1 (0.6)	0	0
Type 1 diabetes mellitus	1 (0.6)	1 (0.6)	0	0

[a] The as-treated population included all patients who received at least one dose of a trial treatment. For the patients in the chemotherapy group who crossed over to the pembrolizumab group after disease progression, only events that occurred during treatment with the assigned chemotherapy regimen are included.
[b] Events were attributed to treatment by the investigator and are listed as indicated by the investigator

on the case-report form. Although decreased neutrophil count and neutropenia may reflect the same condition, they were listed by the investigators as two distinct events; this is also the case for decreased platelet count and thrombocytopenia.
[c] Events are listed in descending order of frequency in the total population.
[d] The immune-mediated events, both those that were and those that were not attributed to study treatment by the investigator, are listed in descending order of frequency in the pembrolizumab group. In addition to specific preferred terms, related terms are also included.

Source: From the New England Journal of Medicine, Reck M, Rodriguez-Abreu D, Robinson AG, Hui R, Csoszi T, Fulop A, et al., pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer, 375(19),1823-33. Copyright ©2016 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

6.4 Ongoing Trials

Details of relevant ongoing trials are listed in Table 14. One ongoing trial with a subgroup of patients that could meet our inclusion criteria was identified in our search. The purpose of this phase III, multinational, randomized, open label study is to determine whether pembrolizumab prolongs overall survival (OS) in patients with advanced or metastatic NSCLC compared to platinum-based in patients with PD-L1 positive tumor, who have had no prior systemic therapy. [65] The study start date was October 2014 and the estimated completion date for the primary outcome measure is February 2018. As of March 2, 2017, the study is ongoing, but not recruiting participants.

Table 14: Ongoing trials of pembrolizumab for patients who had previously untreated advanced or metastatic NSCLC with PD-L1 positive tumor[65]

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
KEYNOTE-042 NCT02220894 Phase III, Multinational, Randomized, Open Label Study Study Start Date: October 2014 Status: study is ongoing, but not recruiting participants (last verified March 2, 2017) Estimated Enrollment: 1240 Estimated Study Completion Date: February 2018 Estimated Primary Completion Date: February 2018 (Final data collection date for primary outcome measure) Sponsor: Merck Sharp & Dohme Corp.	Key Inclusion Criteria: • Histologically or cytologically confirmed diagnosis of advanced or metastatic NSCLC • PD-L1 positive tumor • Measureable disease based on RECIST 1.1 • No prior systemic chemotherapy for the treatment of the participant's advanced or metastatic disease • Age ≥18 years • ECOG PS 0 or 1 • No prior malignancy Key Exclusion Criteria: • EGFR sensitizing mutation and/or EML4 gene/ALK gene fusion positive • No tumor specimen evaluable for PD-L1 expression • Squamous histology and received carboplatin in combination with paclitaxel in the adjuvant setting • The NSCLC can be treated with curative intent with either surgical resection and/or chemoradiation • Prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-cytotoxic T-lymphocyte-associated antigen-4 antibody	Intervention: pembrolizumab 200 mg intravenous (IV) on Day 1 of every 21-day cycle (every 3 weeks, or Q3W) for up to 35 treatments Comparator: Participants receive: carboplatin AUC 5 (maximum dose 750 mg) or AUC 6 (maximum dose 900 mg) + paclitaxel 200 mg/m^2 on Day 1 of every 21-day cycle (Q3W) for a maximum of 6 cycles or carboplatin AUC 5 (maximum dose 750 mg) or AUC 6 (maximum dose 900 mg) + pemetrexed 500 mg/m^2 on Day 1 Q3W for a maximum of 6 cycles participants with non-squamous histologies may go on to receive optional treatment with pemetrexed 500 mg/ m^2 on Day 1 Q3W	Primary: OS in the PD-L1 TPS ≥50% stratum and in all patients Secondary: PFS by Central Independent Radiologists' Review
ALK = anaplastic lymphoma kinase; EGFR = Epidermal growth factor receptor; EML4 = echinoderm microtubule-associated protein-like 4; IV = intravenous; NSCLC = non-small cell lung cancer; OS = overall survival; PD-L1 = programmed cell death ligand 1; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumors; TPS = tumour proportion score			

7 SUPPLEMENTAL QUESTIONS

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

1. What is the accuracy of 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. The information has not been systematically reviewed.

7.1 Accuracy, Utility and Effectiveness

7.1.1 Objective

The PAG had concerns with regard to when the PD-L1 test would be done, the turn-around time for test results and the accuracy of the test results, as well as the coordination 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 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 Findings

These same supplemental questions had been asked in a previous pCODR review of Pembrolizumab (Keytruda) for Non-small Cell Lung Cancer.[66] 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. An updated literature search was undertaken on January 19, 2017 in order to identify any new literature available.

In the previous review, 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.

In the updated literature search, no new reports 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. Also no relevant studies were identified regarding the

clinical utility of PD-L1 testing. Two studies (Roach 2016.[67] and Hirsch2016[68]) were identified regarding the accuracy of diagnostic antibody assays whose findings will be summarized below.

Roach et al[67] presented the analytical and clinical validation for Dako PD-L1 immunohistochemistry (IHC) 22C3 pharmDx assay. Repeatability and reproducibility for PD-L1 IHC 22C3 pharmDx were conducted within Dako and across 3 external Clinical Laboratory Improvement Amendments. Sixteen NSCLC tissues were used for Dako's internal analytical precision studies. Of those, 4 tissues (25%) were chosen to be in the PD-L1 expression range of 40% to 60% TPS. Six instruments, 6 operators, 6 non-consecutive days, 3 lots of reagents, and 6 replicates (intrarun repeatability) were used for the studies as part of the analytical validation conducted at Dako.[67]

A clinically relevant cut off of 50% TPS was used in order to assess the stained tissues for their concordance in positivity and negativity of PD-L1 expression. A TPS <50% was considered as diagnostically negative, and a TPS of ≥50% was considered as diagnostically positive.[67]

Average percent positive agreement (APA), average percent negative agreement (ANA), and overall percent agreement (OA) were calculated for intra-site and inter-site, and intra-observer and inter-observer reproducibility, using 2-sided 95% percentile bootstrap CI. The CIs were calculated by resampling on specimen IHC status; bootstrap samples were produced by separately resampling positive and negative specimens with replacement. Acceptance criteria were defined as: APA, ANA, and OA of at least 85% at the lower bound of a 2-sided 95% percentile bootstrap CI. The Wilson Score method was used to calculate CIs for the positive agreement (PPA), negative agreement (NPA), and OA.[67]

NPA, PPA, and OA of 100% were achieved for all these studies. When the PD-L1 IHC 22C3 pharmDx assay reproducibility was tested at different external laboratories (sites), the concordance was slightly lower with an ANA of 90.8%, APA of 85.8%, and OA of 88.8%. This is to be expected since additional variables were added to the testing. Efforts were made to balance the number of positive specimens and negative specimens for the external reproducibility study. However, the final data showed that the study pathologists identified 21 diagnostic negative specimens and 15 diagnostic positive specimens, which contributed to the wider CI for APA (77% at 95% CI lower bound).

The Dako analytical validation consisted of inter-instrument, inter-operator, inter-day, and inter-lot, and intraday and intra-run variations. A 100% agreement was achieved for all 3 agreement endpoints (NPA, PPA, and OA) for inter-instrument, inter-operator, inter-day, and inter-lot, and intra-day and intra-run, demonstrating high repeatability (Table 15).[67]

Table 15: Agreements and 95% Confidence Intervals (CIs) of PD-L1 IHC 22C3 Precision Studies Performed at Dako[67]

Internal Repeatability	% Agreement (95% CI)
Interinstrument	
NPA	100% (92.9%-100%)
PPA	100% (88.6%-100%)
OA	100% (95.4%-100%)
Interoperator	
NPA	100% (92.7%-100%)
PPA	100% (88.6%-100%)
OA	100% (95.4%-100%)
Interday	
NPA	100% (92.9%-100%)
PPA	100% (88.6%-100%)

Internal Repeatability	% Agreement (95% CI)
OA	100% (95.4%-100%)
Interlot	
NPA	100% (92.6%-100%)
PPA	100% (92.6%-100%)
OA	100% (96.2%-100%)
Intraday	
NPA	100% (88.3%-100%)
PPA	100% (82.4%-100%)
OA	100% (92.4%-100%)
Intrarun	
NPA	100% (92.9%-100%)
PPA	100% (88.6%-100%)
OA	100% (95.4%-100%)
NPA = negative agreement; PPA = positive agreement; OA =overall percent agreement.	

Source: Roach C, et al. Development of a companion diagnostic PD-L1 immunohistochemistry assay for pembrolizumab therapy in non-small-cell lung cancer. Appl Immunohistochem Molecul Morphol. 2016 Jul;24(6):392-7. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4957959

The PD-L1 IHC 22C3 pharmDx assay reproducibility was tested at different external laboratories using inter-site reproducibility, intra-site reproducibility, inter-observer, and intra-observer. Inter-site reproducibility was conducted at 3 external testing laboratories located in the United States and Europe, with each laboratory performed automated staining runs on each of 5 non-consecutive days. Staining results were evaluated using TPS with a 50% cut off by 1 observer at each of the 3 testing laboratories. Statistical analysis was done using a percentile bootstrap method. The following agreements were attained: APA achieved 85.2% with a lower bound of 75.6%, ANA achieved 90.3% with a lower bound of 84.4%, and and OA achieved 88.3% with a lower bound of 81.4%. Intra-site reproducibility was evaluated by testing concordance within each site, across the 5 days. Analysis results yielded APA of 87.6% with a lower bound of 82.5%, ANA of 91.9% with a lower bound of 88.8%, and OA of 90.2% with a lower bound of 86.3%. Statistical analysis for the observer study was done using a percentile bootstrap method in a similar manner to the inter-site study. Analysis results for inter-observer yielded APA of 92.8% with a lower bound of 88.1%, ANA resulted in 92.6% with a lower bound of 87.8%, and OA resulted in 92.7% with a lower bound of 88.1%. Intra-observer performance criteria for APA resulted in 96.5% with a lower bound of 94.3%, ANA resulted in 96.4% with a lower bound of 94.0%, and OA resulted in 96.4% with a lower bound of 94.3% (Table 16).[67]

Table 16: Agreements and 95% Confidence Intervals (CIs) of PD-L1 IHC 22C3 External Reproducibility Performed at 3 Sites[67]

	Intersite	Intrasite	Interobserver	Intraobserver
Total pair-wise comparisons	2700	1080	1674	558
Concordant pair-wise comparisons: negative/positive	1477/907	601/373	761/791	264/274
Discordant pair-wise comparisons	316	106	122	20
ANA (95% CI)	90.3% (84.4%-95.2%)	91.9% (88.8%-94.8%)	92.6% (87.8%-96.7%)	96.4% (94.0%-98.5%)
APA (95% CI)	85.2% (75.6%-92.9%)	87.6% (82.5%-92.2%)	92.8% (88.1%-96.8%)	96.5% (94.3%-98.6%)
OA (95% CI)	88.3% (81.4%-94.3%)	90.2% (86.3%-93.7%)	92.7% (88.1%-96.8%)	96.4% (94.3%-98.6%)
ANA = average percent negative agreement; APA = average percent positive agreement; OA = overall percent agreement				

Hirsch et al.[68] reported the results of phase 1 of the Blueprint PD-L1 IHC Assay Comparison Project. The Blueprint PD-L1 IHC Assay Comparison Project was founded in order to enable a better understanding of similarities and differences between four PD-L1 IHC systems, with a key focus of the project was an assessment of the analytical similarities and differences between the PD-L1 systems to better understand their technical performance, where a comparison of the analytical staining factors reported as percentages of stained cells, as well as selected treatment-determining scoring algorithms developed for each assay and used in clinical trials. However, the results of phase 1 cannot determine whether any of the assays are more specific and/or sensitive or better or worse for treatment decision making.[68] Each of the four PD-L1 IHC assay that were compared was developed with a unique primary antibody against PD-L1, namely, 28-8 (Dako) with nivolumab, 22C3 (Dako) with pembrolizumab, SP263 (Ventana) with durvalumab, and SP142 (Ventana) with atezolizumab. The clinical scoring approaches for each of these diagnostic assays used to classify patients for treatment on the basis of tumoral PD-L1 expression utilize a measure of PD-L1 expression on tumor cell (TC) membranes.[68] the results of phase 1 of the Blueprint PD-L1 IHC Assay Comparison Project reported by Hirsch et al.[68] were a feasibility assessment that included 39 NSCLC samples stained with all four investigational assays.

Dako and Ventana independently stained each of the 39 cases using their respective PD-L1 IHC assay platforms. Three pathologists independently evaluated all 156 immunostained slides from the 39 cases, making a total of 468 observations of raw percentages of cells expressing PD-L1. The pathologists were not blinded to the specific assay. Tumor cell (TC) staining and immune cells (IC) staining were assessed, where TC staining was defined as an estimate of the percentage of TCs exhibiting partial or complete membranous staining and IC staining was defined as an estimate of the percentage of ICs, including macrophages and lymphocytes within the tumor, exhibiting staining. A semi-quantitative scoring system was used to calculate the percentage of TCs exhibiting membrane staining (tumor proportion score [TPS]), and the percentage of ICs stained.[68]

Thirty eight cases were included in the comparison of the scoring algorithm and pre-specified cut off. The 152 slides from the 38 samples were randomized and blinded to specific PD-L1 IHC assay, and each stained sample was evaluated by the three pathologists independently according to the preselected cut off chosen for each assay (1% TC staining for the 28-8 and 22C3 assays, 25% TC staining for the SP 263 assay, and 1% TC staining and/or 1% tumor area infiltrated by PD-L1–positive ICs (TC1/IC1) for the SP142 assay). Each pathologist scored all 152 slides by using only the scoring algorithm(s) with which they had greatest expertise (i.e. pathologist 1 scored all 152 slides, applying the 22C3 and 28-8 algorithms; pathologist 2 scored using the SP142 algorithm; and pathologist 3 scored according to the SP263 algorithm).[68]

TC staining by 22C3, 28-8, and SP263 showed a range of intensities and partial or full circumferential membrane staining. Staining by 22C3, 28-8, and SP263 assays showed relative staining equivalency in TCs. In most cases, SP142 showed weaker staining of TC membranes and fewer positive TCs compared with the other three assays. The 22C3, 28-8, and SP263 assays demonstrated a high correlation for numbers of stained TCs, with minimal inter-assay variability was shown in 22C3 versus 28-8. All comparisons that include SP142 showed lower correlation between assays and more variability between assessments, indicating lower levels of positive TCs when stained with SP142.[68]

Results from Hirsch et al.[68] indicate that there are both similarities and differences with respect to the four PD-L1 systems in terms of dynamic ranges, cell types stained, and overall staining characteristics. Three of the four assays (28-8, 22C3, and SP263) were similar in analytical staining performance assessed by percentage of tumor cells showing cell membrane staining. The SP142 assay generally stained fewer TCs. When pathologists applied the selected

algorithm and/or cutoff appropriate for each assay to determine the PD-L1 expression status of each case slightly more than one-third of cases (36.9%) varied in classification above or below the assay-associated cutoff, 13.1% were unanimously below all of the selected cut offs, and 50% of cases were above the respective pre-specified threshold for each assay. These differences observed were likely due to the variation in definition of cut off.

Separate analyses were conducted by interchanging various cut offs on each set of slides stained by the four different assays and then comparing the overall agreement for each combination with the index scores derived according to the assay and cut off combination selected and specified. For example, the assessment by pathologist 1 using the 28-8 algorithm on the SP142-, SP263-, and 22C3-stained slides was used to determine what proportion of cases would differ when compared with the cut off that was developed for the 28-8 assay.[68] Table 17 shows how the overall percentage of agreement changed for the 38 cases when, for each particular staining assay, each of the four cut offs for each individual assay was applied. In each comparison, the cutoff was held constant and the assay is interchanged. The reference standard for each comparison was the validated cut off and assay combination. In all situations, replacement of the validated cutoff for each assay with any other cut off reduced the overall agreement compared with the reference standard. The 22C3 and SP263 assays, the PD-L1 based classification of cases against all three alternate thresholds agreed in more than 85% of cases when compared with the classification according to the reference assay algorithm. The agreement with the reference assay results is similar (>85%) for the 28-8 assay when classified by either 1% or 25% TPS; however, when the 28-8 assay was assessed according to the SP142 TC1/IC1 algorithm, slightly fewer cases (81.6%) were concordantly classified against the reference SP142 assay (Table 17).[68]

Table 17: Assay Comparison: Overall Percentage of Agreement in Patient Classification When Staining Assays Are "Mismatched" with the Clinical Cut Off[68]

Assay Clone Used for Slide Staining	Scoring Algorithm							
	22C3	1% TPS	28-8	1% TPS	SP142	TC1/IC1	SP263	25% TPS
22C3	38 of 38	(100%)	36 of 38	(94.7%)	33 of 38	(86.8%)	34 of 38	(89.5%)
28-8	36 of 38	(94.7%)	38 of 38	(100%)	31 of 38	(81.6%)	33 of 38	(86.8%)
SP142	24 of 38	(63.2%)	24 of 38	(63.2%)	38 of 38	(100%)	25 of 38	(65.8%)
SP263	34 of 38	(89.5%)	34 of 38	(89.5%)	33 of 38	(86.8%)	38 of 38	(100%)
TPS = tumor proportion score								

Source: Source: Reprinted from Journal Thoracic Oncology, 12(2), Hirsch FR, McElhinny A, Stanforth D, Ranger-Moore J, Jansson M, Kulangara K, et al, PD-L1 Immunohistochemistry Assays for Lung Cancer: Results from Phase 1 of the "Blueprint PD-L1 IHC Assay Comparison Project", 208-222, Copyright 2016, with permission from Elsevier.

7.1.3 Summary

The limited literature search did not identify any evidence to inform on 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, 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. Two reports, were identified that addressed

the accuracy of available diagnostic antibody assays, one of the reports demonstrated that the Dako PD-L1 IHC 22C3 assay is a sensitive, specific, precise, and robust assay, which provides high value clinical utility to identify patients who will benefit from treatment with pembrolizumab. While the report on the Blueprint PD-L1 IHC Assay Comparison Project indicated that three PD-L1 IHC assays (22C3, 28-8, and SP263) were aligned with regard to PD-L1 expression on TCs, whereas one assay (SP142) consistently had fewer TCs expressing PD-L1. All the assays demonstrated IC staining, but with greater variance than expression on TCs. By comparing assays and cut offs, the study indicated that interchanging assays and cut offs could lead to "misclassification" of PD-L1 status for some patients. A main limitation for this study was based on a small number of cases using expert observers on single assays. Another limitation is that the sample was chosen to represent the range of levels of PD-L1 expression, rather than a representative cohort.

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 the treatment of melanoma with pembrolizumab. As a result, details of the phase 1 KEYNOTE 001 trial evaluating pembrolizumab [52] are summarized below (only results for previously untreated patients will be summarized).

KEYNOTE 001 was a multicenter,[52] 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. [52]

The results below describe the previously untreated patients enrolled in KEYNOTE 001.

A total of 101 treatment-naive patients with advanced NSCLC from 8 countries were enrolled between March 1, 2013 and March 26, 2014. These patients were randomly assigned to receive pembrolizumab 2 mg/kg Q3W (n = 6), 10 mg/kg Q3W (n = 49), or 10 mg/kg Q2W (n = 46).[2]

The characteristics of the included patients were noted to be typical of patients with advanced/metastatic NSCLC. A majority of patients had non-squamous NSCLC (79%) versus squamous NSCLC histology (19%). The median age of patients was 68.0 years, 59% of patients were male, and 56% of patients had an ECOG performance status of 1. Most patients were former or current smokers (89%).[2] Of the 91 patients who were evaluable for PD-L1 expression by the clinical trial assay, 27 (29.7%) had Tumour Proportion Score (TPS) ≥50%, 52 (57.1%) had PS 1%–49%, and 12 (13.2%) had PS <1%.[69]

At the time of data cut-off (September 18, 2015), the median follow-up duration was 22.2 months (range, 17.8-30.5). As of this date, 13 (13%) patients were still receiving pembrolizumab, and 36 (35.6%) patients were alive without new anticancer therapy. The results presented focus on the results in the All Subjects as Treated dataset defined as patients who received at least one dose of study treatment.[2]

Median PFS was 6.2 months (95% CI, 4.1–8.6) in the overall population, with a 12-month PFS rate of 35%. Median PFS was 12.5 months (95% CI, 6.2–not reached), 4.2 months (95% CI, 3.1– 6.4), and 3.5 months (95% CI, 2.1–19.0) in patients with ≥50%, 1%–49%, and <1% staining, respectively.[2] Among patients with TPS ≥50%, 12-month PFS rate was 54%, while in patients with TPS 1%–49%, and <1%, it was 25% (Table 18).[2]

Median OS was 22.1 months in the overall population (95% CI, 17.1–27.2 months). In the TPS ≥50% group, median OS was not reached (95% CI, 22.1 months to not reached), 12-month OS, 18-month OS, and 24-month OS were 85%, 73%, and 61%, respectively. In the

TPS 1%-49% group, median OS was 19.5 (95% CI, 10.7 to 22.2 months), 12-month OS, 18-month OS, and 24-month OS were 65%, 50%, and 32%, respectively. In the TPS <1% group, median OS was 14.7 (95% CI, 3.4 months to not reached), 12-month OS, 18-month OS, and 24-month OS were 50%, 50%, and 38%, respectively (Table 18).[2]

Table 18: Key efficacy outcomes in the KEYNOTE 001 in patients who were previously untreated advanced or metastatic NSCLC and received pembrolizumab by PD-L1 expression level.[2]

	Overall N = 101	PD-L1 TPS ≥50% n = 27	PD-L1 TPS 1%-49% n = 52	PD-L1 TPS <1% n = 12
PFS				
PFS, median (95%CI), months	6.2 (4.1 to 8.6)	12.5 (6.2 to NR)	4.2 (3.1 to 6.4)	3.5 (2.1. to 19.0)
12-month PFS, %	35	54	25	25
OS				
OS, median (95%CI), months	22.1 (17.1-27 2)	NR (22.1 to NR)	19.5 (10.7 to 22.2)	14.7 (3.4 to NR)
12-month OS, %	71	85	65	50
18-month OS, %	58	73	50	50
24-month OS, %	44	61	32	38

Source: Single technology appraisal: pembrolizumab for untreated PD-L1 positive metastatic non-small-cell lung cancer [ID990]. NICE; 2017 [Figure 23 and 24][2]

The results from KEYNOTE 001 in previously untreated patients provided supportive evidence on the longer term clinical benefit of pembrolizumab in patients with advanced NSCLC whose tumours strongly express PD-L1, where PFS and OS results were much higher in the subgroup of patients with PD-L1 TPS ≥50%, than those in the subgroups of patients with PD-L1 TPS 1%-49% and PD-L1 TPS <1%. However, there are some limitations in these results. Of the 101 patients with untreated stage IV NSCLC with PD-L1 positive tumours enrolled, only 27 (26.7%) had a TPS ≥50% and are, therefore, of relevance to the patient population reviewed in this report. Also none of the three doses of pembrolizumab administered in KEYNOTE 001, i.e., 2mg/kg Q3W, 10mg/kg Q3W or 10mg/kg Q2W match the 200mg Q3W dose that was used in the KEYNOTE-024 study and which is likely to receive marketing authorization pembrolizumab.

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

APPENDIX A: LITERATURE SEARCH STRATEGY

See Appendix B for more details on literature search methods.

1. Literature search via OVID platform

Database(s): EBM Reviews - Cochrane Central Register of Controlled Trials November 2016, Embase 1974 to 2016 December 19, Epub Ahead of Print, 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.	3204
2	Carcinoma, Non-Small-Cell Lung/	46129
3	NSCLC.ti,ab,kf.	84856
4	(exp Adenocarcinoma/ or Carcinoma, Large Cell/ or exp Carcinoma, Squamous Cell/ or Carcinoma, Adenosquamous/ or Carcinoma/) and (lung* or pulmonary or bronchial).ti,ab,kf.	97774
5	((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.	167370
6	or/2-5	239219
7	1 and 6	629
8	7 use ppez,cctr	169
9	*pembrolizumab/	704

10	(pembrolizumab* or lambrolizumab* or keytruda* or MK-3475 or MK3475 or Merck3475 or Merck-3475 or Sch-900475 or Sch900475).ti,ab,kw.	1759
11	or/9-10	1821
12	exp Non small cell lung cancer/	92388
13	NSCLC.ti,ab,kw.	85751
14	(exp Adenocarcinoma/ or Large cell carcinoma/ or exp Squamous cell carcinoma/ or Carcinoma/) and (lung* or pulmonary or bronchial).ti,ab,kw.	97627
15	((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.	168543
16	or/12-15	256319
17	11 and 16	503
18	17 use oemezd	341
19	8 or 18	510
20	limit 19 to english language	496
21	remove duplicates from 20	391

2. Literature search via PubMed

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

Search	Query	Items found
#9	Search **#7 AND #8**	23
#8	Search **publisher[sb] OR 2016/12/16:2016/12/20[edat]**	529773
#7	Search **#1 AND #6**	144

Search	Query	Items found
#6	Search **#2 OR #3 OR #4 OR #5**	105287
#5	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 tumors[tiab] OR tumour*[tiab] OR malignan*[tiab]) AND (lung*[tiab] OR pulmonary[tiab] OR bronchial[tiab])**	63371
#4	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])**	49077
#3	Search **NSCLC[tiab]**	29049
#2	Search **Carcinoma, Non-Small-Cell Lung[mh]**	39058
#1	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]**	589

3. **Cochrane Central Register of Controlled Trials (Central)**
   Searched via Ovid
4. **Grey Literature search via:**

Clinical trial registries:

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

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

Search: Keytruda/pembrolizumab, non-small cell lung cancer

Select international agencies including:

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

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

Search: Keytruda/pembrolizumab, non-small cell lung cancer

Conference abstracts:

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

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

Search: Keytruda/pembrolizumab, non-small cell lung cancer

APPENDIX B: DETAILED METHODOLOGY OF LITERATURE REVIEW

Literature Search Methods

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

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-) with epub ahead of print, in-process records & daily updates via Ovid; Embase (1974 -) via Ovid; The Cochrane Central Register of Controlled Trials (12 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 Keytruda (pembrolizumab) and non-small cell lung cancer.

No filters were applied to limit the 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 June 30, 2017.

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

Study Selection

One member of the pCODR Methods Team selected studies for inclusion in the review according to the predetermined protocol. All articles considered potentially relevant were acquired from library sources. 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. The SIGN-50 Checklist used in this review is included in Table 7 below.

Table 7: SIGN checklist for controlled trials

SECTION 1: INTERNAL VALIDITY		
In a well conducted RCT study…		Does this study do it?
1.1	The study addresses an appropriate and clearly focused question.	
1.2	The assignment of subjects to treatment groups is randomised.	
1.3	*An adequate concealment method is used.*	
1.4	The design keeps subjects and investigators 'blind' about treatment allocation.	
1.5	The treatment and control groups are similar at the start of the trial.	
1.6	The only difference between groups is the treatment under investigation.	
1.7	All relevant outcomes are measured in a standard, valid and reliable way.	
1.8	What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?	
1.9	*All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention to treat analysis).*	
1.1	Where the study is carried out at more than one site, results are comparable for all sites.	
SECTION 2: OVERALL ASSESSMENT OF THE STUDY		
2.1	6.4.1.1 How well was the study done to minimise bias?	
2.2	6.4.1.2 Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, are you certain that the overall effect is due to the study intervention?	
2.3	6.4.1.3 Are the results of this study directly applicable to the patient group targeted by this guideline?	
2.4	Notes:	

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.

REFERENCES

1. Reck M, Rodriguez-Abreu D, Robinson AG, Hui R, Csoszi T, Fulop A, et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. N Engl J Med. 2016;375(19):1823-33.

2. Single technology appraisal: pembrolizumab for untreated PD-L1 positive metastatic non-small-cell lung cancer [ID990].Committee papers. London: National Institute for Health and Care Excellence; 2017.

3. Canadian Cancer Society's Advisory committee on Cancer Statistics. Canadian cancer statistics 2015 [Internet]. Toronto: Canadian Cancer Society; 2015. [cited 2017 Jan 21]. Available from: https://www.cancer.ca/~/media/cancer.ca/CW/cancer%20information/cancer%20101/Canadian%20cancer%20statistics/Canadian-Cancer-Statistics-2015-EN.pdf

4. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin. 2011 Mar;61(2):69-90.

5. Studies found for: lung cancer and immunotherapy. 2015 [cited 2017 Jan 21]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine; 2000 - . Available from: https://clinicaltrials.gov/ct2/results?term=lung+cancer+and+immunotherapy&type=&rslt=&recr=&age_v=&gndr=&cond=&intr=&titles=&outc=&spons=&lead=&id=&state1=&cntry1=&state2=&cntry2=&state3=&cntry3=&locn=&rcv_s=&rcv_e=&lup_s=&lup_e=.

6. Thomas A, Chen Y, Yu T, Jakopovic M, Giaccone G. Trends and characteristics of young non-small cell lung cancer patients in the United States. Front Oncol [Internet]. 2015 [cited 2017 Jul 13];5:113. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4443720

7. Weiss J, Stinchcombe TE. Treatment of elderly patients with stage IV non-small-cell lung cancer. Expert Rev Anticancer Ther. 2012 Jan;12(1):111-20.

8. Malvezzi M, Bertuccio P, Rosso T, Rota M, Levi F, La VC, et al. European cancer mortality predictions for the year 2015: does lung cancer have the highest death rate in EU women? Ann Oncol. 2015 Apr;26(4):779-86.

9. Jemal A, Ma J, Rosenberg PS, Siegel R, Anderson WF. Increasing lung cancer death rates among young women in southern and midwestern States. J Clin Oncol [Internet]. 2012 Aug 1 [cited 2017 Jul 13];30(22):2739-44. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3402885

10. International Agency for Research on Cancer [Internet]. Lyon (FR): International Agency for Research on Cancer. 2017 [cited 2017 Feb 21]. Available from: https://www.iarc.fr/

11. Starif K, Cohen A, Samet J, editors. Air pollution and cancer [Internet]. Lyon (FR): International Agency for Research on Cancer; 2013. [cited 2017 Jan 31]. (no. 161). Available from: https://www.iarc.fr/en/publications/books/sp161/AirPollutionandCancer161.pdf

12. Hung RJ, McKay JD, Gaborieau V, Boffetta P, Hashibe M, Zaridze D, et al. A susceptibility locus for lung cancer maps to nicotinic acetylcholine receptor subunit genes on 15q25. Nature. 2008 Apr 3;452(7187):633-7.

13. Wang Y, Broderick P, Webb E, Wu X, Vijayakrishnan J, Matakidou A, et al. Common 5p15.33 and 6p21.33 variants influence lung cancer risk. Nat Genet [Internet]. 2008 Dec [cited 2017 Jul 13];40(12):1407-9. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2695928

14. Youlden DR, Cramb SM, Baade PD. The International Epidemiology of Lung Cancer: geographical distribution and secular trends. J Thorac Oncol. 2008 Aug;3(8):819-31.

15. Rajeswaran A, Trojan A, Burnand B, Giannelli M. Efficacy and side effects of cisplatin- and carboplatin-based doublet chemotherapeutic regimens versus non-platinum-based doublet chemotherapeutic regimens as first line treatment of metastatic non-small cell lung carcinoma: a systematic review of randomized controlled trials. Lung Cancer. 2008 Jan;59(1):1-11.

16. Ardizzoni A, Boni L, Tiseo M, Fossella FV, Schiller JH, Paesmans M, et al. Cisplatin- versus carboplatin-based chemotherapy in first-line treatment of advanced non-small-cell lung cancer: an individual patient data meta-analysis. J Natl Cancer Inst. 2007 Jun 6;99(11):847-57.

17. Delbaldo C, Michiels S, Syz N, Soria JC, Le CT, Pignon JP. Benefits of adding a drug to a single-agent or a 2-agent chemotherapy regimen in advanced non-small-cell lung cancer: a meta-analysis. JAMA. 2004 Jul 28;292(4):470-84.

18. NSCLC Meta-Analyses Collaborative Group. Chemotherapy in addition to supportive care improves survival in advanced non-small-cell lung cancer: a systematic review and meta-analysis of individual patient data from 16 randomized controlled trials. J Clin Oncol [Internet]. 2008 Oct 1 [cited 2017 Jul 13];26(28):4617-25. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2653127

19. Fossella F, Pereira JR, von PJ, Pluzanska A, Gorbounova V, Kaukel E, et al. Randomized, multinational, phase III study of docetaxel plus platinum combinations versus vinorelbine plus cisplatin for advanced non-small-cell lung cancer: the TAX 326 study group. J Clin Oncol. 2003 Aug 15;21(16):3016-24.

20. Schiller JH, Harrington D, Belani CP, Langer C, Sandler A, Krook J, et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. N Engl J Med. 2002 Jan 10;346(2):92-8.

21. Scagliotti GV, Parikh P, von PJ, Biesma B, Vansteenkiste J, Manegold C, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. J Clin Oncol. 2008 Jul 20;26(21):3543-51.

22. Maus MK, Mack PC, Astrow SH, Stephens CL, Zeger GD, Grimminger PP, et al. Histology-related associations of ERCC1, RRM1, and TS biomarkers in patients with non-small-cell lung cancer: implications for therapy. J Thorac Oncol. 2013 May;8(5):582-6.

23. Soria JC, Cobo EFM, Lu S, Syrigos KN, Lee KH, Goker E, et al. Afatinib (A) vs erlotinib (E) as second-line therapy of patients (pts) with advanced squamous cell carcinoma (SCC) of the lung following platinum-based chemotherapy: overall survival (OS) analysis from the global phase III trial LUX-Lung 8 (LL8). J Clin Oncol. 2015;33(15 Suppl 1). (Presented at ASCO Annual Meeting; May 29 - Jun 2, 2015; Chicago, IL).

24. Paz-Ares L, de MF, Dediu M, Thomas M, Pujol JL, Bidoli P, et al. Maintenance therapy with pemetrexed plus best supportive care versus placebo plus best supportive care after induction therapy with pemetrexed plus cisplatin for advanced non-squamous non-small-cell lung cancer (PARAMOUNT): a double-blind, phase 3, randomised controlled trial. Lancet Oncol. 2012 Mar;13(3):247-55.

25. Cappuzzo F, Ciuleanu T, Stelmakh L, Cicenas S, Szczesna A, Juhasz E, et al. Erlotinib as maintenance treatment in advanced non-small-cell lung cancer: a multicentre, randomised, placebo-controlled phase 3 study. Lancet Oncol. 2010 Jun;11(6):521-9.

26. Reck M, von PJ, Zatloukal P, Ramlau R, Gorbounova V, Hirsh V, et al. Overall survival with cisplatin-gemcitabine and bevacizumab or placebo as first-line therapy for nonsquamous non-small-cell lung cancer: results from a randomised phase III trial (AVAiL). Ann Oncol [Internet]. 2010 Sep [cited 2017 Jul 13];21(9):1804-9. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2924992

27. Herbst RS, Lynch TJ, Sandler AB. Beyond doublet chemotherapy for advanced non-small-cell lung cancer: combination of targeted agents with first-line chemotherapy. Clin Lung Cancer. 2009 Jan;10(1):20-7.

28. Zinner RG, Obasaju CK, Spigel DR, Weaver RW, Beck JT, Waterhouse DM, et al. PRONOUNCE: randomized, open-label, phase III study of first-line pemetrexed + carboplatin followed by maintenance pemetrexed versus paclitaxel + carboplatin + bevacizumab followed by maintenance bevacizumab in patients ith advanced nonsquamous non-small-cell lung cancer. J Thorac Oncol [Internet]. 2015 Jan [cited 2017 Jul 13];10(1):134-42. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4276572

29. Soria JC, Mauguen A, Reck M, Sandler AB, Saijo N, Johnson DH, et al. Systematic review and meta-analysis of randomised, phase II/III trials adding bevacizumab to platinum-based chemotherapy as first-line treatment in patients with advanced non-small-cell lung cancer. Ann Oncol. 2013 Jan;24(1):20-30.

30. Kwak EL, Bang YJ, Camidge DR, Shaw AT, Solomon B, Maki RG, et al. Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. N Engl J Med [Internet]. 2010 Oct 28 [cited 2017 Jul 13];363(18):1693-703. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3014291

31. Vincent MD, Kuruvilla MS, Leighl NB, Kamel-Reid S. Biomarkers that currently affect clinical practice: EGFR, ALK, MET, KRAS. Curr Oncol [Internet]. 2012 Jun [cited 2017 Jul 13];19(Suppl 1):S33-S44. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3377752

32. Lee CK, Brown C, Gralla RJ, Hirsh V, Thongprasert S, Tsai CM, et al. Impact of EGFR inhibitor in non-small cell lung cancer on progression-free and overall survival: a meta-analysis. J Natl Cancer Inst. 2013 May 1;105(9):595-605.

33. Yang JC, Wu YL, Schuler M, Sebastian M, Popat S, Yamamoto N, et al. Afatinib versus cisplatin-based chemotherapy for EGFR mutation-positive lung adenocarcinoma (LUX-Lung 3 and LUX-Lung 6): analysis of overall survival data from two randomised, phase 3 trials. Lancet Oncol. 2015 Feb;16(2):141-51.

34. Shaw AT, Kim DW, Nakagawa K, Seto T, Crino L, Ahn MJ, et al. Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. N Engl J Med. 2013 Jun 20;368(25):2385-94.

35. Solomon BJ, Mok T, Kim DW, Wu YL, Nakagawa K, Mekhail T, et al. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. N Engl J Med. 2014 Dec 4;371(23):2167-77.

36. Kim DW, Mehra R, Tan DSW, Felip E, Chow LQM, Camidge DR, et al. Ceritinib in advanced anaplastic lymphoma kinase (ALK)-rearranged (ALK+) non-small cell lung cancer (NSCLC): Results of the ASCEND-1 trial [abstract]. J Clin Oncol. 2014;32(15 Suppl 1). (Presented at ASCO Annual Meeting; May 30 - Jun 3, 2015; Chicago, IL).

37. Mok T, Spigel D, Felip E, deMarinis F, Ahn MJ, Groen HJM, et al. ASCEND-2: A single-arm, open-label, multicenter phase II study of ceritinib in adult patients (pts) with ALK-rearranged (ALK+) non-small cell lung cancer (NSCLC) previously treated with chemotherapy and crizotinib (CRZ) [abstract]. J Clin Oncol. 2015;33(15 Suppl 1). (Presented at ASCO Annual Meeting; May 29 - Jun 2, 2015; Chicago, IL).

38. Felip E, Orlov S, Park K, Yu CJ, Tsai CM, Nishio M, et al. ASCEND-3: A single-arm, open-label, multicenter phase II study of ceritinib in ALKi-na‹ve adult patients (pts) with ALK-rearranged (ALK+) non-small cell lung cancer (NSCLC) [abstract]. J Clin Oncol. 2015;33(15 Suppl 1). (Presented at ASCO Annual Meeting; May 29 - Jun 2, 2015; Chicago, IL).

39. Ellis PM, Coakley N, Feld R, Kuruvilla S, Ung YC. Use of the epidermal growth factor receptor inhibitors gefitinib, erlotinib, afatinib, dacomitinib, and icotinib in the treatment of non-small-cell lung cancer: a systematic review. Curr Oncol [Internet]. 2015 Jun [cited 2017 Jul 13];22(3):e183-e215. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4462541

40. Hanna N, Shepherd FA, Fossella FV, Pereira JR, de MF, von PJ, et al. Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. J Clin Oncol. 2004 May 1;22(9):1589-97.

41. Shepherd FA, Dancey J, Ramlau R, Mattson K, Gralla R, O'Rourke M, et al. Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. J Clin Oncol. 2000 May;18(10):2095-103.

42. Kim ES, Hirsh V, Mok T, Socinski MA, Gervais R, Wu YL, et al. Gefitinib versus docetaxel in previously treated non-small-cell lung cancer (INTEREST): a randomised phase III trial. Lancet. 2008 Nov 22;372(9652):1809-18.

43. Shepherd FA, Rodrigues PJ, Ciuleanu T, Tan EH, Hirsh V, Thongprasert S, et al. Erlotinib in previously treated non-small-cell lung cancer. N Engl J Med. 2005 Jul 14;353(2):123-32.

44. American Cancer Society [Internet]. Atlanta (GA): American Cancer Society. A guide to pallative or supportive care; 2014 Sep 23 [cited 2016 Aug 9]. Available from: http://www.cancer.org/treatment/treatmentsandsideeffects/palliativecare/supportive-care

45. Temel JS, Greer JA, Muzikansky A, Gallagher ER, Admane S, Jackson VA, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. N Engl J Med. 2010 Aug 19;363(8):733-42.

46. Novello S, Barlesi F, Califano R, Cufer T, Ekman S, Levra MG, et al. Metastatic non-small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2016 Sep;27(suppl 5):v1-v27.

47. Weiss GJ, Langer C, Rosell R, Hanna N, Shepherd F, Einhorn LH, et al. Elderly patients benefit from second-line cytotoxic chemotherapy: a subset analysis of a randomized phase III trial of pemetrexed compared with docetaxel in patients with previously treated advanced non-small-cell lung cancer. J Clin Oncol. 2006 Sep 20;24(27):4405-11.

48. Gerber DE, Rasco DW, Le P, Yan J, Dowell JE, Xie Y. Predictors and impact of second-line chemotherapy for advanced non-small cell lung cancer in the United States: real-world considerations for maintenance therapy. J Thorac Oncol [Internet]. 2011 Feb [cited 2017 Jul 13];6(2):365-71. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3025081

49. Girard N, Jacoulet P, Gainet M, Elleuch R, Pernet D, Depierre A, et al. Third-line chemotherapy in advanced non-small cell lung cancer: identifying the candidates for routine practice. J Thorac Oncol. 2009 Dec;4(12):1544-9.

50. Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med [Internet]. 2012 Jun 28 [cited 2017 Jul 13];366(26):2443-54. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3544539

51. Mulcahy N. Nivolumab fails as initial lung cancer treatment. In: Medscape. New York (NY): Medscape LLC; 2016 Aug 5.

52. 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 2017 Jan 18];372(21):2018-28. Available from: http://www.nejm.org/doi/pdf/10.1056/NEJMoa1501824

53. 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.

54. Rittmeyer A, Barlesi F, Waterkamp D, Park K, Ciardiello F, von PJ, et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. Lancet. 2017 Jan 21;389(10066):255-65.

55. Drugs.com [Internet]. [unknown]: Drugs.com. Genentech's cancer immunotherapy Tecentriq (atezolizumab) for people with a specific type of metastatic lung cancer; 2016 Oct 18 [cited 2017 Apr 5]. Available from: https://www.drugs.com/newdrugs/fda-approves-genentech-s-cancer-immunotherapy-tecentriq-atezolizumab-specific-type-metastatic-lung-4445.html

56. pan-Canadian Oncology Drug Review manufacturer submission: pembrolizumab, powder for reconstitution for infusion - 50 mg, solution for infusion 100 mg/4mL. Company: Merck Canada Inc. Kirkland (QC): Merck Canada Inc.; 2016 Dec 12.

57. Studies found for: pembrolizumab. 2016 [cited 2017 Jan 21]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine; 2000 - . Available from: https://clinicaltrials.gov/ct2/results?term=pembrolizumab&Search=Search.

58. Merck Clinical Trials [Internet]. Kenilworth (NJ): Merck & Co.; 2009. Pembrolizumab: study search results; 2017 [cited 2017 Jan 31]. Available from: http://www.merck.com/clinical-trials/search.html?kw=pembrolizumab

59. Reck M, Rodriguez-Abreu D, Robinson AG, Hui R, Csoszi T, Fulop A, et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer [supplementary material]. N Engl J Med. 2016;375(19):1823-33.

60. Keytruda: prescribing information [Internet]. Kenilworth (NJ): Merck Sharp & Dohme Corp; 2016 Oct. [cited 2017 Feb 8]. Available from: http://www.merck.com/product/usa/pi_circulars/k/keytruda/keytruda_pi.pdf

61. Brahmer JR, Rodriguez-Abreu D, Robinson AG, Hui R, Csõszi T, Fülöp A, et al. PL04a.01: health-related quality of life for pembrolizumab vs chemotherapy in advanced NSCLC with PD-L1 TPS >50%: data from KEYNOTE-024. J Thorac Oncol. 2017;12(1):S8-S9.

62. Committee for Medicinal Products for Human Use (CHMP). Assessment report: Keytruda (pembrolizumab) [Internet]. London (GB): European Medicine Agency; 2016 Dec 15. [cited 2017 Feb 6]. (European public assessment report). Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/003820/WC500222359.pdf

63. Brahmer JR, Rodriguez-Abreu D, Robinson AG, Hui R, Czõszi T. Progression after the next line of therapy (PFS2) and updated OS among patients with advanced NSCLC and PD-L1 TPS >=50% enrolled in KEYNOTE-024. J Clin Oncol. 2017;35(15 Suppl).

64. Brahmer JR, Rodríguez-Abreu D, Robinson AG, Hui R, Csöszi T, Fülöp A, et al. Progression after the next line of therapy (PFS2) and updated OS among patients with advanced NSCLC and PD-L1 TPS >= enrolled in KEYNOTE-024 [Slide deck]. Alexandria (VA): ASCO; 2017. (Presented at ASCO annual meeting; 2017 2-6 Jun; Chicago, IL).

65. Study of MK-3475 (pembrolizumab) versus platinum-based chemotherapy for participants With PD-L1-positive advanced or metastatic non-small cell lung cancer (MK-3475-042/KEYNOTE-042). 2014 Aug 19 [cited 2017 Mar 3; updated 2017 Feb 15]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): U.S.

National Library of Medicine; 2000 - . Available from: https://clinicaltrials.gov/ct2/show/NCT02220894 Identifier: NCT02220894.

66. pan-Canadian Oncology Drug Review. Final clinical guidance report: pembrolizumab (Keytruda) for non-small cell lung cancer [Internet]. Ottawa: CADTH; 2016 Nov 3. [cited 2017 Feb 28]. Available from: https://www.cadth.ca/sites/default/files/pcodr/pcodr_pembrolizumab_keytruda_nsclc_fn_cgr.pdf

67. Roach C, Zhang N, Corigliano E, Jansson M, Toland G, Ponto G, et al. Development of a companion diagnostic PD-L1 immunohistochemistry assay for pembrolizumab therapy in non-small-cell lung cancer. Appl Immunohistochem Molecul Morphol [Internet]. 2016 Jul [cited 2017 Jan 19];24(6):392-7. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4957959

68. Hirsch FR, McElhinny A, Stanforth D, Ranger-Moore J, Jansson M, Kulangara K, et al. PD-L1 Immunohistochemistry Assays for Lung Cancer: Results from Phase 1 of the "Blueprint PD-L1 IHC Assay Comparison Project". J Thorac Oncol. 2016 Nov 29;12(2):208-22.

69. Rizvi NA, Garon EB, Leighl N, Hellmann MD, Patnaik A, Gandhi L, et al. Optimizing PDL1 as a biomarker of response with pembrolizumab (pembro; MK-3475) as first-line therapy for PDL1-positive metastatic non-small cell lung cancer (NSCLC): Updated data from KEYNOTE-001 [abstract]. J Clin Oncol. 2015;33(15 (Suppl 1)):8026. (Presented at ASCO Annual Meeting; May 29 - Jun 2, 2015; Chicago, IL).