pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Pembrolizumab (Keytruda) for Squamous Non-Small Cell Lung Cancer

January 3, 2020

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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 (Keytruda) for squamous (Sq) 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 Sq 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 Sq NSCLC, a summary of submitted Provincial Advisory Group Input on pembrolizumab Sq NSCLC, and a summary of submitted Registered Clinician Input on pembrolizumab Sq NSCLC, and are provided in Sections 2, 3, 4, and 5 respectively.

1.1 Introduction

The purpose of this review is to evaluate the safety and efficacy of pembrolizumab in combination with carboplatin and paclitaxel or nab-paclitaxel, for the treatment of metastatic, Sq NSCLC in adult patients with no prior systemic chemotherapy.

The reimbursement request is for the treatment of patients with metastatic squamous NSCLC in combination with carboplatin and either paclitaxel or nab-paclitaxel, in adults with no prior systemic chemotherapy treatment for metastatic NSCLC. The reimbursement request is in line with the Health Canada indication.[1]

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

The pCODR systematic review included one randomized controlled trial (RCT), KEYNOTE-407 (KN-407), and the results are summarized below.

KEYNOTE-407

KN-407 was an international, multi-centre, double-blind, phase III, superiority RCT of pembrolizumab in combination with chemotherapy (carboplatin and paclitaxel or nab-paclitaxel) versus placebo with chemotherapy (carboplatin and paclitaxel or nab-paclitaxel) for the first-line treatment of patients with metastatic squamous non-small cell lung cancer (Sq NSCLC), irrespective of PD-L1 tumor proportion score (TPS). Eligible patients were randomised in a 1:1 ratio to receive either 200 milligrams (mg) of pembrolizumab or saline placebo for up to 35 cycles, in combination with carboplatin (at a dose to produce an area under the curve of 6 mg per millilitre per minute) and paclitaxel (200 mg per square metre of body-surface area) or nab-paclitaxel (100 mg per square metre of body-surface area) for 4 cycles. Assignment to the chemotherapy arm was determined prior to randomisation. Treatments were administered intravenously in 3-week cycles. A total of 559 patients underwent randomisation, with 278 randomised to the

pembrolizumab + chemotherapy arm and 281 to the placebo + chemotherapy arm. All patients randomised received at least one dose of the assigned treatment, except for one patient in the placebo + chemotherapy arm. Participants continued treatment until radiographically confirmed progressive disease (PD), occurrence of unacceptable toxic effects, investigator's decision to discontinue the treatment, or withdrawal of consent.

The dual primary endpoints of KN-407 were overall survival (OS) and progression-free survival (PFS), and secondary outcomes included objective response rate (ORR) and duration of response (DOR). PFS, ORR, and DOR were assessed by a blinded independent central review (BICR) of radiologic images. Exploratory endpoints included OS, PFS, and ORR, by PD-L1 subgroup, taxane therapy, and PFS, ORR, DOR were assessed by the investigator as per irRECIST and RECIST 1.1. OS, PFS, and ORR was also explored across multiple pre-specified subgroups such as age, sex, and Eastern Cooperative Oncology Group Performance Status (ECOG PS). Health-related quality of life (HRQoL) was also explored and assessed using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ) Core 30 (EORTC-QLQ-C30) and the EORTC-QLQ-Lung Cancer 13 (EORTC-QLQ-LC13), as well as the EQ-5D questionnaire for economic evaluation. Safety was monitored regularly throughout the study and included all patients who received at least 1 dose of the assigned combination treatment.

Overall, 54.6% (n=305) of participants were ≥65 years of age, 81.4% (n=455) were male, 81.0% (n=453) were from non-East Asia countries, 92.7% (n=518) were current or former smokers, 97.7% (n=546) had predominant Sq histology, and 63.1% (n=353) had a PD-L1 TPS of ≥1%. Baseline characteristics were generally balanced between treatment arms, except for a higher proportion of males (n=235; 83.6%) in the placebo combination arm compared to the pembrolizumab combination arm (n=220; 79.1%) and a higher proportion of patients with ECOG PS 1 in the pembrolizumab combination arm (n=205; 73.7%) compared to the placebo combination arm (n=191; 68.0%).[2] There were also a higher proportion of current smokers (n=82; 29.5%) and a lower proportion of former smokers (n=174; 62.6%) in the pembrolizumab combination arm compared to the current smokers (n=63; 22.4%) and former smokers (n=199, 70.8%) in the placebo combination arm.[3]

Efficacy

The key efficacy outcomes of KN-407 are presented in Table 1. The data cut-off date was April 3rd, 2018, which was the date of the second interim analysis (IA2), where both primary endpoints, OS and PFS, crossed the pre-specified efficacy boundary for statistical significance. A total of 349 events of progressive disease (PD) or death were observed at the time of the analysis. The overall median duration of follow-up was 7.8 months (range: 0.1-19.1).[2]

Overall survival: The median OS was 15.9 months (95% CI: 13.2, not reached [NR]) in the pembrolizumab combination arm (85 deaths) and 11.3 months (95% CI: 9.5, 14.8) in the placebo combination arm (120 deaths).[2,3] There was a significant reduction in the risk of death by 36% in the pembrolizumab combination arm compared to the placebo combination arm (HR: 0.64, 95% CI: 0.49, 0.85; p<0.0001). Exploratory subgroup analyses of OS were consistent with overall trial results, with a clinically meaningful reduction in risk of death observed across all subgroups, however there was no statistically significant difference between treatment arms for patients with PD-L1 TPS ≥50% or patients ≥65 years of age.[2]

Progression-free survival: The median PFS was 6.4 months (95% CI: 6.2, 8.3) in the pembrolizumab combination arm (152 events) compared to 4.8 months (95% CI: 4.3, 5.7) in the placebo combination arm (197 events).[2,3] There was a 44% reduction in the risk of BICR-assessed PD or death in the pembrolizumab combination arm compared to the placebo combination arm (HR: 0.56; 95% CI: 0.45, 0.70; p< 0.0001). Exploratory subgroup

analyses were consistent with the overall trial results, with a statistically and clinically significant reduction in the risk of PD or death seen across all subgroups.[2]

Objective response rate: The ORR was higher in the pembrolizumab combination arm (57.9%, 95% CI: 51.9, 63.8) than in the placebo combination arm (38.4%, 95% CI: 32.7, 44.4), representing a treatment difference of patients experiencing a complete response (CR) or partial response (PR) of 19.5% (95% CI: 11.2, 27.5). Few patients in both treatment arms achieved a best overall response (BOR) of CR (6 patients in the placebo combination arm and 4 patients in the pembrolizumab combination arm).[2] The ORR treatment difference was consistent across all subgroups showing a marked benefit in achieving a CR or PR response with pembrolizumab combination therapy when compared to placebo combination therapy, however the ORR treatment difference was not statistically significant for patients with ECOG PS 0.[3]

Duration of response: The median time to response was 1.4 months in both groups, and median DOR was 7.7 months (95% CI: 1.1, 14.7) in the BICR-assessed pembrolizumab combination arm compared to 4.8 months (95% CI: 1.3, 15.8), with participants experiencing ongoing response in both treatment arms.[2]

Health-related Quality of Life

Study compliance was high (>80%) at both weeks 9 and 18, however, patient numbers decreased at each time point as more participants discontinued from the trial.[4] There was a statistically significant difference between treatment arms in the mean global health score based on the EORTC-QLQ-C30 at both week 9 (LS mean diff: 3.6; 95% CI: 0.3, 6.9) and 18 (LS mean diff: 4.9; 95% CI: 1.4, 8.3).[3,4] However, based on evidence-based guidelines, the clinical relevance of this finding is small.[5] There was no statistically significant difference between treatment arms in the EQ-5D-3L visual analogue scale (VAS) score at week 9, however there was a statistically significant difference between treatment arms at week 18.[6]

Harms

AEs of any grade occurred in 98.2% and 97.9% of patients in the pembrolizumab combination arm and placebo combination arm, respectively. AEs of grade ≥ 3 occurred in 69.8% and 68.2% of participants in the pembrolizumab combination arm and placebo combination arms, respectively.[2] There were a higher proportion of patients in the pembrolizumab combination arm (95.3%) with treatment-emergent AEs (TEAEs) compared to the placebo combination arm (88.9%). Participants with serious AEs (SAEs) were comparable between treatment arms (40.6% vs. 38.2% in the pembrolizumab combination arm and placebo combination arms, respectively); however, a higher proportion of patients in the pembrolizumab combination arm experienced a serious TEAE (25.2% vs. 18.2%). Participants with grade ≥3 TEAEs were comparable between treatment arms (54.7% vs. 55.0% in the pembrolizumab combination arm and placebo combination arms, respectively).[3]

Any grade AEs: The most commonly occurring any grade AEs in both treatment arms included anemia (53.2% vs. 51.8%, pembrolizumab combination arm vs. placebo combination arm, respectively); alopecia (46.0% and 36.4%, respectively); neutropenia (37.8% and 32.9%, respectively); and nausea (35.6% and 32.1%, respectively).[2]

Grade 3 or higher AEs: The most commonly occurring grade ≥ 3 AEs in both treatment arms included anemia (53.2% vs. 51.8%, pembrolizumab combination arm vs. placebo combination arm, respectively); alopecia (46.0% and 36.4%, respectively); neutropenia (37.8% and 32.9%, respectively); and nausea (35.6% and 32.1%, respectively).[2] In both treatment arms, neutropenia was the most commonly occurring grade ≥3 TEAE (21.2% vs.

22.5%, pembrolizumab combination arm vs. placebo combination arm, respectively), followed by anaemia (13.7% vs. 15.4%, respectively).[3]

Serious AEs: In both treatment arms, pneumonia (6.7% vs. 5.8%, pembrolizumab combination arm vs. placebo combination arm, respectively) and febrile neutropenia (3.6% vs. 5.4%) were the most commonly occurring SAEs in both treatment arms. The most common treatment-emergent SAE was febrile neutropenia in both treatment arms (5.0% and 3.2% in the pembrolizumab combination arm and placebo combination arm, respectively).[3]

AEs of interest: AEs of interest included infusions reactions and events with an immune-related cause. These occurred in 28.8% of patients in the pembrolizumab combination arm and 8.6% of patients in the placebo combination arm. Hypothyroidism (7.9%), hyperthyroidism (7.2%), and pneumonitis (6.5%), were commonly occurring AEs of interest in the pembrolizumab combination arm compared to the placebo combination arm (1.8%, 0.7%, and 2.1% for hypothyroidism, hyperthyroidism, and pneumonitis, in the placebo combination arm respectively).[2]

Withdrawals due to AEs: A higher proportion of participants in the pembrolizumab combination discontinued all treatment components (13.3% vs. 6.4% in the placebo combination arm) and any treatment components (23.4% vs. 11.8% in the placebo combination arm) due to any grade AEs (Table # first one in this section). Discontinuation rates were similar for grade ≥ 3 AEs.[2]

Deaths: There were a similar proportion of participants in the pembrolizumab combination arm that experienced an AE resulting in death (n=23; 8.3%) compared to the placebo combination arm (n=18; 6.4%).[2]

Table 1: Highlights of Key Outcomes in the KEYNOTE-407 trial

	KN-407	
	Pembrolizumab + Chemotherapy (N= 278)	**Placebo + Chemotherapy (N=281)**
Primary Outcomes		
Overall survival		
Median months (95% CI)	15.9 (13.2, NR)	11.3 (9.5, 14.8)
HR (95% CI)	0.64 (0.49, 0.85)	
p-value	<0.001	
Progression-free survival (BICR-assessed) †		
Mean months (95% CI)	6.4 (6.2, 8.3)	4.8 (4.3, 5.7)
HR (95%CI)	0.56 (0.45, 0.70)	
p-value	<0.001	
Secondary Outcomes		
Objective response rate (BICR-assessed) †		
Best response (CR + PR), % (95% CI)	57.9 (51.9, 63.8)	38.4 (32.7, 44.4)
Estimated treatment difference (95% CI)	19.5 (11.2, 27.5)	
p-value	N/A	
HrQoL Global Health Status‡		
Change from baseline - week 9††	1.76 (-0.86, 4.37)	-1.84 (-4.40, 0.71)
Difference in LS means	3.60 (0.28, 6.92)	
p-value	0.0337	
Change from baseline - week 18††	4.28 (1.65, 6.91)	-0.57 (-3.34, 2.20)
Difference in LS means	4.85 (1.40, 8.30)	
p-value	0.0060	
Harms Outcome, n (%)	**Pembrolizumab + Chemotherapy (N= 278)**	**Placebo + Chemotherapy (N=280)**

	KN-407	
AE Grade ≥3	194 (69.8)	191 (68.2)
AE (any grade)	273 (98.2)	274 (97.5)
SAE	113 (40.6)	107 (38.1)
TEAE	265 (95.3)	249 (88.9)
TEAE (grade ≥3)	152 (54.7)	154 (55.0)
WDAE	37 (13.3)	18 (6.4)

Data cut-off date: April 3rd, 2018
†Assessed using RECIST 1.1.
‡Assessed using the EORTC QLQ-C30 global health status.
††LS mean reported for change in baseline scores.
Abbreviations:
AE = adverse event; **BICR** = blinded independent central radiologist; **CI** = confidence interval; **CR** = complete response; **DOR** = duration of response; **HR** = hazard ratio; **HRQoL** = health-related quality of life; LS = least squares; **NR** = not reported; **PR** = partial response; **SAE** = serious adverse event; **TEAE** = treatment-emergent adverse event; **WDAE** = withdrawal due to adverse event

Limitations

The key limitations of the KN-407 trial included:

- Investigator and respondent bias may still have existed, despite a double-blinded study, as specific immune-related AEs commonly associated with pembrolizumab may have made treatment assignment predictable. This may have influenced outcomes such as PFS, specifically in terms of delaying or expediting a scan to confirm PD based on suspected treatment regimen.
- Crossover from the placebo combination arm to pembrolizumab monotherapy was allowed, which may confound the results of the analysis of OS. Given the results showed a statistically significant reduction in the risk of death despite the potential for confounding due to crossover, the actual treatment effect, when adjusting for crossover, was larger than reported in the trial.
- There were a higher proportion of patients with ECOG PS 1 and less male patients in the pembrolizumab combination arm compared to the placebo combination arm. The combination of these factors may have biased results in favour of the placebo combination arm.
- The duration of follow-up in KN-407 was short. Long-term OS, PFS, and HRQoL data are required to ensure the results observed in this study are consistent or maintained over a longer period. Additionally, there is the possibility for toxic, delayed immune-related AEs to develop over time with drugs such as pembrolizumab, and the duration of the trial was inadequate to capture these events. Long-term safety data are also required.

1.2.2 Additional Evidence

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

Patient Advocacy Group Input

From a patient's perspective, lung cancer can limit a patient's ability to engage in activities with friends and family, work and engage in tasks of day to day living. Patients can feel isolated and a loss of independence due to their condition, which can lead to depression. Current treatments for patients with Sq NSCLC include chemotherapy and immunotherapy. Both chemotherapy and

immunotherapy were stated to help with disease control, however side effects of immunotherapy were generally described as more tolerable compared to chemotherapy. A concern was raised regarding the use of chemotherapy and immunotherapy as single agents, as patients with Sq NSCLC may progress while on treatment and subsequently may not be able to receive systemic treatment due to the aggressive nature of their disease. The combination of pembrolizumab with chemotherapy would provide patients with the option of the most effective treatment up front. Only input from LCC provided information regarding the combination of pembrolizumab and chemotherapy, however none of the patients providing input had a diagnosis of Sq NSCLC; seven patients with non-squamous NSCLC provided input regarding treatment with the combination of pembrolizumab and chemotherapy. Patients reported that chemotherapy combined with pembrolizumab was effective at controlling disease, reducing tumour size and stabilizing metastases. Side effects were described as tolerable, and patients reported being able to return to work and engage in social activities with friends and families. However, one patient reported having to stop treatment due to having developed diverticulitis, and two other patients reported progression of their disease. Overall, pembrolizumab and chemotherapy was described as an effective treatment with tolerable side effects. Patient values supported by the patient advocacy groups included symptom control and reduction of adverse events, and improved survival and quality of life.

Provincial Advisory Group (PAG) Input

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

Clinical factors:

- Treatment sequencing with pembrolizumab in this setting

Economic factors:

- Appropriate dosing schedule
- Additional resources needed to monitor infusion reaction

Registered Clinician Input

Two joint clinician inputs were received on behalf of a total of 15 registered clinicians; two from Cancer Care Ontario (CCO) and thirteen from Lung Cancer Canada (LCC) for pembrolizumab for patients with metastatic Sq NSCLC.

For patients with PD-L1 ≥50% and PD-L1 <50%, the most appropriate comparators were suggested to be pembrolizumab and platinum doublet chemotherapy, respectively. Clinicians from CCO and LCC agreed that inclusion and exclusion criteria from the Keynote 407 trial were generalizable to and reflective of Canadian patients in clinical practice. While pembrolizumab will not be a new treatment introduced into the treatment space for patients with Sq-NSCLC, it would replace other treatments, immunotherapy and chemotherapy, offered in the first-line setting. For patients with PD-L1 ≥50% who wish to delay or avoid chemotherapy, pembrolizumab may be provided as a monotherapy. However, the treatment regimen for the patient will ultimately depend on disease characteristics in addition to patient preference. With regards to whether pembrolizumab should be provided to patients with a single agent chemotherapy or platinum doublet chemotherapy, both clinician inputs agreed that pembrolizumab should be limited to a combination with any platinum doublet; current evidence does not support the use of pembrolizumab in combination with single agent chemotherapy.

Summary of Supplemental Questions

- Context: Pembrolizumab monotherapy is currently approved and funded in most jurisdictions in Canada for patients with Sq NSCLC with PD-L1 TPS ≥50%. The economic evaluation includes a subgroup analysis that compares pembrolizumab in combination with chemotherapy to pembrolizumab monotherapy in patients with a PD-L1 ≥50% TPS.

- Issue: There are no RCTs comparing pembrolizumab + chemotherapy to pembrolizumab monotherapy for patients with Sq NSCLC with PD-L1 TPS ≥50%.

  Supplemental item: As the submitter has individual patient data from the KEYNOTE trials, an indirect treatment comparison (ITC) was conducted to compare the two treatments and to inform the economic model. The Methods Team offered a summary and critical appraisal of the manufacturer-submitted ITC of pembrolizumab in combination with chemotherapy versus pembrolizumab monotherapy. Of note, PAG is seeking clarity on the most appropriate therapy in this setting (i.e., pembrolizumab in combination with platinum doublet therapies or single agent pembrolizumab).

  See section 7.1 for more information.

Comparison with Other Literature

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

1.2.3 Factors Related to Generalizability of the Evidence

Table 2 addresses the generalizability of the evidence 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).

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
Population	ALK, EGFR , ROS1 mutations	The KN-407 did not exclude patients with specific mutations.	Do the results apply to Sq-NSCLC with mutations such as ALK, EGFR, and ROS1?	Having ALK, EGFR and ROS1 testing not a pre requisite for inclusion in KN 407 is reasonable given that expert consensus guidelines[7] do not recommend these tests routinely for Sq NSCLC (exception being patients < 50 years; light or absent tobacco exposure). The results of KN 407 cannot be generalized to patients with ALK, EGFR or ROS1 molecular abnormalities.
	ECOG Performance Status	The KN-407 trial included patients with ECOG PS 0-1. Pembrolizumab + chemotherapy (n=278) ECOG PS 0: 73 (26.3%); ECOG PS 1: 205 (73.7%) Chemotherapy (n=281) ECOG PS 0: 90 (32.0%); ECOG PS 1: 191 (68.0%)	Do the trial results apply to patients with ECOG PS of 2 or greater? Why or why not?	In clinical practice, platinum doublets are often used in patients with ECOG PS of 2 even though the strongest evidence of benefit is in patients with ECOG PS 0-1. Platinum doublets are not used in patients with ECOG PS of 3-4. Given this historical precedent the clinical guidance panel (CGP) feels that it is appropriate to apply results from KN 407 to patients with ECOG PS 2 but not ECOG PS 3 or 4.

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
	Brain metastases	The KN-407 trial excluded participants with active central nervous system (CNS) metastases and/or carcinomatous meningitis.	Do the trial results apply to patients with brain metastases?	The CGP feels strongly that the results of KN 407 should not be applied to patients with untreated symptomatic brain metastases. KN 407 included patients with treated brain metastases (clinically stable for at least 2 weeks and, had no evidence of new or enlarging brain metastases and were also off steroids 3 days prior to treatment) and asymptomatic brain metastases (ie no neurological symptoms, no requirements for corticosteroids, and no lesion >1.5 cm). The CGP feels these inclusion criteria are quite reasonable to use as a framework for applying KN-407 data to patients with brain metastases in clinical practice.
Intervention	Pembrolizumab in combination with non-platinum-based therapies	The KN-407 trial compared pembrolizumab in combination with a specific platinum-based regimen, carboplatin in combination with paclitaxel or nab-paclitaxel, vs. placebo in combination with carboplatin and paclitaxel or nab-paclitaxel.	For patients who are contraindicated to platinum-based therapies, can pembrolizumab be used with non-platinum-based therapies without affecting safety or efficacy?	NCCN guidelines list Gemcitabine/Docetaxel and Gemcitabine/vinorelbine as category 1 options for first line treatment of patients with metastatic Sq NSCLC and ECOG PS 0-1. These agents were not included in KN-407 thus there is insufficient evidence to support the use of Pembrolizumab in combination with non-platinum based doublets. In addition, the CGP does not support the extrapolation of the findings of KN-407 to pembrolizumab combined with single agent chemotherapy.
	Pembrolizumab in combination with other platinum-based therapies	The KN-407 trial compared pembrolizumab in combination with a specific platinum-based regimen, carboplatin in combination with paclitaxel or nab-paclitaxel, vs. placebo in combination with carboplatin and paclitaxel or nab-paclitaxel. In Canadian	Can pembrolizumab be used with other platinum-based therapies without affecting safety or efficacy?	Although it was stated in the registered clinician input from CCO that pembrolizumab may be given in combination with any platinum doublet, the clinical guidance panel suggests that pembrolizumab + carboplatin/paclitaxel should be the preferred regimen but if the clinical situation dictates it would be reasonable to use other platinum-based therapies (e.g. intolerant to taxane).

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
		practice, other platinum drugs, such as cisplatin		
	Pembrolizumab administered as weight-based dose	The KN-407 trial involved the administration of a fixed dose of pembrolizumab at 200mg.	Can weight-based dosing of pembrolizumab (2mg/kg up to a flat dose cap of 200 mg) be used without affecting efficacy or safety?	The CGP feels that this question is outside of the scope of this review. Evidence from KN-407 supports the use of Pembrolizumab at a fixed dose of 200 mg every 3 weeks. Pembrolizumab is currently funded as 2 mg/kg to a max of 200 mg in most Canadian jurisdictions. Pembrolizumab may eventually move to q6week dosing. The CGP suggest that provinces/jurisdictions convene an expert panel to review dosing/schedule of ICI in metastatic NSCLC.
	Line of therapy	The KN-407 trial included patients who had received no prior systemic therapy for their disease.	Can pembrolizumab in combination with platinum-based therapy be used in second-line (for patients who received platinum-based therapy in first line or received a prior anti PD-1/PD-L1/PD-L2 agents?	In general, KN-407 should not be applied to patients in the second line. However, the CGP feels that it is reasonable to consider the use of Pembrolizumab +Carboplatin/Paclitaxel for "retreatment" of patients that have been previously treated with a platinum doublet in the 1st line metastatic setting who have had a 12 month or greater progression-free interval. It reasonable to add pembrolizumab to patients receiving platinum based doublets in the first line setting when this regimen is approved. The CGP thinks that it is reasonable to apply KN-407 data to patients that have progressed greater than **6 months** after the completion of consolidate durvalumab for Stage III NSCLC. The CGP also thinks that it is reasonable to apply KN-407 data to patients that have progressed greater than **6 months** after the completion of adjuvant ICI in the setting of a clinical trial

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
	Cycles of platinum-based chemotherapy	The KN-407 trial used pembrolizumab or placebo in combination with 4 cycles of platinum-based therapies. In Canadian practice, as well as in line in with international guidelines, 4-6 cycles of platinum-based therapies is recommended. There were no patients that received more than 4 cycles of platinum-based therapies in the KN-407 trial.	Can pembrolizumab be safely administered with more than 4 cycles of platinum-based therapy?	Consensus guidelines[8] recommend the use of 4-6 of platinum doublet chemotherapy in advanced Sq NSCLC. Six cycles are not clearly superior to four cycles thus the use of four cycles as the standard of care arm in KN-407 is appropriate. The CGP recommends the use of 4 cycles of platinum based chemotherapy in combination with pembrolizumab based on the KN-407. Caution should be used in extending this to 6 cycles as there is no clear benefit from this strategy.

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
Comparator	Pembrolizumab monotherapy	Currently, the first line treatment for advanced stage Sq-NSCLC patients with PD-L1 TPS ≥50% is pembrolizumab monotherapy. The KN-407 trial included patients regardless of PD-L1 TPS (including patients that were PD-L1 negative). The submitter provided an ITC comparing pembrolizumab in combination with chemotherapy vs. pembrolizumab monotherapy in Sq-NSCLC patients with PD-L1 TPS ≥50% (please refer to section 7). There was no statistically significant difference between pembrolizumab + chemotherapy compared to pembrolizumab monotherapy in terms of efficacy (OS and PFS). There was suggestion of clinical significance in PFS benefit associated with pembrolizumab + chemotherapy compared to pembrolizumab monotherapy.	In patients with PD-L1 TPS ≥50%, is there a preference and evidence to support the use of pembrolizumab monotherapy over pembrolizumab in combination with platinum-based chemotherapy?	In patients with PD-L1 TPS > /= 50% pembrolizumab mono therapy represents the standard first line therapy. KN-407 showed that pembrolizumab +Carboplatin/paclitaxel is superior to Carboplatin/Paclitaxel in this patient population, thus representing an alternative first line therapy. The CGP supports having both options available to patients as these regimens have not been directly compared and indirect comparison as part of this review shows no clear regimen that is superior in OS.

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
Outcomes	Appropriateness of primary and secondary outcomes	The primary outcomes in the KN-407 included OS and BICR-assessed PFS. Secondary outcomes included ORR, DOR, HRQoL, and safety.	Were the primary and secondary outcomes appropriate for the trial design?	Primary and secondary end points are appropriate.
Setting	Countries participating in the trial	The trial was in 125 sites in 17 countries including Canada.	Are there any known potential differences in the practice patterns between other countries that the trial was conducted in Canada?	Nab-paclitaxel is not used in the treatment of NSCLC in Canada. The OS and PFS benefit was maintained when patients receiving nab-paclitaxel were excluded.

1.2.4 Interpretation

Burden of Illness and Need

Lung cancers are the most common cause of cancer in Canada, with approximately 28,600 new cases in 2017.[9] NSCLC makes up nearly 85% of lung cancer diagnosis with Sq cell carcinoma representing 20-30% of this group (KN-407). Of patients presenting with lung cancer an estimated 17% will be alive in 5 years.[9] Sq NSCLC represents a particularly difficult disease to treat as it typically lacks oncogenic driver mutations and maintenance therapy has not been shown to improve overall survival.

Effectiveness

KEYNOTE- 407 was a randomized phase III trial in patients with metastatic Sq NSCLC. Participants were required to have good performance status (ECOG 0-1), measurable disease and a tumour sample available for PD-L1 assessment. Participants were randomized 1:1 to pembrolizumab, carboplatin and paclitaxel or nab-paclitaxel (n=278) versus placebo, carboplatin and paclitaxel or nab-paclitaxel (n=281). Patients with active brain metastases, a history of pneumonitis, or autoimmune disease, or thoracic radiation > 30Gy in the preceding 6 months were not eligible. Participants received pembrolizumab / placebo in combination with chemotherapy for four cycles, then up to an additional 31 cycles of pembrolizumab / placebo. Treatment continued until disease progression, unacceptable toxicity, or patient withdrawal of consent. Patients discontinuing pembrolizumab after 35 treatments without progression, were eligible to receive an additional year of pembrolizumab at the time of progression. Patients receiving placebo were eligible to cross over to pembrolizumab at the time of confirmed disease progression. The primary outcomes of the trial were OS and PFS by blinded independent central radiology review (BICR). Secondary outcomes included ORR, duration of response and safety. There were no major issues with the clinical trial design.

The patient population of KEYNOTE -407 is typical patient for large randomized trials in NSCLC with the caveat being that it was restricted to Sq cell histology. The median age was 65 with nearly 80% of population being male and 92% being current or former smokers. The sex and smoking breakdown were consistent with demographics from IMPOWER 131 which was also restricted to Sq NSCLC. A total of 8% of participants had brain metastases and 75% had PDL1 TPS < 50%. Standard doses of carboplatin/paclitaxel were used but 40% of trial participants received nab-paclitaxel which is not approved for the treatment of Metastatic NSCLC in Canada. The CGP feels that these results are generalizable to the Canadian patient population since the clinical benefit was maintained when restricted to patients receiving only paclitaxel. Additionally, pembrolizumab was administered as a fixed dose of 200mg, rather than weight-based dosing that is commonly reimbursed in Canadian healthcare. The median follow-up of participants was only 7.8 months, so the OS results are still immature.

KEYNOTE -407 met both its primary study outcomes (OS and PFS). OS was significantly improved for patients randomized to pembrolizumab, carboplatin and paclitaxel/nab-paclitaxel compared with placebo, carboplatin and paclitaxel/nab-paclitaxel (median OS 15.9 vs 11.3 months, HR 0.64, 95%CI 0.49-0.85). PFS was significantly improved (median PFS 6.4 vs 4.8 months, HR 0.56, 95%CI 0.45-0.70). OS and PFS benefit were seen across all planned subgroups. The ORR was higher in patients randomized to pembrolizumab and chemotherapy versus chemotherapy alone (57.9% vs 38.4%) and this improvement in ORR held across all PD-L1 subgroups. Using the EORTC-QLQ-C30 measure, pembrolizumab plus chemotherapy also demonstrated improved quality of life at 9 and 18 weeks when

compared to placebo plus chemotherapy. There was no statistically significant difference between treatment arms in the EQ-5D-3L visual analogue scale (VAS) score at week 9, however there was a statistically significant difference between treatment arms at week 18.

Safety

Adverse events of grade 3 or higher occurred in 69.8% of the pembrolizumab-combination group versus 68.2% of patients in the placebo-combination arm. Discontinuation of all treatment components was higher in the pembrolizumab-combination arm 13.3% versus 6.4%. Adverse events leading to death occurred in 8.3% of patients on pembrolizumab-combination versus 6.4% in placebo-combination arm. More Immune related adverse events occurred the pembrolizumab arm than the control arm (28.8 vs 8.6%).

The results of the KEYNOTE-407 trial support the implementation of pembrolizumab in combination with carboplatin/paclitaxel as initial therapy or advanced and metastatic NSCLC.
The improvements in OS and PFS are clinically significant. This improved efficacy is associated with an increased risk of discontinuation of therapy. While there is a greater risk of immune mediated adverse events, chemotherapy did not increase the frequency of these events compared single agent pembrolizumab. There is an acceptable balance of improved clinical outcomes weighed against toxicity.

The findings from KEYNOTE-407 are generalizable to the large majority of patients with advanced and metastatic NSCLC. Results of Keynote 407 should not be applied to patients with both Sq NSCLC and targetable molecular abnormalities such as EGFR mutations, ALK and ROS1 translocations. These patients were not explicitly excluded from this trial due to the rarity of these molecular abnormalities in Sq NSCLC but given this rarity these results are not applicable to this patient population.

Keynote 407 included only patients with ECOG 0-1. In clinical practice, platinum doublets are often used in patients with ECOG PS of 2 even though the strongest evidence of benefit is in patients with ECOG PS 0-1. Platinum doublets are not used in patients with ECOG PS of 3-4. Given this historical precedent the clinical guidance panel (CGP) feels that it is appropriate to apply results from KN 407 to patients with ECOG PS 2 but not ECOG PS 3 or 4. The trial included only patients with measurable disease, but would be applicable to patients with evaluable disease as well. Patients who receive pembrolizumab plus chemotherapy in the first-line setting would not be eligible for second-line ICI. KN-407 allowed patients to receive up to 30 Gy of thoracic radiation as long as it was completed 7 days prior to initiating systemic therapy. Doses higher than 30 gy were only allowed if received greater than 6 months prior to initiating therapy. Given the safety profile of durvalumab as consultative therapy post concurrent chemoradiation (PACIFIC Trial) it would be reasonable to confer pembrolizumab plus chemotherapy after greater than 30 GY of thoracic radiation provided 14 days has elapsed from completion of radiation.

There are some questions that cannot be answered directly with available data.

- The CGP recognizes that prior decisions regarding pembrolizumab have recommended pembrolizumab dosing at 2mg/kg up to a maximum of 200mg. The CGP feels that it is beyond the scope of this review to reopen this decision. Thus, CGP notes that KN-407 uses the 200 mg flat dosing but that the Canadian health system has

previously decided that this flat dosing yields equal outcomes to dosing 2mg/kg up to a maximum of 200mg. Complicating matters is that there is emerging data on dosing pembrolizumab at 400 mg flat dose every 6 weeks. Given the complexity of this topic the CGP recommends that the dosing and schedule for immune checkpoint inhibitors (ICIs) be reviewed via a separate panel.

- KEYNOTE-407 allowed patients to receive pembrolizumab for up to 35 cycles. Patients free of progression at this time discontinued therapy, but were allowed to restart pembrolizumab if they progressed within the two year follow up period. This is consistent with other trials of pembrolizumab. There are no data presented on the efficacy of this approach, and given the short median follow up these data will not be imminently forthcoming nor how many patients were retreated. The CGP believes patients who complete two years of pembrolizumab and discontinue therapy without progression, should have the option for retreatment with pembrolizumab. The optimal duration of this retreatment is unknown. Whether restrictions should be placed on the timeframe between completion of therapy and documented disease progression (ie 6 months or more) is also unknown.

- In patients with PD-L1 TPS > /= 50% pembrolizumab monotherapy represents the standard first line therapy. KN-407 showed that pembrolizumab +carboplatin/paclitaxel is superior to carboplatin/paclitaxel in this patient population, thus representing an alternative first line therapy. The CGP supports having both options available to patients as these regimens have not been directly compared and indirect comparison as part of this review shows no clear regimen that is superior in OS.

- Patients who received consolidation durvalumab following concurrent chemoradiation, or adjuvant ICI therapy, should be considered for pembrolizumab plus chemotherapy for recurrent or metastatic NSCLC if there has been at least 6 months since completion of the ICI therapy.

- The CGP recommends that patients being treated with platinum based-doublet therapy be able to add pembrolizumab to chemotherapy during cycles 1-4 of chemotherapy. The CGP does not recommend platinum doublets being added to patients on pembrolizumab mono-therapy.

1.3 Conclusions

The Clinical Guidance Panel members believe there is a net overall clinical benefit from the addition of pembrolizumab to carboplatin/paclitaxel or nab-paclitaxel in patients with advanced / metastatic Sq NSCLC. KEYNOTE -407 is a well designed randomized clinical trial that demonstrates a clinically meaningful improvement in both OS (median OS 15.9 vs 11.3 months, HR 0.64, 95%CI 0.49–0.85 p < 0.001) and PFS (median PFS 6.4 vs 4.8 months, HR 0.56, 95%CI 0.45-0.70) for pembrolizumab plus chemotherapy, versus chemotherapy alone. The improved efficacy came with an acceptable safety profile with grade 3 or higher adverse events occurring in approximately equal numbers in both arms of the trial. ICI are currently used in metastatic Sq NSCLC so oncologists are comfortable with managing immune related AE. Sq NSCLC represents a significant health burden and pembrolizumab combined with chemotherapy is an improved treatment option.

Pembrolizumab combined with a platinum doublet chemotherapy would become the initial therapy for patients with advanced/metastatic Sq NSCLC, ECOG PS 0-2 with no contraindications to ICI therapy and PD-L1 TPS < 50%. For patients with advanced/metastatic Sq NSCLC, ECOG PS 0-

2, no contraindications to ICI therapy and PD-L1 TPS >/= 50% pembrolizumab mono therapy or pembrolizumab combined with a platinum doublet chemotherapy would be the standard first line treatment option. Patients who received consolidation durvalumab following concurrent chemoradiation, or adjuvant ICI therapy, should be considered for pembrolizumab plus chemotherapy for recurrent or metastatic NSCLC if there has been at least 6 months since completion of the ICI therapy.

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

Lung cancers is the most common cause of cancer in Canada, with approximately 28,600 new cases in 2017.[9] Lung Cancer is also the largest cause of cancer death in Canada with an estimated 21,100 deaths in 2017. This number represents a greater total than the deaths attributable to Breast Cancer, Colorectal Cancer and Pancreatic Cancer combined. Smoking is the dominant risk factor for lung cancer with smoking is the attributable cause of nearly 80% of all lung cancers.[10] Non-Small Cell Lung Cancer (NSCLC) makes up nearly 85% of lung cancer diagnosis with Sq cell carcinoma representing 20-30% of this group (KN-407). Of patients presenting with lung cancer an estimated 17% will be alive in 5 years.[9]

2.2 Accepted Clinical Practice

Historically the treatment algorithm for advanced NSCLC did not differentiate between Sq and non-squamous histology. In the late 2000s Cisplatin/Pemetrexed was shown to be superior to Cisplatin/Gemcitabine in non-squamous NSCLC.[11] Pemetrexed maintenance therapy was subsequently shown improve overall survival in non squamous NSCLC.[12] For Sq NSCLC initial therapy consisting of a platinum-doublet with cisplatin or carboplatin in combination with gemcitabine, vinorelbine, paclitaxel, or docetaxel without subsequent maintenance remained the standard of care.[13]

Treatment algorithms for advanced adenocarcinoma NSCLC also evolved with the discovery of oncogenic driver molecular abnormalities and systemic therapies to target these abnormalities. Patients with EGFR, ALK or ROS1 now receive oral tyrosine kinase inhibitors (TKIs) as first line therapy[14] given the superior ORR and PFS when these therapies are compared to platinum-based chemotherapy. These molecular abnormalities are exceedingly rare in Sq NSCLC and guidelines suggest only testing for these abnormalities in patients under <50 and/or light smoking history.[7]

Immune checkpoint inhibitors (ICI) gained prominence by revolutionizing the treatment of metastatic melanoma. These inhibitors work by blocking pathways that lead to an inhibitory final to T-Cell Activation. ICIs targeting Programmed Cell Death–1 (PD-1) receptor and its ligand (PD-L1) have been shown to be efficacious in advanced NSCLC and now represent an approved form of therapy.

Nivolumab (PD-1 inhibitor), Pembrolizumab (PD-1 inhibitor), and Atezolizumab (PD-L1 inhibitor)[15-17] all showed statistically significant improved overall survival (OS) when compared to docetaxel chemotherapy in the 2nd line setting. This improvement in overall survival came despite only a modest objective response rate (15-20% across trials compared to 9-12% for Docetaxel) and no improvement in median progression free survival. In addition to improvement in overall survival, these agents are also less toxic then docetaxel chemotherapy as demonstrated by Checkmate-017 having treatment-related adverse events of grade 3 or 4 n 7% of the patients in the nivolumab group as compared with 55% of those in the docetaxel group.

Immune checkpoint inhibitors have fatigue and infusion reactions as potential adverse effects. Additionally, immune mediated adverse events can also occur including pneumonitis, colitis,

diarrhea, hepatitis, nephritis, skin toxicities and thyroid dysfunction. Rare side effects exist and treatment algorithms to manage immune mediated side effects are now well established.[18]

Keynote-024 was a RCT comparing pembrolizumab mono therapy to platinum doublet chemotherapy in patients with advanced NSCLC and PD-L1 TPS >/= 50%. (KEYNOTE - 024 NEJM) Pembrolizumab showed improved median progression-free survival (10.3 months vs 6.0 months) overall survival (hazard ratio for death, 0.60; 95% CI, 0.41 to 0.89; P = 0.005) and response rate (44.8% vs. 27.8%). Pembrolizumab also had a grade 3 or higher adverse event rate of 26.6% compared to 53.3% for chemotherapy. This trial led to pembrolizumab being approved as first line treatment in advanced NSCLC and PD-L1 TPS >/= 50%. Updated data from Keynote-024 shows median OS was 30.0 months (95% CI, 18.3 months to not reached) with pembrolizumab and 14.2 months (95% CI, 9.8 to 19.0 months) with chemotherapy (hazard ratio, 0.63; 95% CI, 0.47 to 0.86).[19]

Keynote-042[20] attempted to expand the indication for first line pembrolizumab to patients with PDL1 TPS >= 1%. It was a RCT comparing pembrolizumab mono therapy to platinum doublet chemotherapy in patients with advanced NSCLC and PD-L1 TPS >/= 1%. This was a positive trial but for the group of interest PDL1 TPS 1-49% exploratory analysis showed no OS benefit with pembrolizumab versus chemotherapy for patients with PD-L1 TPS 1%–49% (13.4 and 12.1 months respectively).

Keynote 189[21] was a RCT comparing pembrolizumab plus platinum/pemetrexed with platinum/pemetrexed in metastatic non squamous NSCLC. The pembrolizumab combination hazard ratio of 0.49 (95% CI, 0.38 to 0.64; P<0.001) with an estimated improvement in survival at 12 months of 20%. The benefit also held across all PDL1 subgroups. Adverse events were manageable, with grade 3 or higher events occurring in 67.2% of the patients in the pembrolizumab-combination group and in 65.8% of those in the placebo-combination group. Based on this data pembrolizumab + chemotherapy in metastatic non squamous NSCLC is now approved by Health Canada and pCODR has completed its evaluation.

Keynote 407[2] asked the same questions as Keynote-189 in the squamous cell NSCLC population. It was a RCT comparing pembrolizumab plus carboplatin/paclitaxel (or nab paclitaxel) versus carboplatin/paclitaxel (or nab paclitaxel) alone in metastatic Sq NSCLC. The trial showed an improvement in overall survival with a median OS 15.9 months for pembrolizumab combination and 11.3 months in the placebo combination arm (hazard ratio for death, 0.64; 95% CI, 0.49 to 0.85; P<0.001). The overall survival benefit was consistent regardless of the level of PD-L1 expression. Adverse events of grade 3 or higher occurred in 69.8% of the patients in the pembrolizumab-combination group and in 68.2% of the patients in the placebo combination group.

Chemotherapy plus pembrolizumab will now be the preferred strategy in advanced Sq NSCLC in patients PDL1 negative or PDL1 TPS 1-49%. For patients with PDL1 TPS >50% pembrolizumab mono therapy or chemotherapy plus pembrolizumab will be an acceptable option.

Patients with Advanced Squamous Cell Lung Cancer PDL1 > = 50%		
Line of Therapy	[Current Algorithm]	[Proposed Algorithm]
1st-Line	Pembrolizumab	Pembrolizumab or Carboplatin/Paclitaxel +Pembrolizumab
Maintenance		Pembrolizumab if receiving with Carboplatin/paclitaxel in 1st Line
2nd-Line	Platinum Based Chemotherapy	Platinum Doublet if receiving Pembrolizumab mono therapy Docetaxel if receiving Pembrolizumab + chemotherapy in 1st line
3rd Line	Docetaxel	Docetaxel if pembrolizumab mono therapy in 1st line.

Patients with Advanced Squamous Cell Lung Cancer PDL1 < 50% or PD-L1 Status unknown		
Line of Therapy	[Current Algorithm]	[Proposed Algorithm]
1st-Line	Platinum Based Chemotherapy	Carboplatin/Paclitaxel + Pembrolizumab
Maintenance		Pembrolizumab
2nd-Line	Nivolumab, Pembrolizumab (if PD-L1 1-49%), or atezolizumab	Docetaxel
3rd Line	Docetaxel	

2.3 Evidence-Based Considerations for a Funding Population

In the Canadian context, Ho et al. [22] found that approximately 25% of patients with advanced Sq NSCLC received 1st line chemotherapy. 85% of patients receiving first line chemotherapy received a platinum doublet. This same study found approximately 40% of patients received 2nd line therapy. Keynote 407 had a cross over rate of 32-42%.

Total Lung Cancer Deaths	21100
Proportion attributable to NSCLC (85%)	17850
Proportion attributable to Sq NSCLC (25%)	4462
Proportion that receive 1st line chemo (25%)	1115
Proportion with PD-L1 TPS < 50% (70%)	780
Proportion that receive 2nd line therapy (40%)	312

Given that ICI represent the standard 2nd line therapy for Sq NSCLC with PD-L1 TPS < 50% approximately, 480 additional patients would now have access to ICI for advanced Sq NSCLC.

2.4 Other Patient Populations in Whom the Drug May Be Used

Keynote-407 included patients with ECOG performance status 0-1. Given that Canadian clinicians will sometimes offer platinum doublets to patients with ECOG PS 2, it is reasonable to expect clinicians to apply results from Keynote-407 to patients with ECOG PS 2. Patients over the age 65 represented over half the patient population in Keynote407 and there was no maximum age exclusion. Keynote-407 excluded patients with prior exposure to ICIs and thus it remains an open question how applicable these data will be in patients who have progressed after durvalumab in the stage III setting or ICIs in the adjuvant setting (clinical trial participants).

3 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

The following patient advocacy group(s) provided input on pembrolizumab (Keytruda) for metastatic Sq NSCLC and their input is summarized below: Lung Cancer Canada (LCC), the Ontario Lung Association (OLA), and the British Columbia Lung Association (BCLA).

LCC obtained information through various means between January and February of 2019, including an environmental scan, a patient questionnaire, one-on-one patient interviews. In addition, LCC obtained information from a national survey of lung cancer patients and caregivers conducted in August 2015 titled the Faces of Lung Cancer Survey. LCC also drew from information they provided to pCODR for another submission for pembrolizumab in combination with chemotherapy for patients with non-squamous NSCLC. A total of 91 patients and 72 caregivers completed the Faces of Lung Cancer Survey; all patients had or previously have had lung cancer, and all caregivers were caring for, or had cared for patients with lung cancer. Table 1 provides a summary of patients and caregivers obtained through the environmental scan, questionnaire and one-on-one interviews. In total, information was obtained from three patients and two caregivers via the environmental scan, one patient via the one-on-one interview, and two patients from the questionnaire.

Table 1: Patient and Caregiver Respondents via LCC's Patient Input

Source	Gender	Age	Patient /Caregiver
Environ Scan	M	N/A	Caregiver
Environ Scan	M	N/A	Caregiver
Environ Scan	M	N/A	Patient
Environ Scan	F	53	Patient
Environ Scan	M	N/A	Caregiver
Interview	M	61	Patient
Questionnaire	M	75	Patient
Questionnaire	M	73	Patient

OLA obtained information via one phone interview conducted in November 2018 with a patient with lung cancer, and 115 online surveys completed by individuals living with a chronic lung condition between December 2018 and February 2019; upon follow-up with OLA, it was confirmed that three of the survey respondents were people living with a diagnosis of lung cancer. The input of the three respondents with lung cancer was incorporated into sections 3.1.1 and 2.1.2. While 88% of respondents of the online survey indicated living with a chronic lung condition, only three respondents had a diagnosis of lung cancer. OLA also incorporated input from a certified respiratory educator; the role of the certified respiratory educator was stated to involve answering the Lung Line and educating others about living with lung diseases. The certified respiratory educator reviewed sections related to disease experience, experiences with available treatments and outcomes. All information obtained by OLA were from individuals living in Canada. None of the patients responding to OLA's survey had experience with pembrolizumab in combination with chemotherapy.

BCLA did not obtain information from any patients for their input. Instead, BCLA incorporated input from caregivers and clinicians which helped to inform section 3.1 of this summary.

From a patient's perspective, lung cancer can limit a patient's ability to engage in activities with friends and family, work and engage in tasks of day to day living. Patients can feel isolated and a loss of independence due to their condition, which can lead to depression. Current treatments for patients with Sq NSCLC include chemotherapy and immunotherapy. Both chemotherapy and immunotherapy were stated to help with disease control, however side effects of immunotherapy were generally described as more tolerable compared to chemotherapy. A concern was raised regarding the use of chemotherapy and immunotherapy as single agents, as patients with Sq NSCLC may progress while on treatment and subsequently may not be able to receive systemic treatment due to the aggressive nature of their disease. The combination of pembrolizumab with chemotherapy would provide patients with the option of the most effective treatment up front. Only input from LCC provided information regarding the combination of pembrolizumab and chemotherapy, however none of the patients providing input had a diagnosis of Sq NSCLC; seven patients with non-squamous NSCLC provided input regarding treatment with the combination of pembrolizumab and chemotherapy. Patients found that chemotherapy combined with pembrolizumab was effective at controlling disease, reducing tumour size and stabilizing metastases. Side effects were described as tolerable, and patients reported being able to return to work and engage in social activities with friends and families. However, one patient did report having to stop treatment due to having developed diverticulitis, and two other patients reported progression of their disease. Overall, pembrolizumab and chemotherapy was described as an effective treatment with tolerable side effects. Patient values supported by the patient advocacy groups included symptom control and reduction of adverse events, and improved survival and quality of life.

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. Please see below for a summary of specific input received from the patient advocacy groups.

3.1 Condition and Current Therapy Information

3.1.1 Experiences Patients have with Lung Cancer

LCC stated that lung cancer is the leading killer of all cancers in Canada with five-year survival rates of 17% for patients, and even lower for patients with advanced disease (Canadian Cancer Statistics, 2017). Sq NSCLC was stated to be an aggressive form of lung cancer accounting for approximately one third of all NSCLC cases, is associated with a history of smoking, and is more common among men and an older population. BCLA also commented on the high prevalence of lung cancer globally, and the poor prognosis associated with the condition as it typically presents in the metastatic incurable setting.

With regards to the diagnosis of patient's disease, OLA commented on the lengthy process involving many appointments, numerous referrals to specialists and related stress and frustration. The following quotes are from a patient, and the daughter of a patient, respectively: *"It took close to a year, with many appointments and referrals to finally get to the right specialist and receive a proper diagnosis and learn about my prognosis," "The most frustrated thing for me was how long it took to get her diagnosed."*

OLA also discussed patients' need for more information regarding their diagnosis to help them understand their condition and next steps. According to OLA patients were not given enough information about the disease, either cancer or lung cancer specifically, treatment options, and their individual-specific prognosis. Several respondents mentioned feeling rushed during appointments and would prefer language that is *"easy to understand."*

Common symptoms patients present with include a persistent cough, wheezing, coughing up blood, discomfort when swallowing, hoarseness, loss of appetite and weight loss. OLA

also included the following symptoms as a result of lung cancer: pain, stated to be very intense at times, sleep disturbances, and increased triggers within the air/allergens. Both LCC and OLA included the following symptoms: cough, shortness of breath, chest pain or chest tightness and extreme fatigue or exhaustion. Specifically regarding fatigue, OLA stated that patients felt the exhaustion was difficult to handle, and that they had to plan their days around managing this symptom.

Symptoms were stated to vary frequently and were difficult to manage. Two patients interviewed by LCC stated experiencing coughing with blood, and another experienced hoarseness. LCC noted the fear and worry that may result from a diagnosis of lung cancer; one respondent's spouse presented with the symptom of hoarseness, was diagnosed with stage IV squamous cell carcinoma of the lung and was given a prognosis of a couple of weeks. In addition to the poor prognoses of patients with Sq NSCLC, LCC highlighted the lack of available treatment options for these patients. Currently, chemotherapy and immunotherapy are available for patients, however LCC suggests a need for more available therapies.

According to OLA, the ability to work, travel, socialize and participate in leisure and physical activities were aspects of daily living that lung cancer was stated to affect. *"I need supplemental oxygen for every action, and I suffer from terrifying breathless episodes."* OLA also stated that relationships with family and friends, independence, emotional well-being and the financial situations were also affected due to lung cancer. As one patient stated: *"it affects every aspect of my day to day life. It takes longer to get dressed and do my personal hygiene. My ability to carry out tasks and activities is greatly reduced and I can no longer lift heavy objects. I can't walk distances and get tired very quickly."*

3.1.2 Patients' Experiences with Current Therapy for Lung Cancer

According to LCC, chemotherapy was an effective treatment option for patients, and may be used as a single agent, part of a doublet, or combined with radiation. One patient's caregiver commented that their spouse's tumour reduced to one third of its original size, when the patient was subsequently treated with radiation therapy and, four years post diagnosis, was declared as having no evidence of disease in August of 2018. The side effects related to chemotherapy are varied; LCC stated that some patients experience few side effects while others report nausea, vomiting, dizziness, shortness of breath and fatigue. One patient was stated to have experienced an increased heart rate and subsequently stopped receiving chemotherapy. Side effects of chemotherapy were mentioned to impact a patient's ability to work. For example, one patient was forced to stop working due to his symptoms leading to financial hardship for him and his family. Chemotherapy was also reported to weaken patients' immune systems, by means of lowering white and red blood cell counts, which impedes their ability to work, and spend time with family and friends. One patient was admitted to a hospital for ten days due to their red blood cell levels being so low.

LCC also noted that pembrolizumab is another treatment patients are currently receiving. One patient was diagnosed with stage four Sq NSCLC with metastasis to the lymph nodes, mediastinum, ribs and spine, was not a candidate for radiation or surgery, and was given just up to three months of survival; this patient was initially treated with chemotherapy until only it was recommended that she should be transferred to hospice care. However, once receiving a second opinion the patient was placed on pembrolizumab, and current scans showed all whole-body tumours were shrinking. The patient stated, "I actually feel great. Most days, I forget that I'm living with cancer." The child of a patient receiving pembrolizumab stated that the treatment controlled their father's cancer, shrinking the tumour by almost half and helped to shrink the metastases in his bones and kidneys.

For patients with Sq NSCLC who were stated by LCC to experience a high symptom burden, pembrolizumab was effective at relieving symptoms of lung cancer. According to the FOLCR survey, patients felt very sick before treatment with immunotherapy, but continued to feel better within days of their first treatment up to their first few treatments. One patient stated pembrolizumab decreases the severity of his cough and allowed him to have a more normal family life; he stated, *"it's allowed me to live."* In general, LCC stated that side effects of pembrolizumab were manageable. One patient felt normal except for experiencing itchy skin. Most patients responding to the FOCLR reported that side effects were mild and easily manageable. Even in cases of stronger side effects, LCC reported that symptoms were managed by over the counter medications or prescription drugs. However, even in cases of more severe side effects, LCC reported that they were tolerable and did not interfere with day-to-day life. Of note, one patient reportedly discontinued pembrolizumab due to pneumonitis.

Other concurrent non-anticancer treatments patients were currently using were stated by OLA to include Spiriva, Advair, Symbicort, Daxas, Prednisone, Atrovent, Serevent, Onbrez, Tudorza and Ventolin as needed. OLA mentioned that one patient was on so many medications they could not list them. Another patient mentioned undergoing radiation, while another was receiving a double lung transplant earlier in 2018. OLA stated that currently available treatments for patients do provide some amounts of relief for certain symptoms, including fatigue, shortness of breath, cough, appetite loss and low energy. However, other symptoms were stated to require better management, such as, palpitations, dry mouth, mouth sores, *"light-headedness"*/ *"dizziness"*, shakiness, impact on mood, loose bowels, headaches and difficulty sleeping.

According to OLA, patients desire treatments to that will allow them to maintain their independence, reduce the amount of assistance required from others, and increase their energy levels. Patient's also wanted greater education or training for general practitioners to increase their knowledge of lung diseases and reduce delays in diagnosis and treatment. No interviewees, including those with advanced disease, were fond of the idea of receiving no treatment. Patients expressed a desire to better understand their treatment options and the implications of those treatment options, greater treatment options in general, reduction of side effects and improved quality of life. LCC also stated that greater treatment options provide patients with a sense of hope, and can improve their quality of life. Greater treatment options may potentially allow patients to extend their survival, allowing patients to spend time doing things they enjoy with their loved ones, and hopefully survive long enough until another treatment is found. OLA also mentioned the emotional toll of lung cancer, as patients can feel isolated and a loss of their independence resulting in depression.

Main outcomes related to lung cancer patients and caregivers expressed, according to OLA, were a need to slow the progression of disease, reduce symptoms or side effects, including pain, fatigue, cough, shortness of breath, appetite loss, low energy, the inability to fight infection, burning of skin and impacts on their mood. Access, in terms of cost burden related to new treatments, was also something patients and caregivers wanted reduced or eliminated, which was also reported as a problem for patients without private insurance in the BCLA input. More respiratory and lung cancer specialists, a better coordinated health system, the ability to conduct treatments at home in order to reduce the time patients and caregivers need to take off work and reduce disruptions of daily routines, were also stated as being important to patients and caregivers. Trade-offs for patients that would be considered according the BCLA input included less side effects and improved quality of life.

3.1.3 Impact of Lung Cancer and Current Therapy on Caregivers

As stated by LCC, caregivers worry that a diagnosis of lung cancer is a death sentence for their loved ones. Caregivers also experience stigma related to the negative implications associated with lung cancer. The stigma can make caregivers feel emotionally burdened, and caregivers may isolate themselves resulting in anxiety, worry and depression. One caregiver developed severe depression as a result of her spouse's diagnosis of lung cancer and had to be placed on medication. The emotional toll of lung cancer may also affect their loved ones, potentially leading to a lower quality of life for both the patient and the caregiver. LCC stated that caregivers are involved in various activities to help patients cope with the lung cancer, treatments and coordination of care. As both immunotherapy and chemotherapy are delivered to patients intravenously, caregivers must juggle caretaking responsibilities with the needs of their family, home and jobs. Based on the FOLCR survey, caregivers lost time at work leading to reduced productivity and possible financial difficulties due to their caretaking responsibilities. Based on the FOLCR survey, 59% of caregivers reduced the number of hours they worked and 8% quit their jobs.

3.2 Information about the Drug Being Reviewed

3.2.1 Patient Expectations for and Experiences To Date with Pembrolizumab

None of the respondents from surveys or interviews on behalf of OLA or BCLA reported having experience with pembrolizumab. LCC provided input regarding pembrolizumab, however stated that patients who provided their experiences with the drug were diagnosed with non-squamous NSCLC. LCC stated that they did not believe there was any reason that the experiences of patients with non-squamous NSCLC would be any different from patients with Sq NSCLC; however, they did not provide any evidence to support their belief. In total, seven patients with non-squamous NSCLC informed this section; one patient received pembrolizumab in the first-line, two patients in the second-line, and the rest were unknown. All of these patients received pembrolizumab in combination with chemotherapy.

LCC stated that patients found pembrolizumab to be effective at reducing tumour size and controlling patients' lung cancer. Pembrolizumab helped to reduce symptoms, including pleural effusion, shrink tumours and stabilize metastases. One patient was able to return to work, garden and playing with their grandchildren after treatment with pembrolizumab, and another patient was able to return to work full-time.

The combination of pembrolizumab and chemotherapy was offered to one patient who was not eligible for surgery or radiation due to the location of their tumour; pembrolizumab plus chemotherapy provided this patient with hope of surviving lung cancer, as their cancer was termed stable. Another patient received pembrolizumab as a first line treatment, however experienced progression where the patient was then switched to pembrolizumab in combination with carboplatin. After one week, the patient noticed improvements in breathing, coughing, and found that their months-long experience with pleural effusion (and thoracentesis) was resolved; for this patient, their tumours reduced in size by 30%-40%, and metastases were no longer visible.

According to LCC, in general, side effects while receiving pembrolizumab were manageable. One patient stated that *"it wasn't awful when I went on the combo. I had more fatigue and some nausea but I was able to work full time." "Getting through the four cycles that included the carbo was the most challenging but totally doable for me."* One caregiver noted that *"His tumours had all shrunken by 60-80% before he had to have a break. He is now putting on weight and is very energetic and getting lots of things done*

now that he is not fatigued and sleeping all the time. He had cachexia and was literally wasting away. Had gone from 220 lbs to 150…now up to 162." LCC stated that one patient had stop treatment, as they developed diverticulitis, and were then prescribed prednisone and antibiotics. Some patients did experience progression while receiving pembrolizumab in combination with chemotherapy; one patient had to change their course of treatment as their scans showed their tumour had grown, while another patient developed progression with treatment.

LCC noted that Canadian patients currently do not have access to this form of treatment.

3.3 Additional Information

LCC highlighted that patients with Sq NSCLC have high unmet need with few options available to them. Patients who receive chemotherapy or immunotherapy as a single agent in the first line setting may experience progression, and subsequently may be ineligible for systemic second-line treatment due to the aggressive nature of their disease. By combining chemotherapy with immunotherapy in the first line, it could serve as a strategy for treating patients with incurable lung cancer and limited options. According to LCC, patients with Sq NSCLC tend to be older and present with aggressive disease, therefore chemotherapy in combination with pembrolizumab may provide a more effective treatment option with a greater chance for survival. Consultation with oncologists to determine risks, tolerability and incorporate any comorbidities was stated as being important in determine who is eligible for chemotherapy in combination with pembrolizumab. LCC stated that chemotherapy plus pembrolizumab may not be suitable for all patients, as it carries additional side effects. However, given the benefits LCC stated that pembrolizumab combined with chemotherapy aligns with patient values.

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 (www.cadth.ca/pcodr). PAG identifies factors that could affect the feasibility of implementing a funding recommendation.

Overall Summary

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

Clinical factors:

- Treatment sequencing with pembrolizumab in this setting

Economic factors:

- Appropriate dosing schedule
- Additional resources needed to monitor infusion reaction

Please see below for more details.

4.1 Currently Funded Treatments

Platinum doublet therapies (e.g., carboplatin or cisplatin in combination with gemcitabine, paclitaxel, or vinorelbine) are standard of care for first-line treatment of advanced Sq NSCLC. In most jurisdictions, single agent pembrolizumab is available for patients with PD-L1 ≥50%. For patients not eligible for platinum-based therapies, they may receive single agent gemcitabine or vinorelbine.

The funding request is for pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel. Nab-paclitaxel are not funded in any jurisdictions for advanced NSCLC.

PAG is seeking clarity on the most appropriate comparator for pembrolizumab in this setting (i.e., platinum doublet therapies or single agent pembrolizumab).

For patients with ALK positive mutations, crizotinib is available in all jurisdictions. Crizotinib is currently under review at pCODR as a single agent as first-line treatment for patients with ROS1-positive advanced NSCLC. For patients with EGFR positive mutations, afatinib is available in all jurisdictions and gefitinib in some jurisdictions. At the time of this PAG input, osimertinib is currently under review at pCODR for the first-line treatment of patients with locally advanced or metastatic NSCLC whose tumours have EGFR mutations. Dacomitinib is also currently under review at pCODR for the first-line treatment of patients with locally advanced or metastatic NSCLC with EGFR-activating mutations.

4.2 Eligible Patient Population

In the KEYNOTE-407 trial, patients were excluded if they had active central nervous system (CNS) metastases and/or carcinomatous meningitis, did not have an ECOG of 0 or 1, or had prior treatment with any PD-1/PD-L1/PD-L2 agent. PAG is seeking guidance on whether these subgroups of patients would be eligible for pembrolizumab in this setting.

The funding request is for the treatment of patients with metastatic Sq NSCLC in combination with carboplatin and either paclitaxel or nab-paclitaxel, in adults with no prior systemic chemotherapy treatment for metastatic NSCLC. PAG is seeking confirmation

that pembrolizumab in this setting is intended for first-line use (i.e., clarity regarding no other systemic chemotherapy treatment versus no other systemic treatment).

PAG noted that the reimbursement request is for pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel. Although out of scope of the review, PAG is seeking clarity on the use of pembrolizumab in combination with other platinum-based chemotherapy (e.g., cisplatin) or non-platinum based regimens.

If recommended for reimbursement, PAG noted patients on first-line treatment (i.e., platinum-doublet therapy, gemcitabine, vinorelbine, or pembrolizumab) who have not progressed, would need to be addressed on a time-limited basis. If appropriate to add pembrolizumab (for patients on platinum-doublet therapy) or platinum-doublet therapy (for patients on single agent pembrolizumab) or to switch to pembrolizumab in combination with platinum-doublet therapy, PAG is seeking guidance on the appropriate timeframe (e.g., at first dose or final dose of first-line treatment).

4.3 Implementation Factors

The dose is 200mg for Sq NSCLC in the funding request and KEYNOTE-407 trial. PAG noted that pembrolizumab for first- and second-line NSCLC can be administered at 2 mg/kg up to a total dose amount of 200 mg (dose capped at 200 mg). Although fixed dose would minimize drug wastage, PAG is seeking guidance on weight-based dosing of 2 mg/kg up to a flat dose cap of 200 mg in this setting, given the high cost of fixed dose compared to weight based dose for patients weighing less than 100 kg. PAG also identified emerging data of dosing pembrolizumab at 400 mg every 6 weeks, PAG is seeking guidance on the appropriateness of alternate dosing/schedule (i.e., 400 mg or 4 mg/kg up to a flat dose cap of 400 mg every 6 weeks).

PAG is seeking clarity on treatment duration as in KEYNOTE-407, treatment was up to 35 cycles. What stopping rules should be used for pembrolizumab in the maintenance setting and are the usual immunotherapy stopping rules appropriate (10% increase in total tumour burden confirmed with a second CT scan 6-8 weeks following the last scan if progression is suspected)?

Pembrolizumab is an add-on therapy which would increase costs and budget impact. PAG also noted that additional health care resources would be required for pre-medication, drug preparation, chair time and monitoring for toxicities such as immune-mediated reactions post-infusion. Treatment with pembrolizumab, particularly maintenance treatment up to 35 cycles, would require increased: nursing resources, pharmacy resources, clinic visits given treatment is every three weeks, chair time, blood work, laboratory testing (e.g., TSH, cortisol), and supportive care drugs (e.g., vitamin B12, folic acid). Grade 3 or 4 immune-related side effects may require emergency visits.

As pembrolizumab is currently used in a number of other indications, drug wastage could be minimized with vial sharing. However, vial sharing may not be feasible in smaller outpatient cancer centres. PAG noted that introducing a 25 mg vial would be an enabler to implementation.

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.

4.4 Sequencing and Priority of Treatments

PAG is seeking guidance, for patients who receive pembrolizumab in this setting,

- Overall treatment sequencing of all available treatments for first-line NSCLC.
- Second-line treatment options following progression.
- Confirmation that patients would not receive subsequent PD-1 or PD-L1 inhibitors (e.g., nivolumab) in the second-line setting.
- Following completion of 35 cycles of treatment, appropriateness of re-treatment and the time interval between end of treatment and relapse.

For patients with PD-L1 ≥50%, single agent pembrolizumab is available in most jurisdictions, PAG is seeking clarity on whether these patients should receive single agent pembrolizumab or the pembrolizumab combination (with carboplatin and either paclitaxel or nab-paclitaxel).

With respect to treatment sequencing, PAG is seeking guidance on whether patients with mutations (EGFR, ALK, or ROS-1) should be treated with pembrolizumab in combination with platinum doublet therapy in the first-line setting then subsequently with targeted therapies, or whether patients should be treated with targeted therapies first.

PAG is also seeking confirmation that for patients that completed first-line platinum doublet therapy, pembrolizumab would be reserved for the next line of therapy (if TPS of PD-L1 ≥1%) or nivolumab (if PD-L1 is unknown) as per their pERC recommendations.

4.5 Companion Diagnostic Testing

PAG noted that PD-L1 testing is currently completed upon diagnosis. PAG is seeking confirmation that PD-L1 testing is not required for pembrolizumab in this setting.

4.6 Additional Information

None.

5 SUMMARY OF REGISTERED CLINICIAN INPUT

Two joint clinician inputs were received on behalf of a total of 15 registered clinicians; two from Cancer Care Ontario (CCO) and thirteen from Lung Cancer Canada (LCC) for pembrolizumab for patients with metastatic Sq NSCLC.

For patients with PD-L1 ≥50% and PD-L1 <50%, the most appropriate comparators were suggested to be pembrolizumab and platinum doublet chemotherapy, respectively. Clinicians from CCO and LCC agreed that inclusion and exclusion criteria from the Keynote 407 trial were generalizable to and reflective of Canadian patients in clinical practice. While pembrolizumab will not be a new treatment introduced into the treatment space for patients with Sq NSCLC, it would replace other treatments, immunotherapy and chemotherapy, offered in the first-line setting. For patients with PD-L1 ≥50% who wish to delay or avoid chemotherapy, pembrolizumab may be provided as a monotherapy. However, the treatment regimen for the patient will ultimately depend on disease characteristics in addition to patient preference. With regards to whether pembrolizumab should be provided to patients with a single agent chemotherapy or platinum doublet chemotherapy, both clinician inputs agreed that pembrolizumab should be limited to a combination with any platinum doublet; current evidence does not support the use of pembrolizumab in combination with single agent chemotherapy.

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

5.1 Current Treatment(s) for this Squamous Non-Small Cell Lung Cancer

Both clinician inputs stated that single agent pembrolizumab was the most appropriate comparator for patients with Sq NSCLC and PD-L1 ≥50%, except for patients from Prince Edward Island as they currently do not have access to publicly funded pembrolizumab in the first-line. Both inputs also identified platinum doublet chemotherapies as the most appropriate comparator for patients with Sq NSCLC and PD-L1 <50%. The LCC input identified paclitaxel with gemcitabine or vinorelbine as the commonly used platinum doublet regimen.

Input from LCC noted that single agent immunotherapy with nivolumab or pembrolizumab is available in all Canadian provinces, including Prince Edward Island, in the second-line after progression on first-line chemotherapy; LCC stated that currently Canadian patients can receive both chemotherapy and immunotherapy in some sequence.

5.2 Eligible Patient Population

Both CCO and LCC stated that inclusion and exclusion criteria from the Keynote 407 trial were generalizable and reflective of patients seen in clinical practice. The CCO input identified they would use the treatment combination under review in Sq NSCLC patients with PD-L1 <50% and who have an ECOG performance status of 0 or 1, as the median overall survival (OS) with standard therapy is currently less than one year for this patient population. In addition, the CCO input expressed a desire to combine pembrolizumab with other standard platinum doublets used in first line, such as gemcitabine and carboplatin or gemcitabine and cisplatin for patients who are intolerant to taxanes. On the other hand, the LCC stated that there are data to support the use of pembrolizumab in combination with platinum/paclitaxel or nab-paclitaxel to improve care for almost all patients with advanced Sq NSCLC regardless of PD-L1 expression. The LCC identified that all patients ultimately progress after first-line therapy, and many patients are not candidates for second-line therapy despite there being options that exist with known survival benefit. One reason identified for this is because the Sq NSCLC patient population is more likely to be older, current or former smokers, and have co-morbidities, and thus this translates into less physiological reserve and a population that is vulnerable to a decline in performance status

that would make them ineligible for second line options. Thus, by combining platinum doublet with immunotherapy as a treatment in the first-line setting, patients with incurable lung cancer can be guaranteed access to both chemotherapy and immunotherapy and are no longer at risk of having progression before they have an opportunity to receive the other therapy in second line. This ability to optimize therapy was also identified as being very important in this patient population because there are fewer effective chemotherapy options. For example, pemetrexed, which plays an important in treating patients with non-squamous NSCLC, is not efficacious among patients with Sq NSCLC.

CCO stated preference to use pembrolizumab for patients with stage III disease who have good performance status, but who are not amenable to curative treatment for any reason, for example patients who decline surgery, and patients whose disease cannot be safely treated with radiation therapy.

5.3 Relevance to Clinical Practice

LCC identified that the combination of pembrolizumab with platinum doublet chemotherapy is not a true "new" therapy in the management of patients with Sq NSCLC; patients receiving platinum doublet in the first-line will receive immunotherapy in the second-line, and patients with PD-L1 ≥50% will receive pembrolizumab in the first-line and platinum doublet upon progression. However, the use of chemotherapy and immunotherapy in combination in the first-line was acknowledged by LCC as a new strategy, as current best practices expose patients to chemotherapy and immunotherapy over both first and second-lines of therapy.

In addition, the LCC highlighted that currently, first-line single agent pembrolizumab is reserved for patients with PD-L1 ≥50%. Some patients may have unknown PD-L1 status at the time of starting first-line treatment. The LCC indicted that upwards of one-third would be expected to be PD-L1 ≥50% of these patients with unknown PD-L1 status. However, patients with unknown PD-L1 status would have to be treated with platinum doublet first, despite this being an inferior strategy to receiving immunotherapy in patients with PD-L1 ≥50% as determined from the KEYNOTE-024 trial, and thus would be a disservice to this group of patients. Hence, access to pembrolizumab with chemotherapy for all patients, regardless of PD-L1 status, would prevent this group of patients from missing out on the best therapy.

Separating chemotherapy and immunotherapy into separate lines of therapy may preclude patients from treatment in the second-line as some patients will deteriorate after progressing on their first-line therapy. The combination of pembrolizumab and chemotherapy will ensure that patients receive the most effective therapies up front. LCC suggested that there may be synergistic effects between chemotherapy and immunotherapy when delivered together, and that the combination of the treatment used in the first-line may account for the significant survival benefit observed in Keynote 407. While pembrolizumab and chemotherapy showed greater toxicity than chemotherapy alone due to immunotherapy side effects, CCO stated these side effects were generally manageable, and there was a clinically significant improvement in OS compared to standard of care. Similarly, LCC also stated that due to the different mechanisms of action and adverse effect profiles of pembrolizumab and platinum plus paclitaxel or nab-paclitaxel, data do not seem to show a compounded risk for any particular adverse effect in patients. LCC suggests that the evidence of superior efficacy does not seem to come at a cost of tolerability or safety compared to current strategies of immunotherapy or chemotherapy as separate lines of treatment.

For patients with a PD-L1 ≥50%, LCC stated pembrolizumab may still be used as a single agent for patients who prefer to delay or avoid chemotherapy. For patients where an aggressive first-line strategy is preferred, for example a patient with large tumour burden or rapid progression of

clinical symptoms in whom obtaining a significant tumour response quickly is important, the combination of immunotherapy and chemotherapy would be used. The choice of either options gives clinicians and patients the ability to tailor a treatment plan to the patient's personal goals and clinical status.

For patients with PD-L1 <50%, LCC stated that the combination of chemotherapy and immunotherapy in the first line may reduce the risk of patients deteriorating before having the option of receiving immunotherapy in the second-line. While patients with PD-L1 <50% may have a lower response to immunotherapy compared to patients with PD-L1 ≥50%, the potential for benefit still exists. LCC also stated that combination chemotherapy and immunotherapy will not replace platinum doublets alone in this patient group, but rather allow for more strategies to best meet an individual patient's needs. Conversely, the CCO stated that pembrolizumab would be the new standard of care for patients with Sq NSCLC and PD-L1 of <50% who are fit enough to tolerate it.

Contraindications were stated to be the same as those that already exist for each drug individually.

5.4 Sequencing and Priority of Treatments with Pembrolizumab

CCO stated pembrolizumab would replace current platinum doublet as first-line therapy among patients with PD-L1 positive status. However, if pembrolizumab in combination with chemotherapy is selected as the first-line therapy, LCC stated it would replace sequential first and second-line treatment options with platinum doublet chemotherapy followed by immunotherapy, or vice versa. LCC identified that there is currently no evidence to suggest that receiving immunotherapy in the second-line following receipt of immunotherapy first-line will be beneficial. Upon progression after receiving pembrolizumab and chemotherapy first-line, LCC expects that patients will go on to receive standard single agent chemotherapy or enroll in clinical trials for second-line therapy.

For patients who receive the full two years (35 cycles) of pembrolizumab in the first-line setting without experiencing progression, but experience progression once they are off-treatment, LCC stated that these patients should be offered the option of being rechallenged with pembrolizumab. The Keynote 407 and Keynote 010 trials were stated as evidence supporting rechallenging patients with pembrolizumab; rechallenging patients with pembrolizumab was part of the trial design in Keynote 407, and the Keynote 010 trial showed that 79% of patients who were rechallenged had a partial response or stable disease with re-institution of pembrolizumab.

Finally, LCC stated that the cost impact per lifetime of treatment of a single patient on the healthcare budget would be much less by introducing pembrolizumab in combination with chemotherapy in the first line, versus introducing a whole new line of therapy or new agent in the treatment algorithm.

5.5 Companion Diagnostic Testing

CCO stated that PD-L1 testing currently occurs routinely. LCC stated that companion diagnostic testing was not applicable in this case.

Reflex testing for PD-L1 status is not standard across Canada, and many centres refer tissue to outside labs, including out of province, which results in delays and may pose a barrier to determining PD-L1 status to optimize treatment. Some patients also do not have adequate tissue

for valid PD-L1 status to be determined, as the test requires a minimum of 100 viable tumour cells for analysis

5.6 Implementation Questions

5.6.1 For patients with PD-L1 ≥50%, is there a preference to provide these patients with single agent pembrolizumab or the combination of pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel?

Refer to section 5.3 above.

5.6.2 The funding request is for pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel. Nab-paclitaxel is not funded in any jurisdictions for advanced NSCLC. Are the results from these trials generalizable to Canadian clinical practice (e.g., pembrolizumab with non-platinum based chemotherapy for patients with a contraindication to platinum-based chemotherapy)?

CCO agreed that pembrolizumab may be given in combination with any platinum doublet, but not with single agent chemotherapy. LCC also highlighted that there are currently no phase three clinical trial data to inform decision making regarding single agent pembrolizumab with single agent chemotherapy in the first-line. However, LCC identified that there are currently ongoing trials examining the best management strategy for patients with poorer performance statuses. Without evidence to suggest otherwise, LCC stated that the indication for pembrolizumab in the first-line should be limited to patients receiving platinum doublets.

The majority of patients with an ECOG performance status of 0 or 1 were reported to receive platinum doublet chemotherapy. LCC stated that most patients are eligible for some type of platinum doublet, and the majority of Sq NSCLC patients currently receive carboplatin and paclitaxel in this setting. As Sq NSCLC patients are more likely to be older and with co-morbidities, cisplatin-based regimens are less frequently provided. LCC also highlighted that nab-paclitaxel is currently not used as a part of Canadian practice for NSCLC, therefore if there were access to pembrolizumab with a platinum doublet it would be used with carboplatin and paclitaxel.

LCC highlighted that there are a minority of patients who are candidates for chemotherapy, but not platinum based therapy, however these patients were stated to still be eligible for single agent immunotherapy based on pERC recommendations for second-line pembrolizumab, nivolumab and atezolizumab. pERC recommendations specify the second-line agents can be used in the setting of disease progression or after “cytotoxic chemotherapy”, which is not limited to only platinum doublet chemotherapy regimens.

6 SYSTEMATIC REVIEW

6.1 Objectives

The primary objective of this systematic review is to evaluate the safety and efficacy of pembrolizumab in combination with carboplatin and paclitaxel or nab-paclitaxel, for the treatment of metastatic, squamous cell (Sq), non-small cell lung cancer (NSCLC) in adult patients with no prior systemic chemotherapy.

Supplemental Questions and Comparison with Other Literature most relevant to the pCODR review and to the Provincial Advisory Group were identified while developing the review protocol and are outlined in section 7 and section 8.

Supplemental Issue 1: Summary and critical appraisal of indirect treatment comparison (ITC) of pembrolizumab + platinum-based chemotherapy versus pembrolizumab monotherapy.

6.1 Methods

6.1.1 Review Protocol and Study Selection Criteria

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

Table 6.1: Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Published or unpublished RCTs In the absence of RCT data, fully published clinical trials investigating the safety and efficacy of pembrolizumab plus chemotherapy should be included.	Adult patients (≥18 years of age) with metastatic, squamous cell, NSCLC, with no prior chemotherapy for disease Subgroups: - Age - Sex - ECOG PS - PD-L1 expression - Smoking status - Paclitaxel vs. nab-paclitaxel - Prior adjuvant or neoadjuvant therapies - Number and type of metastases	Pembrolizumab (KEYTRUDA®) + carboplatin + paclitaxel *or* nab-paclitaxel	Platinum doublet chemotherapy: Cisplatin *or* carboplatin + paclitaxel, vinorelbine, *or* gemcitabine Patients ineligible for platinum-based therapies: single agent gemcitabine or vinorelbine Patients with ≥ 50% PD-L1: single agent pembrolizumab	Primary: - **OS** - PFS Secondary: - ORR - TTP - **HRQoL** **Safety:** - **AEs** - **TRAEs** - **SAEs** - **WDAEs**
Abbreviations: **AE** = adverse event; **ECOG PS** = Eastern Cooperative Oncology Group Performance Status; **HRQoL** = health-related quality of life; **NSCLC** = non-small cell lung cancer; **ORR** = objective response rate; **OS** = overall survival; **PD-L1** = programmed death-ligand 1; **PFS** = progression-free survival; **RCT** =				

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Randomized controlled trial; **SAE** = serious adverse event; **Sq** = squamous cell carcinoma; **TRAEs** = treatment-related adverse events; **TTP** = time to progression; **WDAEs** = withdrawals due to adverse events				

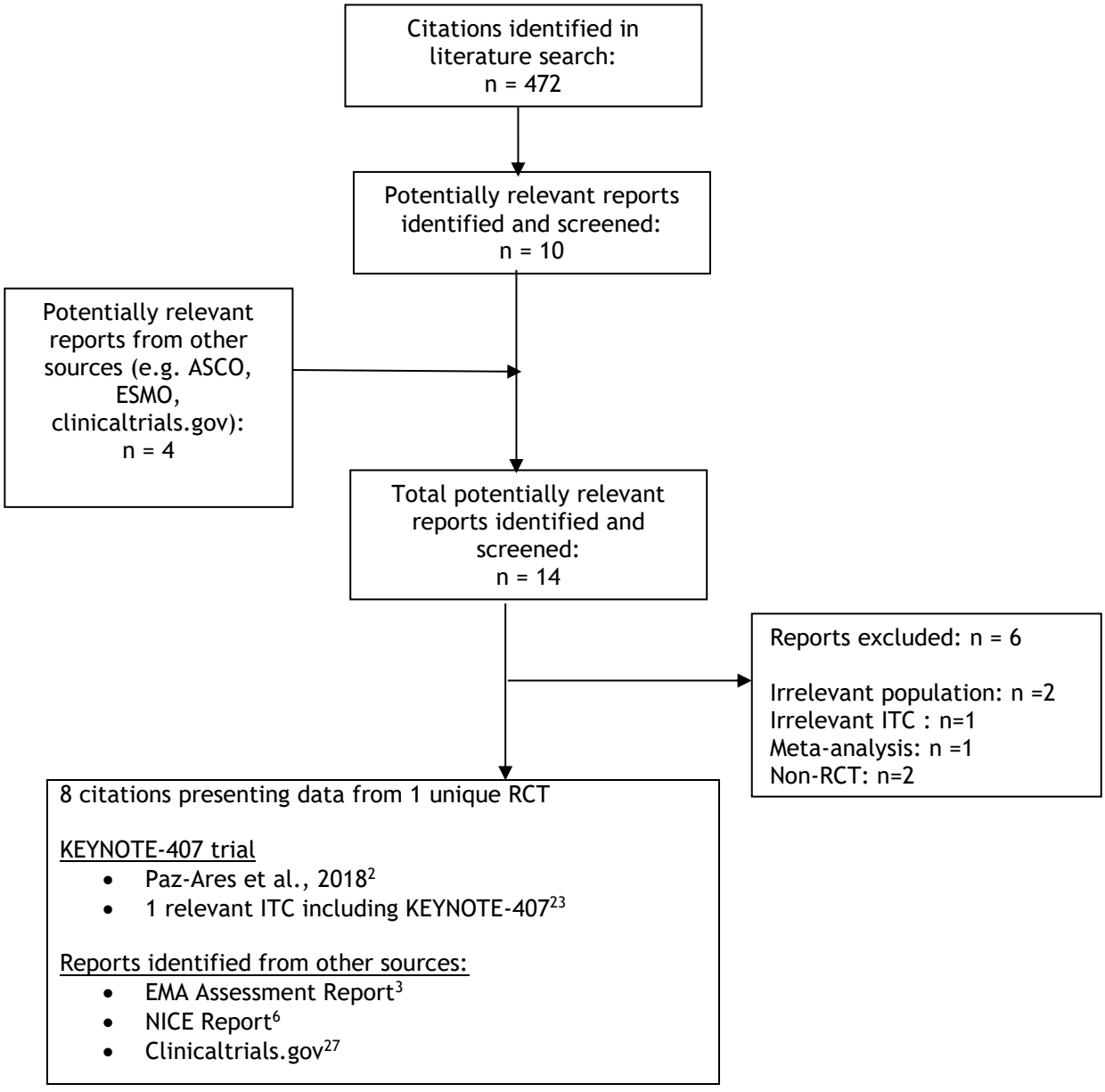
** Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions)*

6.2 Results

6.2.1 Literature Search Results

Of the 14 potentially relevant reports identified, 8 citations reporting data from one randomized clinical trial (RCT) were included in the pCODR systematic,[2,3,6,23-27] and 6 citations were excluded.[28-33] Citations were excluded because they included an irrelevant study population (did not include Sq-NSCLC);[28,30] or the study design was a meta-analysis,[29] a non-randomized clinical trial,[31,32] or an irrelevant indirect treatment comparison (ITC).[31-33]

Figure 6.1: QUOROM Flow Diagram for Inclusion and Exclusion of studies



Note: Additional data related to the KEYNOTE-407 trial were also obtained through requests to the Submitter by pCODR.[4,34-37]

6.2.2 Summary of Included Studies

One randomized clinical trial, KEYNOTE-407 (KN-407), met the selection criteria for this systematic review. Key trial characteristics, including study design, eligibility criteria, intervention details, and trial outcomes, are summarized in Tables 6.2 and 6.3.

6.2.2.1 Detailed Trial Characteristics

Table 6.2: Summary of Trial Characteristics of the Included Studies

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
Study: KEYNOTE-407 MK-3475-407 NCT02775435 **Characteristics:** Ongoing, Phase III, superiority, double-blind, placebo-controlled, randomized (1:1 ratio) trial n = 559 randomized (n = 278 in pembrolizumab + chemotherapy arm; n = 281 to placebo + chemotherapy arm) n= 558 treated (n = 278 in pembrolizumab + chemotherapy arm; n = 280 to placebo + chemotherapy arm) **Number of centres and number of countries:** 137 sites in 17 countries including Canada, Australia, China, France, Germany, Hungary, Italy, Japan, Mexico, Netherlands, Poland, Russia, South Korea, Spain, Thailand, Turkey, and the United States **Patient Enrolment Dates:** August 19th, 2016 to December 29th, 2017 **Data cut-off dates:** IA1 – October 27th, 2017 IA2 – April 3rd, 2018 IA3 - To be performed after approximately 415 PFS events are observed **Final Analysis Date:**	<u>Key Inclusion Criteria:</u> - ≥ 18 years of age - Stage IV Sq-NSCLC (mixed histology accepted if squamous component) - No prior systemic therapy - Measurable disease based on RECIST 1.1 - Tumor tissue sample for PD-L1 assessment - ECOG PS 0 or 1 - Adequate organ function - Life expectancy of ≥ 3 months <u>Key Exclusion Criteria:</u> - Major surgery <3 weeks; radiation to lung (>30 Gy) <6 months; or palliative radiotherapy <7 days prior to first dose on study - Live-virus vaccine <30 days before first dose - Prior malignancy <5 years and not treated with curative intent (with some skin, cervical, and bladder cancer exceptions) - Active CNS metastases or carcinomatous meningitis (stable or asymptomatic brain metastases not requiring corticosteroids accepted) - Peripheral neuropathy that is CTCAE v.4 grade ≥2 - Severe hypersensitivity reaction to another mAb - Known sensitivity to carboplatin or paclitaxel or nab-paclitaxel - Active autoimmune disease <2 years prior to first dose requiring systemic treatment - Use of chronic systemic steroids - Active infection requiring therapy - Known history of HIV - Active HBV or HCV infection - Interstitial lung disease - History of pneumonitis that required IV glucocorticoids	<u>Intervention:</u> Pembrolizumab (200 mg) + Carboplatin (AUC 6) + Paclitaxel (200 mg/m^2) or nab-paclitaxel (100 mg/m^2) every 3 weeks <u>Comparator:</u> Saline placebo (200 mg) + Carboplatin (AUC 6) + Paclitaxel (200 mg/m^2) or nab-paclitaxel (100 mg/m^2) every 3 weeks	<u>Primary:</u> - OS - PFS <u>Secondary:</u> - ORR - DOR <u>Exploratory:</u> - HRQoL - Subgroup analysis (PD-L1 expression) on OS, PFS, and ORR

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
To be performed after approximately 361 deaths are observed **Estimated study completion date**: February 15th, 2021 **Funding:** Merck Sharp & Dohme Corp.	- Prior anti-PD-1, PD-L1, PD-L2 agent including pembrolizumab - Prior or current use of investigational therapies or devices - Known psychiatric of substance abuse disorder that would interfere with participation		
Abbreviations: AUC = area under the curve; CNS = central nervous system; CTCAE = common terminology criteria adverse events; DOR = duration of response; ECOG PS= Eastern Cooperative Oncology Group performance score; Gy = gray; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HRQoL = health related quality of life; IA = interim analysis; IV = intravenous; mAb = monoclonal antibody; mg = milligram; mg/m2 = milligram per square meter of body surface; n = sample size; ORR = objective response rate; OS= overall survival; PD-1 = programmed cell death 1; PD-L1 = programmed death-ligand 1; PD-L2 = programmed death-ligand 2; PFS = progression-free survival; RECIST = response evaluation criteria in solid tumours; Sq-NSCLC = squamous cell, non-small cell lung cancer			

Table 6.3: Select quality characteristics of included studies of pembrolizumab + carboplatin + paclitaxel in patients with Sq NSCLC

Study	Treatment vs. Comparator	Primary outcome	Required sample size	Sample size	Randomization method	Allocation concealment	Blinding	ITT Analysis	Final analysis	Early termination	Ethics Approval
KN-407	Pembrolizumab + carboplatin + paclitaxel or nab-paclitaxel vs. saline placebo + carboplatin + paclitaxel or nab-paclitaxel	Dual OS and PFS	560	559	Yes, central system via IVRS/ IWRS in a 1:1 ratio	Yes, central system via IVRS/ IWRS	Yes, double-blind (chemo therapy was open-label)	Yes	No	No	Yes
Abbreviations: ITT = intention to treat; IVRS = interactive voice response system; IWRS = interactive web response system; KN = KEYNOTE; OS = overall survival; PFS = progression-free survival; vs. = versus											

a) Trials

KEYNOTE-407 (KN-407) is an ongoing, international, phase III, superiority, double-blind, placebo-controlled, randomized controlled trial (RCT). The objective of KN-407 is to compare the efficacy and safety of pembrolizumab in combination with carboplatin and paclitaxel or nab-paclitaxel (hereafter referred to as the pembrolizumab + chemotherapy arm) versus saline placebo in combination with carboplatin and paclitaxel or nab-paclitaxel (hereafter referred to as the placebo + chemotherapy arm) as first-line therapy in patients with metastatic squamous non-small cell lung cancer. The trial was conducted in 125 sites across 17 countries, including 7 sites across Canada in Quebec, Ontario, and Nova Scotia.[2]

Trial Design

The study design for KN-407 included a screening phase, initial treatment phase, second course (retreatment) phase, and a crossover phase.[2] Details for these phases are listed below:

Screening Phase:

During a 28 day period, patients that provided informed consent were assessed for eligibility (key inclusion and exclusion criteria are listed in Table 6.2), and had baseline disease evaluations (for example, tumor assessments and clinical/laboratory examinations). Patients could be rescreened, if they initially failed to meet study criteria.[2] One of the main reasons reported for rescreening was if a participant was unable to complete all screening procedures (i.e. tumor imaging, PD-L1 testing, etc.) within the screening window allowed in the trial.[36]

Treatment Phase:

Randomization and Treatment Allocation

Patients were randomized and allocated to treatment through a central interactive voice response system/integrated web response system (IVRS/IWRS) in a 1:1 ratio. The choice of paclitaxel or nab-paclitaxel was determined by the investigator prior to randomization and documented in the interactive voice response system (IVRS)/interactive web response system (IWRS). Treatment allocation/randomization was stratified according to 3 factors:

1) PD-L1 expression: tumor proportion score ≥1% vs. <1% (PD-L1 inevaluable patients included in the <1% group)
2) Choice of taxane chemotherapy: paclitaxel vs. nab-paclitaxel
3) Geographic region of enrolling site: East-Asia vs. non-East Asia[2]

Treatment

Patients were randomized to receive either pembrolizumab and carboplatin and paclitaxel or nab-paclitaxel, or saline placebo in combination with carboplatin and paclitaxel or nab-paclitaxel. Treatment with pembrolizumab or saline placebo continued for up to 35 cycles (approximately 2 years) and was administered with chemotherapy for the first 4 cycles, or until radiographically confirmed progressive disease (PD), occurrence of unacceptable toxic effects, investigator's decision to discontinue the treatment, or withdrawal of consent. Participants who obtained a complete response (CR) could consider stopping treatment. If toxic events were attributed to one component of the treatment, that component alone could be discontinued. At the discretion of the investigator, patients were able to continue treatment after the first imaging assessment that showed PD until a second imaging assessment 28 days later as per immune-related response evaluation criteria in solid tumours (irRECIST). If PD was unconfirmed at the second imaging assessment and participants were clinically stable, treatment could continue until PD was confirmed by the site investigator.[2]

End of Treatment

Participants completed a mandatory safety follow-up visit approximately 30 days after the last trial dose or before the start of a new antineoplastic treatment, whichever occurred first. Participants with an adverse event (AE) of grade >1 were further followed until the resolution of the AE to grade 0-1 or start of a new antineoplastic treatment. Participants were followed for up to 2 years. Participants

who discontinued for reasons other than PD were considered to still be on study and continued with regularly scheduled assessments, and information on new treatments started, PD, and death were collected. Participants who were potential candidates for crossover with radiographically confirmed PD (verified by central review) could be unblinded upon investigator request. Participants in the placebo combination arm had the option to crossover and receive open-label pembrolizumab monotherapy. Participants in the pembrolizumab combination arm with PD, but were benefitting clinically in the opinion of the investigator, could continue to receive open-label pembrolizumab monotherapy to complete 35 cycles, and the details of the Crossover Phase are listed below. Participants in the pembrolizumab combination arm that experienced a CR, partial response (PR), or stable disease (SD) during treatment and experienced PD during the 2 year follow-up period, or discontinued treatment for reasons other than PD, were eligible for retreatment with pembrolizumab monotherapy, discussed in the Second Course (Retreatment) Phase section below.[2]

Survival Follow-Up

Participants who experienced radiologically confirmed PD or started a new anticancer therapy were moved into the survival follow-up phase and contacted by telephone every 12 weeks to assess survival status and post-study treatment information until death, withdrawal of consent, or the end of the study, whichever occurred first.[2]

<u>Second Course (Retreatment) Phase:</u>

Participants randomized to receive pembrolizumab, or participants who were randomized to placebo and crossed over to pembrolizumab monotherapy, were eligible for retreatment for up to 17 cycles if:

- Initial treatment with pembrolizumab was stopped after obtaining a confirmed CR, were treated for at least 8 cycles, and received at least 2 cycles beyond the date initial CR was declared, or
- Had SD, PR, or CR, and stopped pembrolizumab after 17 cycles for reasons other than PD or intolerability.

In addition, the following criteria had to be met:

- Experienced radiographic PD, as assessed by investigator according to irRECIST after stopping initial treatment with pembrolizumab due to achievement of a confirmed CR.
- Did not receive any other systemic anti-cancer treatment since the last dose of pembrolizumab (local treatment, such as radiation or surgery, and patients with stable brain metastases allowed)
- Continued to meet the following eligibility criteria:
    - Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0 or 1
    - Adequate organ function (as defined by laboratory values outlined in the protocol)
    - If female and of childbearing potential, must not be pregnant

- Must not be not receiving other investigational or systemic anticancer therapies, or had recent major surgery or radiation to the lung that is > 30 gray (Gy)
- Expected to require any other form of antineoplastic therapy while on study
- Received a live-virus vaccine
- Known history of prior malignancy with the exception of participants that underwent potentially curative therapy with no recurrence for 5 years or participants who underwent successful definitive resection of basal cell carcinoma of the skin, superficial bladder cancer, Sq cell carcinoma of the skin, in situ cervical cancer, or other in situ cancers
- Had a severe hypersensitivity reaction to a monoclonal antibody
- Has active autoimmune disease that has required systemic treatment in the past 2 years
- Requires the use of chronic systemic steroids
- Has interstitial lung disease or a history of pneumonitis that required oral or IV glucocorticoids[2]

Crossover Phase:

Participants in the placebo + chemotherapy arm who were unblinded after verification of PD from the blinded independent central radiological review (BICR), had the option to crossover and receive pembrolizumab monotherapy at the discretion of the investigator if the following criteria were met:

- AEs (except alopecia and peripheral neuropathy) due to therapy improved to ≤ Grade 1 according to Common Terminology Criteria for Adverse Events (CTCAE) version 4
- Stable brain metastases (crossover if unstable due to new or progressing brain metastases were not allowed)
- ECOG PS 0 or 1
- Did not receive other anticancer systemic therapies other than the chemotherapy administered during the treatment phase
- If palliative radiotherapy (30 Gy or less) was required, it was completed ≤ 7 days prior to the first dose of crossover trial treatment
- Adequate organ function

Participants who discontinued chemotherapy due to AEs, withdrew consent, or discontinued for any reason other than PD were not eligible for crossover. Treatment with pembrolizumab could not be initiated earlier than 21 days after the last dose of chemotherapy. Participants who crossed over and experienced a CR could hold pembrolizumab and be considered for the Second Course (Retreatment) Phase.

Participants in the pembrolizumab combination arm with BICR-confirmed PD and were experiencing clinical benefit, had the option to continue pembrolizumab to complete up to 35 cycles.[2]

Sample Size

The planned sample size was approximately 560 participants with the following assumptions:

1. The enrolment period is 15.5 months and the ramp-up period of enrollment is 7 months
2. Median progression-free survival (PFS) is 6 months in the control group
3. Median overall survival (OS) is 12 months in the control group with a true hazard ratio (HR) of 0.7
4. Annual drop-out rate for PFS is 3%, and for OS is 1%
5. The number of events and alpha (α) levels of interim analyses (IAs) and final analysis are as specified in the study statistical analysis plan (SAP) in the protocol (see below)

To detect a HR of 0.7 for OS with 361 deaths and a one-sided significance level, the study has around 85% power at α=0.01, ~90% power at α=0.02, and 92% power at 0.025. The final analysis occurs after 361 deaths are observed.

To detect a HR of 0.7 for PFS with 415 PFS events and a one-sided significance level, the study has around 90% power at α=0.01, ~92% power at α=0.015, 94% power at α=0.02, and 95% power at 0.025.

With 200 participants, at α=0.005 (one-sided), the study has 84% power to detect a 25% difference in objective response rate (ORR) (50% vs. 25%) and 97% power to detect a 30% difference (50% vs. 20%) in ORR. At α=0.0025 (one-sided), the study has 94% power to detect a 25% difference in ORR or 99% power to detect a 30% difference in ORR.[2]

Disease Assessments

Disease was assessed using tumor imaging acquired through computed tomography (CT), or magnetic resonance imaging (MRI) when CT is contraindicated or for imaging of the brain. Tumour imaging was scheduled at weeks 6, 12, and 18 and then every 9 weeks through week 45 and every 12 weeks thereafter. Local investigator assessment was used for all assessments and submitted to a central imaging vendor for BICR assessment, and the primary measure for assessment for tumor response was conducted using RECIST 1.1. The primary analyses (outlined in the next section) were reported based on BICR assessment, and sensitivity or exploratory analyses may have included investigator assessed results. The central imaging vendor verified PD following local site investigator-assessed PD, and expedited verification of PD was requested when the participant was a candidate for crossover (requested at initial instance of PD or at the confirmation scan 28 days later). Participants with PD that was verified by central review of their initial radiological scan could continue treatment until a repeat imaging scan was conducted at the discretion of the investigator. Repeat imaging was assessed by irRECIST by the investigator. Participants discontinued treatment if confirmed PD at the second assessment by irRECIST, with the exception of participants who were clinically benefitting and tumor burden was stable at the second imaging scan (did not increase).[2]

Study Endpoints and Statistical Analyses

Primary Endpoints

KN-407 had dual primary endpoints of OS and PFS. OS was defined as the time from randomization to death due to any cause, and participants without documented death at the time of analysis were censored at the date of last known contact. PFS was defined as the time from randomization to the first documented disease progression using RECIST 1.1 by BICR or death due to any cause, whichever occurred first. Censoring rules at the time of primary analysis for PFS are as follows:

- If no PD, death, or anticancer therapy initiated, participant is censored at last disease assessment
- If no PD or death, and anticancer therapy is initiated, participant is censored at last disease assessment prior to the new anticancer therapy
- PD or death documented after ≤1 missed disease assessment, participant is considered progressed at date of documented PD or death
- PD or death documented after ≥2 missed disease assessments, participant is considered progressed at date of documented PD or death

Further, two sensitivity analyses with different censoring rules were performed, the first of which censored participants at the last disease assessment prior to missing ≥2 disease assessments, and the second considered participants progressed if not on study treatment at time of analysis (and no documented PD or death).

The dual primary hypotheses of OS and PFS were evaluated by comparing the treatment difference of the pembrolizumab combination arm to the placebo combination arm using a stratified log-rank test. The magnitude of the treatment difference, i.e. the HR, was estimated using a stratified Cox regression model with Effron's of tie handling, and event rates over time were estimated within each treatment arm using the Kaplan-Meier (K-M) method. The stratification factors used for randomization (PD-L1 TPS, choice of taxane, and geographic region) were applied to both the log-rank test and Cox model. The restricted mean survival time (RMST) method was to be used if the proportional hazards assumption was not met. An exploratory analysis of PFS (PFS2) would potentially be conducted, defined as the time of randomization to subsequent PFS or death after initiation of a new anti-cancer therapy. Adjustment for the effect of crossover on OS would potentially be conducted if appropriate using recognized methods such as the two-stage method or Rank Preserving Structural Failure Time model.

PD that occurred during the Second Course Phase was not counted in the primary analysis. The intention to treat (ITT) population was used for primary endpoint analyses, which included all randomized participants.[2]

Secondary Endpoints

Secondary endpoints included ORR and duration of response (DOR). ORR was defined as the proportion of subjects who experienced a CR or PR. The difference in ORR between the two treatment arms and the associated 95% confidence interval (CI) was calculated using the stratified Miettinen and Nurminen method with strata weighting by sample size and single treatment covariate. ORR that occurred in the Second Course Phase was not counted in the primary analysis. DOR was defined as the time from first documented CR or PR until PD or death, for participants that experienced CR or PR responses. Participants who did not have PD

or die at the time of analysis for DOR were censored at the date of their last tumor assessment. DOR was summarized descriptively using K-M medians and quartiles, if sample size permitted using only the participants with CR or PR. The ITT population was used for secondary endpoint analyses.[2]

Exploratory Endpoints

Pre-specified exploratory endpoints included OS and BICR-assessed PFS and ORR by PD-L1 subgroup (i.e., ≥1% vs <1%) and by choice of taxane therapy (i.e., paclitaxel or nab-paclitaxel) as per RECIST 1.1; and PFS, ORR, and DOR by investigator-assessed irRECIST and RECIST 1.1. Health-related quality of life (HRQoL) in the overall population and by PD-L1 was also explored, and is discussed below. Treatment effect (OS, PFS, and ORR) across the following subgroups was also explored: age, ECOG PS, sex, race, geographic region, smoking status, brain metastasis, PD-L1 expression, and taxane chemotherapy.[2]

Health-related Quality of Life

The analysis of HRQoL was exploratory with no prespecified hypotheses. HRQoL was assessed using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (EORTC-QLQ-C30) and Lung Cancer 13 (EORTC-QLQ-LC13), which is a supplemental lung cancer-specific module. Additionally, the European Quality of Life (EuroQoL) EQ-5D-3L questionnaire was also used. The EORTC-QLQ-C30 contains 30 items including five functional dimensions (physical, role, emotional, cognitive, and social), 3 symptom measures (fatigue, nausea/vomiting), and pain), and six single items (dyspnea, sleep disturbance, appetite loss, constipation, diarrhea, and financial impact). It also includes a global health and quality of life scale, which uses a 7 point scale (1 = very poor and 7 = excellent) and other items are scored on a 4 point scale. A clinically relevant change in score on any scale of the EORTC QLQ-C30 has been estimated to 10 points.[38] Evidence-based guidelines for the interpretation of clinically relevant differences for cross-sectional analyses (between treatment arm differences at a single time point) of each of the EORTC QLQ-C30 subscales has also been developed by Cocks et al., 2011, and will be used to interpret results.[5] The EORTC QLQ-LC13 includes lung cancer-associated symptom items (including cough, hemoptysis, dyspnea, and site-specific pain) and treatment-related symptoms (including sore mouth, dysphagia, peripheral neuropathy, and alopecia), which are score on a 4 point scale (ranging from 1 = not at all to 4 = very much).

The EQ-5D-3L was also used to measure HRQoL for the purposes of economic evaluation, and it includes five health state dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Dimensions are rated on a 3 point scale, where 1 indicates an extreme problem and 3 indicates no problem. The EQ-5D-3L also includes a visual analogue scale (VAS), in which the participant rates their general state of health from 0 (worst health) to 100 (best health) at the time of the assessment. The EQ-5D-3L was completed by participants first before completing the EORTC-QLQ-C30 and EORTC QLQ-LC13.[2]

Safety

Safety assessments were conducted regularly throughout the study and included recording vital signs, laboratory and physical examinations, monitoring adverse events (AEs), electrocardiogram assessments, and ECOG PS evaluations.

AEs were graded by the investigator according to the CTCAE version 4, and were monitored throughout the study and for a minimum of 30 days post-treatment. Serious AEs (SAEs) were collected for up to 90 days after the end of treatment, or

for 30 days following cessation of treatment if a new anticancer therapy was initiated.

The all subjects as treated (ASaT) population was used for the safety analyses, which includes all participants who received at least one dose of study treatment. Participants who were randomized to one treatment arm, but incorrectly received the other treatment arm medication for the entire treatment period will be included in the treatment arm corresponding to actual study treatment received. Participants who received the incorrect treatment for one cycle, but received the correct study treatment as assigned for all other cycles, will be analyzed according to the randomized treatment group. At least one laboratory or vital sign measurement obtained subsequent to at least one dose of study treatment was required for the inclusion in the analysis.

Safety analyses followed a tiered approach, illustrated in Table 6.4. Tier 2 safety endpoints were assessed with point estimated and 95% CIs for between-group comparisons, whereas for Tier 3 only point estimates were provided. The between-treatment difference was analyzed using the Miettinen and Nurminen method. For the primary safety analyses participants in the placebo + chemotherapy arm who crossed over to pembrolizumab were censored at the time of crossover (i.e., AEs occurring with pembrolizumab treatment excluded). An exploratory safety analysis was conducted for the crossover population including all safety events.[2]

Table 6.4: Tiered analysis strategy for safety endpoints

Safety Tier	Safety Endpoint	p-Value	95% CI for Treatment Comparison	Descriptive Statistics
Tier 2	Any AE		X	X
	Any Grade 3-5 AE		X	X
	Any Serious AE		X	X
	Onset and Duration of First Grade 3-5 AE		X	X
	Any Drug-Related AE		X	X
	Any Serious and Drug-Related AE		X	X
	Any Grade3-5 and Drug-Related AE		X	X
	Dose Modification Due to AE		X	X
	Discontinuation Due to AE		X	X
	Death		X	X
	Specific AEs, SOCs (including ≥4 of subjects in one of the treatment groups)		X	X
Tier 3	Specific AEs, SOCs (incidence <4 of subjects in all of the treatment groups)			X
	Change from Baseline Results (Labs, ECGs, Vital Signs)			X
There are no Tier 1 AEs pre-specified in this protocol.				

Source: EMA Assessment Report, 2019; Table 28, page 42/103[3]

Interim Analyses

There are four analyses planned for the study, interim analysis 1 (IA1), interim analysis 2 (IA2), and interim analysis 3 (IA3) and the final analysis, with the endpoints, timing, and purpose of each analysis summarized in Table 6.5. IA1 was performed at the data cut-off date of October 27th, 2017 and the data cut-off for IA2 was April 3rd, 2018. The KN-407 trial is ongoing. All results presented in this

report are from IA2 due to the positive results reported for PFS and OS as of the data cut-off date of April 3rd, 2018 for IA2. These results include all primary and secondary objectives, as well as exploratory endpoints. Subsequent analyses (IA3) and the final analysis will be performed as needed.[2]

In their feedback on the pERC initial recommendation, the sponsor, registered clinicians (Cancer Care Ontario and Lung Cancer Canada), and patient group (Lung Cancer Canada) refer to updated Keynote 407 data with longer follow-up which were presented at the ESMO 2019 Annual Meeting. The CADTH Methods Team noted that the updated data were not provided by the sponsor during the review process (prior to September 19, 2019) and were published after the September 19, 2019 pERC meeting. Of note: pERC deferred making a recommendation for pembrolizumab during the first deliberation on September 19, 2019 because the Committee required additional economic information from the review team. Following the deferral of the Initial Recommendation, the review team provided additional economic information and pERC deliberated on pembrolizumab at the October 17, 2019 pERC meeting. The updated data with longer follow-up presented at the ESMO 2019 Annual Meeting is considered "new information" and therefore, will not be considered by pERC in their Reconsideration of the Initial Recommendation of pembrolizumab for squamous NSCLC.

Table 6.5: Summary of KEYNOTE-407 Analysis Strategy

Analyses	Key Endpoints	Timing	Estimated Time after First Participant Randomized	Primary Purpose of Analysis
IA1	ORR	~ 200 subjects are followed for ~ 28 weeks so that each patient has at least 4 tumor assessments	~ 15 months	• Demonstrate ORR superiority
IA2	PFS OS	~ 332 PFS events have been observed.	~ 20 months	• Demonstrate PFS superiority • Demonstrate OS superiority
IA3	PFS OS	~ 415 PFS events have been observed	~ 25 months	• Demonstrate PFS superiority • Demonstrate OS superiority
Final Analysis	OS	~ 361 deaths have occurred.	~ 31 months	• Demonstrate OS superiority

Source: EMA Assessment Report, 2019; Table 23, pages 14-15/103[3]

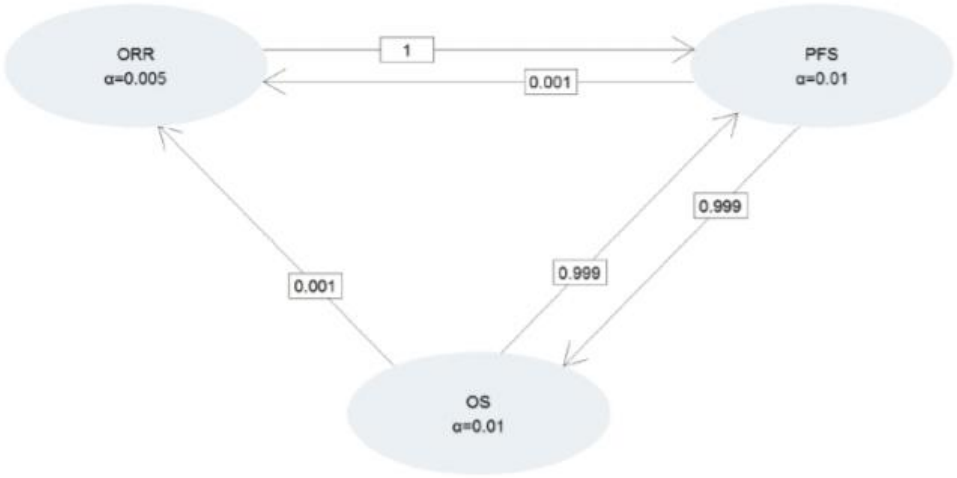
Multiplicity

KN-407 used the graphical method of Maurer and Bretz to control for multiplicity for testing multiple hypotheses as well as interim analyses, illustrated in Figure 6.2. With this approach, study hypotheses can be tested more than once, and when a null hypothesis is rejected, the alpha allocated to that test can be reallocated to other hypothesis tests. The weights for reallocation are represented in the boxes on the lines connecting hypotheses in Figure 6.2. The overall type I error rate was controlled at 0.025 (one-sided) for the testing of OS, PFS, and ORR. The initially allocated alpha was 0.01 for OS and PFS, but it could be tested at α=0.02 (if the PFS, but not the ORR null hypothesis is rejected), or α=0.025 (if both the ORR and

PFS null hypotheses are rejected). The Lan-DeMets O'Brien-Fleming approximation spending function was used for the calculation of efficacy bounds of OS and PFS.

As outlined in Table 6.5, at the time IA2 was performed, approximately 332 PFS events were to be observed and it was estimated approximately 212 deaths would be observed at this time. As of the cut-off date for IA2, 349 PFS events were observed and 205 deaths, and the multiplicity-adjusted, one-sided alpha spent was 0.0008 for PFS and 0.0029 for OS.[2]

Figure 6.2: Maurer and Bretz method to control for multiplicity as used in the KEYNOTE-407 trial



Source: EMA Assessment Report, 2019; page 15/103[3]

Protocol Amendments

The original protocol was dated 24-Mar-2016, and included 4 major amendments up to the data cut-off date of April 3rd, 2018. These changes are outlined in Table 6.6.[3]

Table 6.6: Overview of changes in protocol amendments for KN-407

Amendment Nb	Global or Local	Date	Rationale and Key Changes
01	China	27-Jul-2017	• Extended the enrollment period to achieve the required numbers of participants and events to investigate the efficacy and safety in Chinese patients with NSCLC.
02	Global	26-Oct-2017	• Updated the statistical design for the evaluation of long term treatment effect in OS and PFS. • This amendment was never officially published
03	Global	13-Nov-2017	• Updated the statistical design to optimize the evaluation of long term treatment effect in OS and PFS.
04	China	20-Nov-2017	• Updated the statistical design to optimize the evaluation of long term treatment effect in OS and PFS.
Note: Table includes protocol amendments implemented up to the data cutoff date 03-APR-2018			

Source: EMA Assessment Report, 2019; Table 4, pages 16-17/103[3]

Funding

The trial was funded by Merck Sharp & Dohme (MSD). All 22 authors reported receiving financial compensation from MSD in the form of grants (for the study conduct and/or for activities external to the study), lecture or speaking fees, advisory board fees, employment, and stock grants. Three of the 22 authors were directly employed by MSD.[2]

b) Populations

A total of 559 participants were randomized from 125 sites (participants were screened at 137 sites), with 278 participants assigned to the pembrolizumab + chemotherapy arm, and 281 to the placebo + chemotherapy arm. Demographic characteristics are summarized in Table 6.7. The median age was 65 years in both treatment arms, ranging from 29 to 87 in the pembrolizumab combination arm and 36 to 88 in the placebo combination arm. The majority of participants were from non-East Asia countries (n=453; 81.0%); current or former smokers (n=518; 92.7%); had predominant squamous histology (n=546; 97.7%); and had PD-L1 expressing tumors with a tumor proportion score (TPS) ≥1% (n=353; 63.1%). Just over a quarter of patients had a PD-L1 TPS score ≥50% (n=146; 26.1%). There were 44 (7.9%) participants with baseline brain metastases included in the trial. Overall, baseline and disease characteristics were balanced between groups, with the exception of the following:

- Sex: A higher proportion of participants in the placebo combination arm were male (n=235; 83.6%) compared to the pembrolizumab combination arm (n=220; 79.1%).
- ECOG PS: A higher proportion of participants in the pembrolizumab combination arm had an ECOG PS of 1 (n=205; 73.7%) compared to the placebo combination arm (n=191; 68.0%). A higher proportion of patients in the placebo combination arm had an ECOG PS of 0 (n=90; 32.0%) compared to the pembrolizumab combination arm (n=73; 26.3%).[2]
- Smoking status: While never smokers were balanced between treatment arms (7.9% vs. 6.8% in the pembrolizumab and placebo combination arms, respectively), there were a higher proportion of current smokers (n=82; 29.5%) in the pembrolizumab combination arm than the placebo combination arm (n=63; 22.4%). The proportion of former smokers was higher in the placebo combination arm (n=199, 70.8%) than in the pembrolizumab combination arm (n=174; 62.6%).[3]

Table 6.7. Baseline demographics and disease characteristics of KEYNOTE-407

Characteristic	Pembrolizumab Combination (N=278)	Placebo Combination (N=281)
Age		
Median (range) — yr	65 (29–87)	65 (36–88)
<65 yr — no. (%)	127 (45.7)	127 (45.2)
Male sex — no. (%)	220 (79.1)	235 (83.6)
Region of enrollment — no. (%)		
East Asia	54 (19.4)	52 (18.5)
Rest of the world	224 (80.6)	229 (81.5)
ECOG performance-status score — no. (%)†		
0	73 (26.3)	90 (32.0)
1	205 (73.7)	191 (68.0)
Smoking status — no. (%)		
Current or former	256 (92.1)	262 (93.2)
Never	22 (7.9)	19 (6.8)
Histologic features — no. (%)		
Squamous	272 (97.8)	274 (97.5)
Adenosquamous‡	6 (2.2)	7 (2.5)
Brain metastases — no. (%)	20 (7.2)	24 (8.5)
PD-L1 tumor proportion score — no. (%)§		
<1%	95 (34.2)	99 (35.2)
≥1%	176 (63.3)	177 (63.0)
1–49%	103 (37.1)	104 (37.0)
≥50%	73 (26.3)	73 (26.0)
Could not be evaluated¶	7 (2.5)	5 (1.8)
Previous therapy for nonmetastatic disease — no. (%)		
Thoracic radiotherapy	17 (6.1)	22 (7.8)
Neoadjuvant or adjuvant therapy	5 (1.8)	8 (2.8)

* Patients in the pembrolizumab-combination group received pembrolizumab, carboplatin, and either paclitaxel or nanoparticle albumin-bound (nab)–paclitaxel. Patients in the placebo-combination group received placebo, carboplatin, and either paclitaxel or nab-paclitaxel. There were no significant differences between groups at a two-sided alpha level of 0.05.

† Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with 0 indicating no symptoms and higher scores indicating greater disability.13

‡ Patients whose tumors were of a mixed histologic subtype were eligible for enrollment if there was a squamous component in the specimen.

§ The programmed death ligand 1 (PD-L1) tumor proportion score was defined as the percentage of tumor cells with membranous PD-L1 expression.

¶ PD-L1 expression could not be evaluated because specimens had an inadequate number of tumor cells or no tumor cells. For stratification purposes, patients with PD-L1 expression that could not be evaluated were

included in the subgroup of patients with a PD-L1 tumor proportion score of less than 1%; these patients were excluded from analyses of efficacy according to the PD-L1 tumor proportion score.

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c) Interventions

Treatment Dosing Schedule

All treatments were administered intravenously (IV) in 3-week cycles as follows:

Drug: Pembrolizumab Dose: 200 mg Cycle Day(s): 1 Number of cycles: up to 35	AND	Drug: Carboplatin Dose: AUC 6 Cycle Day(s): 1 Number of cycles: 4	AND	Drug: Paclitaxel Dose: 200 mg/m^2 Cycle Day(s): 1 Number of cycles: 4
OR				OR
Drug: Saline Placebo Dose: 200mg Cycle Day(s): 1 Number of cycles: up to 35				Drug: Nab-paclitaxel Dose: 100 mg/m^2 Cycle Day(s): 1, 8, 15 Number of cycles: 4

Patients who received paclitaxel also received premedication with a glucocorticoid, a type 1 antihistamine, and a type 2 antihistamine according to local guidelines. Premedication was not required for patients who received nab-paclitaxel. Participants remained on treatment until radiographically confirmed progressive disease (PD), occurrence of unacceptable toxic effects, investigator's decision to discontinue the treatment, or withdrawal of consent.[2]

Treatment Duration and Exposure

The mean duration of treatment was 6.3±4.1 months in the pembrolizumab + chemotherapy arm and 4.7±3.5 months in the placebo + chemotherapy arm. A higher proportion of participants in the placebo-combination arm received all four doses of carboplatin (78.8%) compared to the pembrolizumab-combination arm (73.2%). A higher proportion of participants in the pembrolizumab-combination who received paclitaxel received all 4 doses (78.7%) compared to the placebo-combination arm (71.3%). Among patients who received nab-paclitaxel, only 22.9% in the pembrolizumab combination arm and 21.2% in the placebo combination arm received all 12 doses (4 cycles). Most patients receiving nab-paclitaxel received between 5-11 doses (66.1% vs. 64.9% in the pembrolizumab and placebo combination arms, respectively). The mean doses of nab-paclitaxel were similar between the two treatment arms at 9.0±3.1 and 8.7±2.0 doses in the pembrolizumab combination arm and placebo combination arm, respectively.[2]

As of the data cut-off date, April 3rd, 2018, 121 (43.5%) participants in the pembrolizumab combination arm and 72 (25.7%) participants in the placebo combination arm remained on study treatment. A total of 12 (4.3%) participants with received a median of 3 cycles (range, 1-10) of pembrolizumab monotherapy following BICR confirmation of PD in the pembrolizumab combination arm. In the

placebo combination arm, 75 (26.7%) patients crossed over to receive pembrolizumab monotherapy following PD with an additional 14 (5.0%) patients receiving a subsequent PD-1 or PD-L1 inhibitor outside the KN-407. The treatment crossover rate including all participants receiving a PD-1 or PD-L1 inhibitor internal and external to the trial in the ITT population was 31.7%, and 42.8% among those who discontinued their assigned treatment for any reason.[2]

As mentioned earlier, if toxic events were attributed to one component of the treatment, that component alone could be permanently discontinued. Overall, more participants in the pembrolizumab + chemotherapy arm (n=65; 23.4%) discontinued any treatment component compared to the placebo + combination arm (n=33; 7.9%). Comparing the pembrolizumab + chemotherapy arm vs. placebo + chemotherapy arm, more participants discontinued pembrolizumab (17.3% vs. 7.9%), carboplatin (11.2% vs. 7.5%), and paclitaxel or nab-paclitaxel (15.8% vs. 10.0%).[2] Out of the 48 (17.3%) patients in the pembrolizumab + chemotherapy arm who discontinued pembrolizumab, only 5 (1.8%) patients discontinued pembrolizumab while chemotherapy continued (i.e., discontinued < 4 doses of pembrolizumab); whereas 23 (8.3%) patients discontinued pembrolizumab and chemotherapy at the same time and 20 (7.2%) patients discontinued pembrolizumab after chemotherapy was already completed.[35]

Previous Anticancer Therapies and Procedures

Previous anticancer therapies for non-metastatic disease included prior adjuvant/neo-adjuvant therapy and radiation. A total of 5 (1.8%) participants in the pembrolizumab combination arm received prior adjuvant/neo-adjuvant therapy, which was similar to the placebo combination arm (n=8, 2.8%). A total of 35 (12.6%) of participants received any prior radiation in the pembrolizumab combination arm, and 17 (6.1%) received prior thoracic radiation. This was similar to the placebo combination arm, where 38 (13.5%) participants received prior radiation, and 22 (7.8%) received prior thoracic radiation.[3]

Concomitant Medications

All participants in the paclitaxel arm receive concomitant premedication of a glucocorticoid and antihistamines, listed until the treatment dosing schedule. Palliative and supportive care was permitted for medical conditions and symptom management. Surgery or radiotherapy for tumor control was prohibited, with the exception of radiotherapy for symptom management.

Medications or vaccinations prohibited in the exclusion criteria were not allowed during the ongoing trial (for example, chronic systemic steroids, systemic therapies for autoimmune diseases, etc.). The following therapies were not allowed during the Screening, Treatment, Crossover, and Second Course phases: anticancer treatments not specified as in protocol, investigational agents other than pembrolizumab, live vaccines within 30 days prior to first dose and while on study treatment, systemic glucocorticoids (only allowed to modulate immune-related AEs, pre-medication for CT scan or paclitaxel, or chronic obstructive pulmonary disease exacerbation), and routine use of colony-stimulated factors.[2]

Subsequent Interventions

At the time of IA2, 44 (15.8%) and 110 (39.1%) of participants in the pembrolizumab combination arm and placebo combination arm, respectively, received any subsequent therapy (Table 6.8). In the pembrolizumab combination arm, 1.4% (n=4) of participants received immunotherapy (all outside of the KN-407 trial), whereas the majority (31.7%; n=89) of participants received immunotherapy in the placebo

combination arm.[4] In the placebo combination arm, 75 (26.7%) participants crossed over within the trial to receive pembrolizumab monotherapy, and 15 (5.3%) received pembrolizumab, nivolumab, or atezolimab outside the KN-407 trial.[3] TPS PD-L1 scores of participants in the placebo combination arm that crossed over to pembrolizumab monotherapy were balanced between groups (PD-L1 TPS <1%, 1-49%, and ≥50%).[36] The majority of participants in the pembrolizumab combination arm received other subsequent therapies (14.3%; n=40), with gemcitabine and docetaxel being the most commonly administered therapies at 8.6% (n=24) and 6.5% (n=18), respectively. In the placebo + combination arm, gemcitabine (n=16; 5.7%) and docetaxel (n=7; 2.5%) were the most common administered subsequent therapies aside from immunotherapy. All subsequent post-treatment therapies used (with the exception of placebo + chemotherapy arm patients that crossed over to pembrolizumab) are summarized in Table 6.9.[3]

Table 6.8: Summary of subsequent anticancer therapies in the KN-407 trial based on the ITT population

Regimen	Pembrolizumab-Chemotherapy Group (N=278) Number of patients (% of ITT)	Placebo-Chemotherapy Group (N=281) Number of patients (% of ITT)
Summary:		
Any subsequent therapy	44 (15.8%)	110 (39.1%)
No subsequent therapy	234 (84.2%)	171 (60.9%)
Still on assigned therapy	121 (43.5%)	72 (25.6%)
Types of Subsequent Therapies*:		
Immunotherapy	4 (1.4%)	89 (31.7%)
Crossover to in-study pembrolizumab	Not applicable	75 (26.7%)
Immunotherapy outside of study	4 (1.4%)	14 (5.0%)
Other subsequent therapy	40 (14.4)	21 (7.5%)

Source: Merck Canada Inc., 2018; Table 3; page 21/44[37] Keytruda clinical rationale. For the first-line treatment of patients with metastatic squamous non-small cell lung cancer (NSCLC), in combination with carboplatin and either paclitaxel or nab-paclitaxel. In: pan-Canadian Oncology Drug Review manufacturer submission: Keytruda (pembrolizumab), powder for reconstitution for infusion - 50mg, solution for infusion 100mg/4mL vial. Kirkland (QC): Merck Canada Inc.; 2018 Feb 08. Accessed 2019 Sep 11.

Table 6.9: Subsequent post-treatment therapies used in the KN-407 trial

	Pembro Combo		Control	
	n	(%)	n	(%)
Subjects in population	278		281	
With one or more concomitant medications	44	(15.8)	45	(16.0)
With no concomitant medication	234	(84.2)	236	(84.0)
antineoplastic and immunomodulating agents				
antineoplastic agents	**44**	**(15.8)**	**43**	**(15.3)**
atezolizumab	1	(0.4)	2	(0.7)
carboplatin	7	(2.5)	7	(2.5)
cisplatin	10	(3.6)	5	(1.8)
docetaxel	18	(6.5)	7	(2.5)
etoposide	1	(0.4)	0	(0.0)
gefitinib	1	(0.4)	0	(0.0)
gemcitabine	24	(8.6)	16	(5.7)
gimeracil (+) oteracil potassium (+) tegafur	4	(1.4)	2	(0.7)
hydrazine sulfate	0	(0.0)	2	(0.7)
nedaplatin	1	(0.4)	0	(0.0)
nivolumab	2	(0.7)	10	(3.6)
paclitaxel	2	(0.7)	4	(1.4)
paclitaxel albumin	1	(0.4)	0	(0.0)
pembrolizumab	1	(0.4)	3	(1.1)
pemetrexed disodium	0	(0.0)	1	(0.4)
ramucirumab	3	(1.1)	1	(0.4)
vinorelbine tartrate	7	(2.5)	3	(1.1)
various				
all other therapeutic products	**1**	**(0.4)**	**1**	**(0.4)**
investigational drug	1	(0.4)	1	(0.4)
(unspecified) **therapeutic**	**0**	**(0.0)**	**1**	**(0.4)**
radiopharmaceuticals	0	(0.0)	1	(0.4)
strontium chloride Sr 89				

Every subject is counted a single time for each applicable specific concomitant medication. A subject with multiple concomitant medications within a medication category is counted a single time for that category.

A medication class or specific medication appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

1 participant crossed over to pembrolizumab monotherapy within the study before receiving atezolizumab outside of the study; thus, a total of 14 participants were included in the crossover calculations.

Database Cutoff Date: 03APR2018

Source: EMA Assessment Report, 2019; Table 22, page 34/103[3]

d) Patient Disposition

The patient disposition flow diagram for KN-407 is illustrated in Figure 6.3. Of 779 patients screened for eligibility, 561 patients met all eligibility criteria. A total of 218 participants did not meet eligibility criteria depicted in Figure 6.3, with common reasons for screen failure including lack of confirmed diagnosis of stage IV Sq NSCLC (n=31), failure to provide tumor tissue (n=29), lack of written informed consent (n=29), ECOG PS ≥ 2 (n=28), and lack of adequate organ function (n=19). Two participants were excluded prior to randomization due to physician's decision. A total of 559 participants were randomly assigned to the pembrolizumab + chemotherapy (n=278) and placebo + chemotherapy arm (n=280). In the pembrolizumab combination arm, 169 (60.8%) participants were assigned to paclitaxel and 109 (39.2%) to nab-paclitaxel. In the placebo combination arm, 167 (59.4%) participants were assigned to paclitaxel and 114 (40.6%) participants were assigned to nab-paclitaxel. All participants received the assigned treatment, with the exception of one participant randomized to the placebo combination arm that did not start study treatment.[2]

As of the April 3rd, 2018, data cut-off date, 121 participants in the pembrolizumab combination arm and 72 participants in the chemotherapy combination arm remained on study treatment. A total of 365 (65.3%) participants discontinued study treatment, 157 (56.5%) in the pembrolizumab combination arm and 208 (74.3%) in the placebo combination arm. Discontinuation due to radiographic or clinical PD was higher in the placebo combination arm compared to the pembrolizumab combination arm, at 59.1% (n=166) and 35.6% (n=99), respectively. Discontinuation due to AEs was higher in the pembrolizumab combination group (n=48; 17.3%) compared to the placebo combination group (n=25; 8.9%). Discontinuation due to reasons other than PD or AEs (physician decision, withdrawal of consent, and lost to follow-up) were slightly higher in the placebo combination group (6% vs. 3.6%, placebo-combination arm vs. pembrolizumab combination arm, respectively), mainly due to more participants withdrawing consent (3.2% vs. 1.8%, respectively). Overall, discontinuation due to reasons other than PD were higher in the pembrolizumab combination arm (n=58; 20.9%) compared to the placebo combination arm (n=42; 15.3%).[2]

Protocol Deviations

The number of important protocol deviations were similar, reported to be 46 (16.5%) and 47 (16.7%) in the pembrolizumab combination and placebo combination arms, respectively. Safety reporting followed by study intervention, were the most common categories with a major protocol deviation for both treatment arms. Protocol deviations are summarized in Table 6.10 below.

Of the important protocol deviations, 2 were deemed to be clinically significant and both patients were included in the ITT analysis. One participant in the control group was inadvertently administered blinded pembrolizumab/placebo for another clinical trial instead of the assigned placebo for the KN-407 trial, and the infusion was stopped after 10 minutes (1/3rd of dose received). Another participant received placebo instead of pembrolizumab at Cycle 6 only.[3]

Figure 6.3: Participant disposition flow diagram for the KN-407 trial

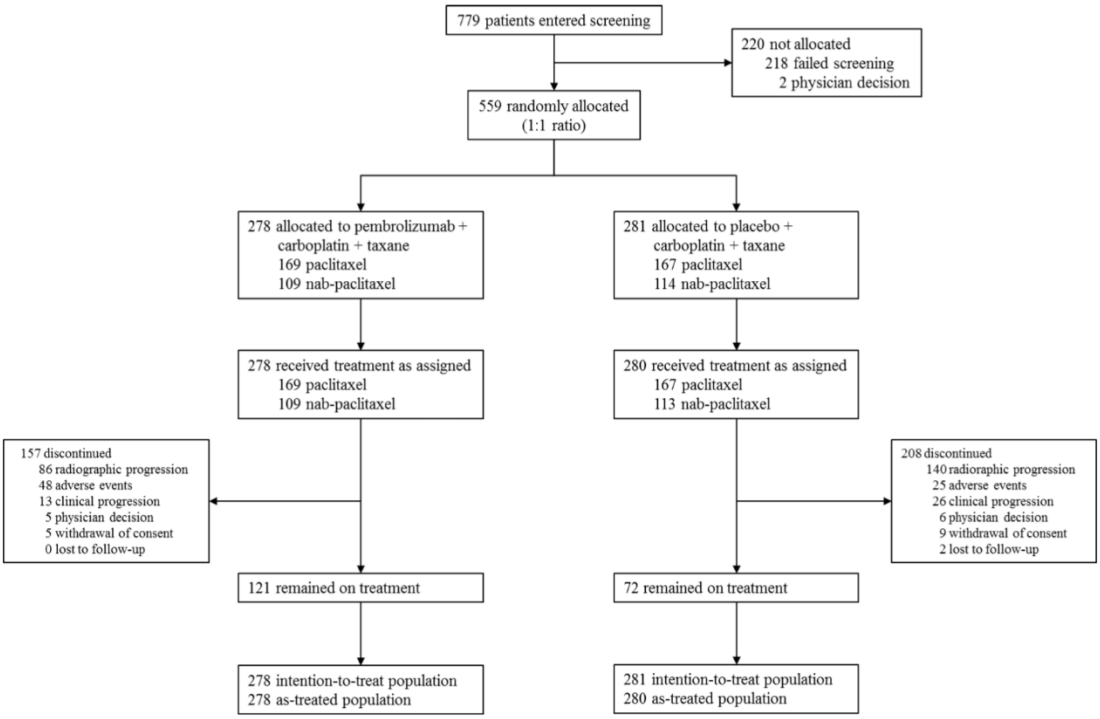

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Table 6.10: Classification of important protocol deviations in the KN-407 trial, ITT population

Protocol Deviation Category	Pembrolizumab Combination n = 278 n (%)	Placebo Combination n = 281 n (%)
Total important protocol deviations*	46 (16.5)	47 (16.7)
Safety Reporting	16 (5.8)	17 (6.0)
Study Intervention	15 (5.4)	10 (3.6)
Trial Procedures	10 (3.6)	6 (2.1)
Inclusion/exclusion criteria	4 (1.4)	5 (1.8)
Informed Consent Form	3 (1.1)	5 (1.8)
Prohibited Medications	2 (<0.1)	7 (2.5)
Discontinuation Criteria	2 (<0.1)	0 (0)
*One patient may have had multiple important protocol deviations and were listed once under each relevant category		

e) Limitations/Sources of Bias

Overall, KN-407 was a well-designed, RCT. Key limitations and sources of bias include:

- Due to the different mechanisms of action of the study treatment regimens, it is still possible for investigator bias, and potentially respondent bias, to be introduced despite a double-blinded study. Investigators, and even participants, may have realized they were on treatment with pembrolizumab due to the occurrence of specific immune-related AEs that are more commonly associated with pembrolizumab, which may have influenced outcomes such as PFS (specifically, delaying or expediting a scan to confirm PD based on suspected treatment regimen).
- Crossover from the placebo combination arm to pembrolizumab monotherapy was allowed, which may confound the results of the analysis of OS. Given the results showed a statistically significant reduction in the risk of death despite the potential for confounding due to crossover (HR: 0.64; 95% CI: 0.49, 0.85; p<0.001), the treatment effect when adjusted for crossover was larger than reported in the trial (HR: 0.57; 95% CI: 0.40, 0.81; 0.0018).[2,36]
- There were a higher proportion of patients with ECOG PS 1 and less male patients in the pembrolizumab combination arm compared to the placebo combination arm. The combination of these factors may have biased results in favour of the placebo combination arm. Patients with a higher ECOG PS status may have worse outcomes. A number of meta-analyses pooling different immune checkpoint inhibitors (ICIs), such as pembrolizumab, nivolumab, etc., across multiple tumor types, have suggested that the treatment benefit of ICIs may be less pronounced in female subgroups, although this was not seen in subgroup analyses in this trial.[39-41]
- The duration of follow-up in KN-407 is relatively short, given these results were based on an interim analysis. Long-term OS,PFS, and HRQoL data are required to ensure the results observed in this study are consistent or maintained over a longer period of time. Specifically, HRQoL was reported at week 9 and week 18, and week 18 coincides with approximately 4.5 months and 6 cycles of treatment.[4,6,26] HRQoL data was collected every cycle for the first 7 cycles, followed by every 3 cycles thereafter until week 48 as per protocol.[2] A later time point, despite decreasing compliance and completion rates, may have been more informative of the longer term impact of treatment on HRQoL.[3,26] Additionally, there is the possibility for toxic, delayed immune-related AEs to develop over time with drugs such as pembrolizumab, and the duration of the trial is inadequate to capture these events. Long-term safety data are also required.

6.2.2.2 Detailed Outcome Data and Summary of Outcomes

Efficacy Outcomes

Efficacy analyses were performed using the ITT, which included a total of 559 patients. As of the IA2 data cut-off date, the median duration of follow-up, defined as the time from randomization to death or date of data cut-off (for those alive), was 7.8 months (range, 0.1 to 19.1).[2]

Primary Endpoints

Overall Survival

A total of 205 deaths occurred in the ITT population, with 85 deaths in the pembrolizumab combination arm and 120 deaths in the placebo combination arm (Table 6.11).[3] The median overall survival was 15.9 months (95% CI: 13.2, NR) in the pembrolizumab combination arm and 11.3 months (95% CI: 9.5, 14.8) in the placebo combination arm. Illustrated in Figure 6.4, the pembrolizumab combination arms statistically significantly reduced the risk of death by 36% compared to the placebo combination arm (HR: 0.64, 95% CI: 0.49, 0.85; p<0.0008). The K-M estimates of the rate of survival at 12 months were 65.2% and 48.3% in the pembrolizumab combination arm and placebo combination arms, respectively.

OS by PD-L1 TPS was also explored and is illustrated in Figure 6.5. A reduction in the risk of death was seen across all PD-L1 TPS subgroups (TPS <1%; TPS 1-49%; and TPS ≥50%), however, in participants with TPS score ≥50%, there was no statistically significant difference between treatment arms (HR: 0.64; 95% CI: 0.37, 1.10).

Subgroup analysis of OS was consistent with the overall trial results, with a clinically meaningful reduction in risk of death observed across all subgroups, shown in Figure 6.6. It is important to note there was no statistically significant difference in the ≥65 years of age subgroup (HR: 0.74, 95% CI: 0.51, 1.07).[2]

The pre-specified sensitivity analyses of OS adjusting for cross-over were also conducted and were consistent with the primary results of the trial. The reported treatment effect was larger when adjusting OS for crossover, with a 43% reduction in the risk of death associated with the pembrolizumab combination arm compared to the placebo combination arm (HR: 0.57; 95% CI: 0.40, 0.81; 0.0018).[36]

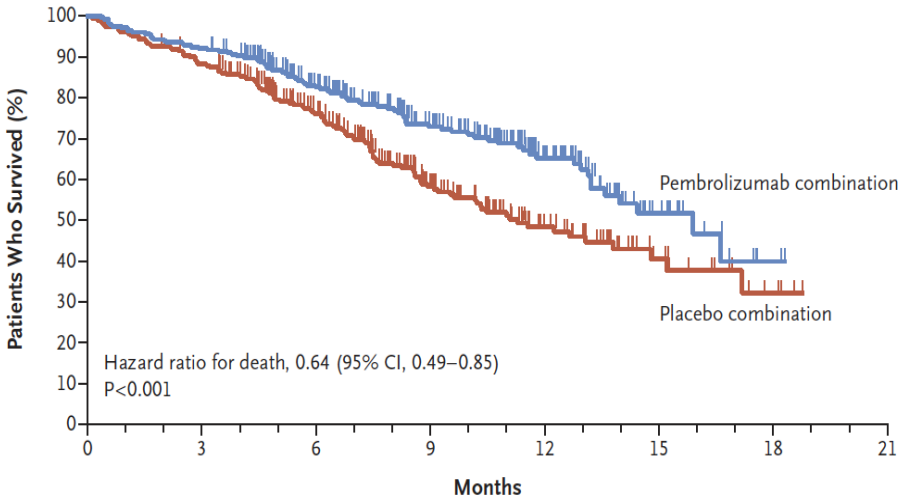
Table 6.11: Overall survival analysis in the KN-407 trial, ITT population

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median OS† (Months) (95% CI)	OS Rate at Month 6 in %† (95% CI)	vs. Control	
							Hazard Ratio‡ (95% CI)‡	p-Value‡‡
Pembro Combo	278	85 (30.6)	2362.3	3.6	15.9 (13.2, .)	82.6 (77.4, 86.6)	0.64 (0.49, 0.85)	0.0008
Control	281	120 (42.7)	2160.0	5.6	11.3 (9.5, 14.8)	76.1 (70.5, 80.8)	---	---

† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with treatment as a covariate stratified by PD-L1 status (TPS ≥ 1% vs. < 1%), taxane chemotherapy (paclitaxel vs. nab-paclitaxel) and geographic region (East Asia vs. non-East Asia).
‡‡ One-sided p-value based on stratified log-rank test.
Database Cutoff Date: 03APR2018

Source: EMA Assessment Report, 2019; Table 8, page 21/103[3]

Figure 6.4: Kaplan-Meier estimates of overall survival by treatment group, ITT population



No. at Risk								
Pembrolizumab combination	278	256	188	124	62	17	2	0
Placebo combination	281	246	175	93	45	16	4	0

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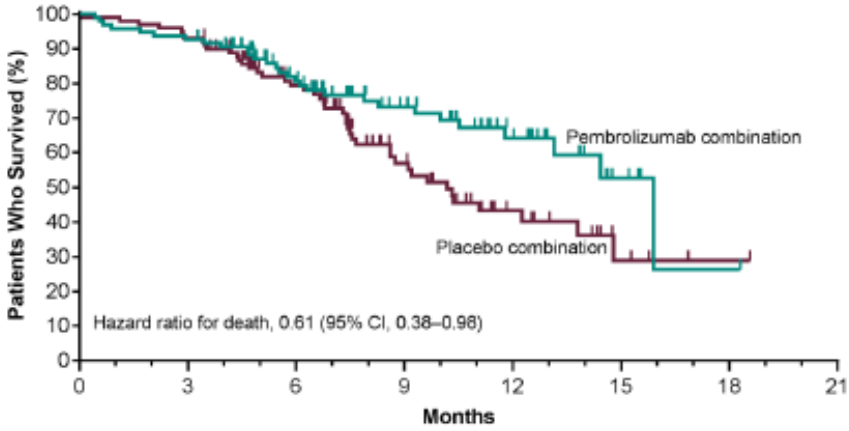
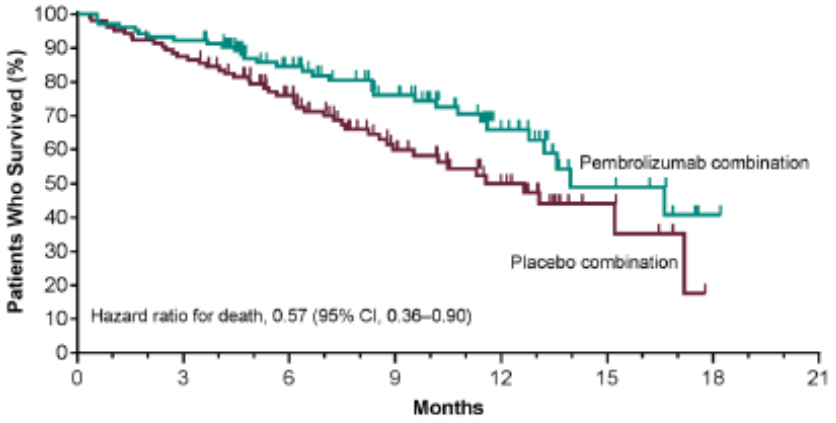
Figure 6.5: Kaplan-Meier estimates of overall survival by treatment group and PD-L1 tumor proportion score (TPS), ITT population

(A) Tumor proportion score <1%



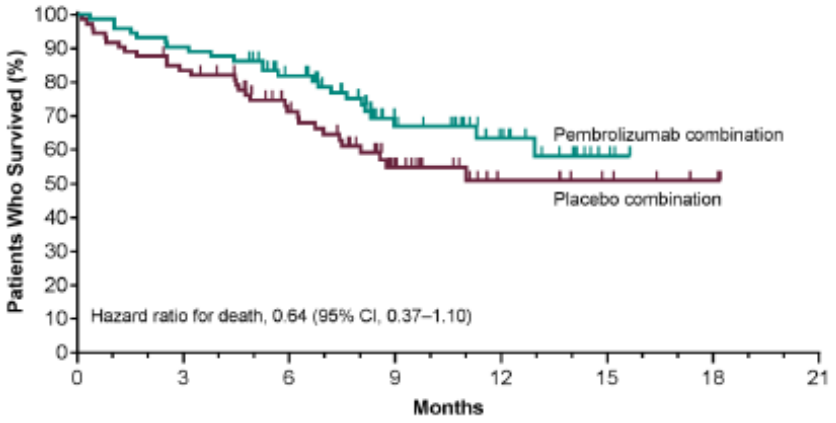
No. at Risk								
Pembrolizumab combination	95	88	62	41	20	5	1	0
Placebo combination	99	92	63	32	14	4	1	0

(B) Tumor proportion score 1-49%



No. at Risk								
Pembrolizumab combination	103	95	68	50	25	9	1	0
Placebo combination	104	90	66	37	21	6	0	0

(C)Tumor proportion score ≥50%



No. at Risk								
Pembrolizumab combination	73	66	53	28	15	3	0	0
Placebo combination	73	60	42	21	9	5	2	0

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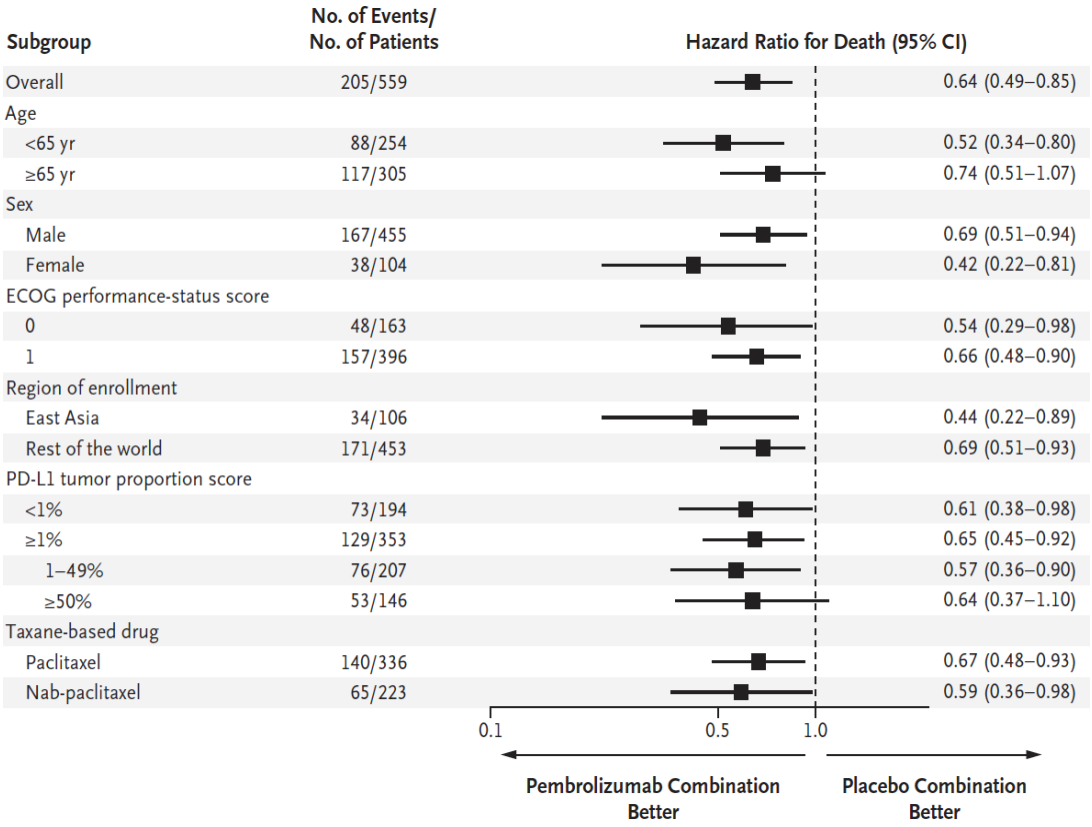
Figure 6.6: Subgroup analyses of overall survival in the KEYNOTE-407 trial



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Progression-free survival

A total of 349 events of BICR assessed PD or death occurred in the ITT population, with 152 PFS events in the pembrolizumab combination arm and 197 in the placebo combination arm (Table 6.12).[3] The median PFS was 6.4 months (95% CI: 6.2, 8.3) in the pembrolizumab combination arm compared to 4.8 months (95% CI: 4.3, 5.7) in the placebo combination arm. Illustrated in Figure 6.7, the combination of pembrolizumab + chemotherapy statistically significantly reduced the risk of progression or death by 44% compared to placebo + chemotherapy (HR: 0.56; 95% CI: 0.45, 0.70; p< 0.001). Investigator assessed PFS was consistent with these results (HR: 0.55; 95% CI: 0.45, 0.68).[2] One sensitivity analysis for PFS (censoring at the last disease assessment without PD when PD or death is documented after more than one disease assessment) was conducted, and it was consistent with the primary analysis for PFS (HR: 0.54; 95%CI: 0.44, 0.68).[36]

PFS by PD-L1 TPS was explored and is illustrated in Figure 6.8. A statistically significant reduction in the risk of PD or death was seen across all PD-L1 TPS subgroups, TPS <1% (HR: 0.68, 95% CI: 0.47, 0.98), TPS 1-49% (HR: 0.56; 95% CI: 0.39, 0.80), and TPS ≥50% (HR: 0.37; 95% CI: 0.24, 0.58).

Subgroup analyses for PFS are illustrated in Figure 6.9. A statistically significant reduction in the risk of PD or death was seen across all subgroups.[2]

Table 6.12: Progression-free survival analysis in the KN-407 trial, ITT population

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median PFS† (Months) (95% CI)	PFS Rate at Month 6 in %† (95% CI)	vs. Control	
							Hazard Ratio‡ (95% CI)‡	p-Value‡‡
Pembro Combo	278	152 (54.7)	1716.9	8.9	6.4 (6.2, 8.3)	64.3 (58.0, 69.9)	0.56 (0.45, 0.70)	<0.0001
Control	281	197 (70.1)	1358.1	14.5	4.8 (4.3, 5.7)	41.6 (35.3, 47.7)	---	---

Progression-free survival is defined as time from randomization to disease progression, or death, whichever occurs first.

† From product-limit (Kaplan-Meier) method for censored data.

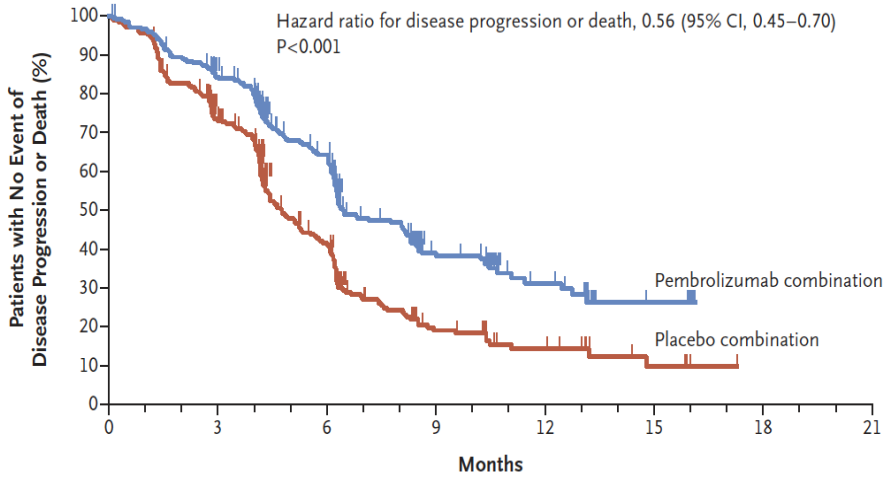
‡ Based on Cox regression model with treatment as a covariate stratified by PD-L1 status (TPS ≥ 1% vs. < 1%), taxane chemotherapy (paclitaxel vs. nab-paclitaxel) and geographic region (East Asia vs. non-East Asia).

‡‡ One-sided p-value based on stratified log-rank test.

Database Cutoff Date: 03APR2018

Source: EMA Assessment Report, 2019; Table 9, page 22/103[3]

Figure 6.7: Kaplan-Meier estimates of progression-free survival by treatment group, ITT population



No. at Risk								
Pembrolizumab combination	278	223	142	57	23	5	0	0
Placebo combination	281	190	90	26	12	4	0	0

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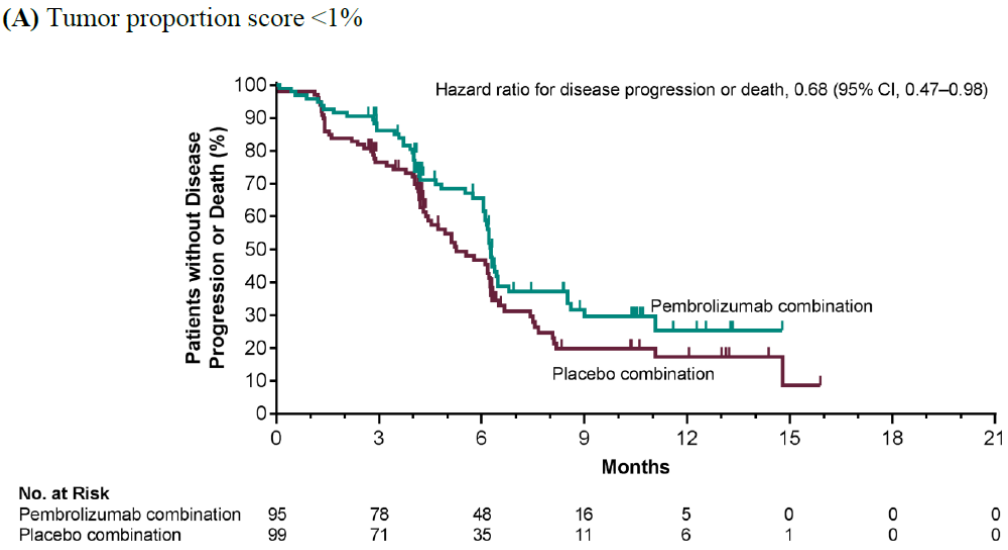
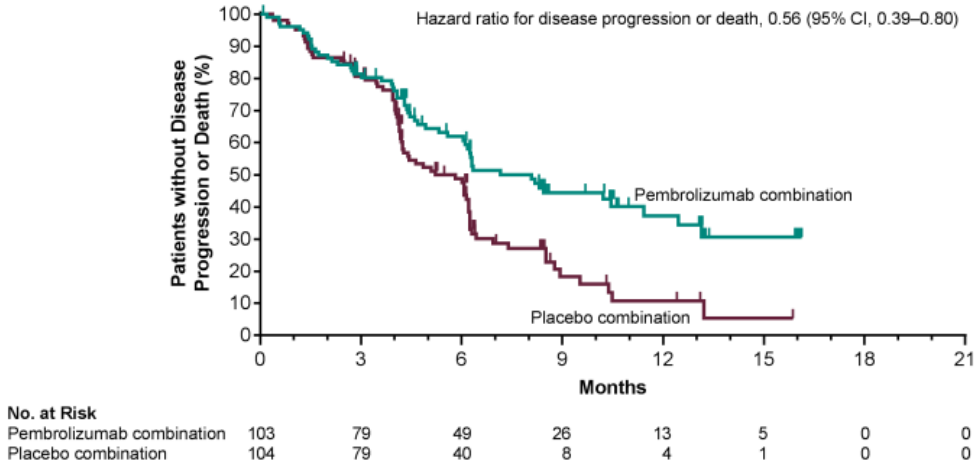
Figure 6.8: Kaplan-Meier estimates of progression-free survival by treatment group and PD-L1 tumor proportion score (TPS), ITT population

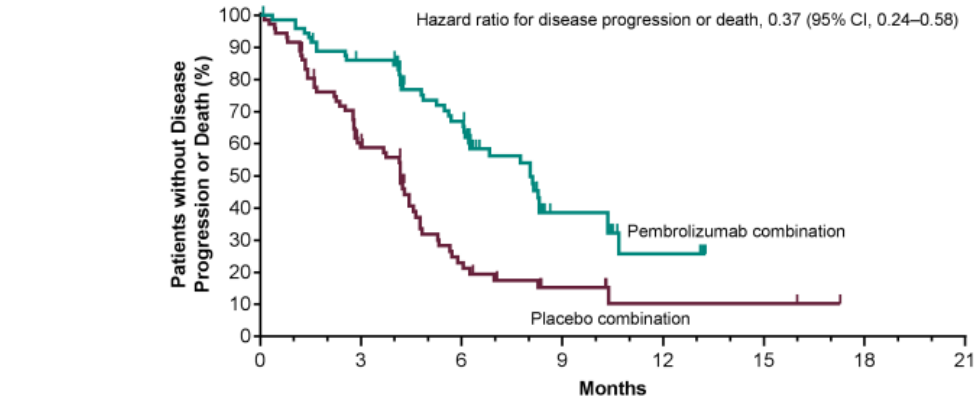


(B) Tumor proportion score 1-49%



No. at Risk								
Pembrolizumab combination	103	79	49	26	13	5	0	0
Placebo combination	104	79	40	8	4	1	0	0

(C) Tumor proportion score ≥50%



No. at Risk								
Pembrolizumab combination	73	60	41	12	4	0	0	0
Placebo combination	73	38	13	5	2	2	0	0

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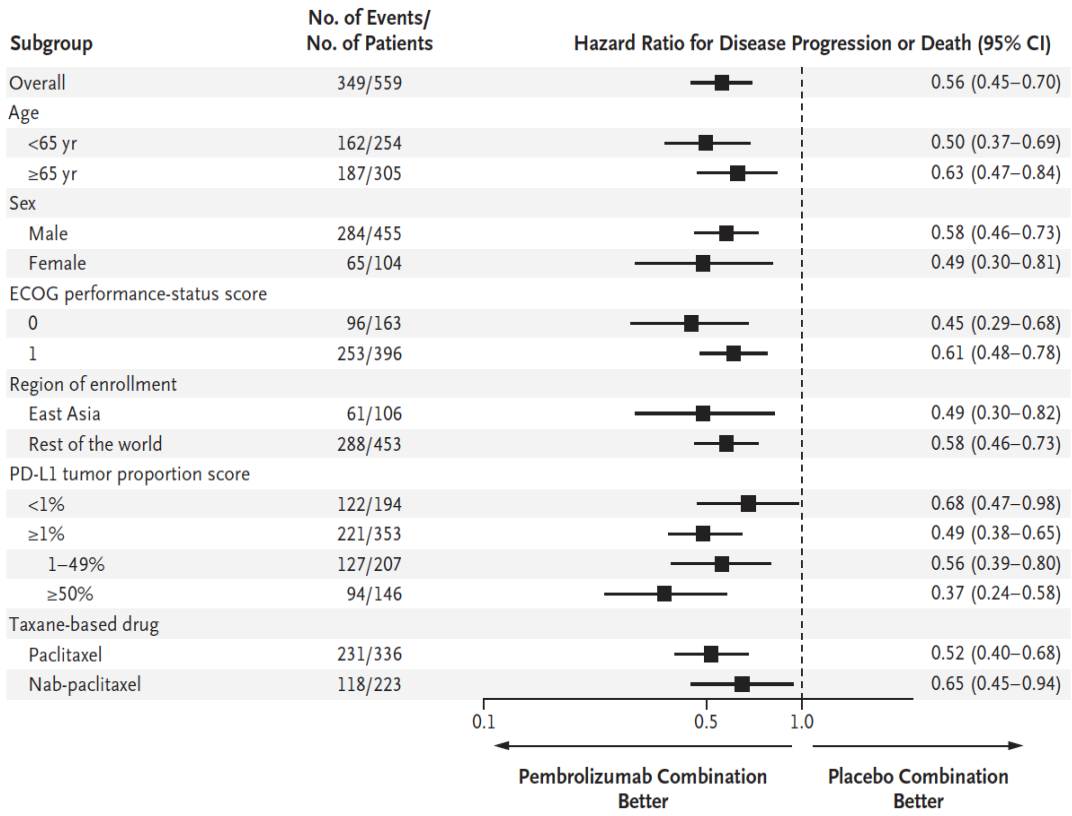
Figure 6.9: Subgroup analyses of progression-free survival in the KEYNOTE-407 trial



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Secondary Endpoints

Objective Response Rate (ORR)

As shown in Table 6.13, the BICR-assessed ORR was higher in the pembrolizumab combination arm (ORR: 57.9%, 95% CI: 51.9, 63.8) than in the placebo combination arm (ORR: 38.4%, 95% CI: 32.7, 44.4), with a treatment difference of 19.5% (95% CI: 11.2, 27.5). This was generally consistent with the investigator-assessed ORR, although the investigator-assessed ORR was estimated to be slightly lower in both treatment arms and the treatment difference was larger at 23.5% (95% CI: 15.4, 31.3). This is primarily be due to more participants being assessed by investigators as having stable disease (SD), whereas in the BICR, more participants were assessed as having a PR in the placebo combination arm. Few participants in both treatment arms experienced a best overall response (BOR) of a complete response, although it was slightly higher in the placebo combination arm (6 participants vs. 4 participants, respectively). A higher proportion of participants in the pembrolizumab combination arm experienced a BICR-assessed BOR of a partial response compared to the placebo combination arm (56.5% vs. 36.3%, respectively). A higher proportion of participants in the placebo combination arm had a BOR of stable disease compared to the pembrolizumab combination arm (37.0% vs. 28.1%, respectively), as assessed by BICR.[2]

As shown in Figure 6.10, the ORR treatment difference was consistent across all subgroup analyses, showing a marked benefit in achieving a CR or PR response with pembrolizumab combination therapy when compared to placebo combination therapy. For participants with ECOG PS 0, the ORR treatment difference was not statistically significant (ORR diff: 11.1%; 95% CI: -4.3, 26.0).[3]

Table 6.13. Summary of response analyses in the KEYNOTE-407 trial, ITT population

Variable	Blinded, Independent, Central Radiologic Review		Investigator Review	
	Pembrolizumab Combination (N=278)	Placebo Combination (N = 281)	Pembrolizumab Combination (N = 278)	Placebo Combination (N = 281)
Objective response†				
No. of patients	161	108	153	89
% (95% CI)	57.9 (51.9–63.8)	38.4 (32.7–44.4)	55.0 (49.0–61.0)	31.7 (26.3–37.5)
Estimated treatment difference (95% CI)‡	19.5 (11.2–27.5)		23.5 (15.4–31.3)	
Time to response — mo§				
Median	1.4	1.4	1.4	1.4
Range	1.1–6.1	1.0–4.5	1.1–6.2	1.0–8.3
Duration of response — mo§‖				
Median	7.7	4.8	7.3	4.9
Range	1.1+ to 14.7+	1.3+ to 15.8+	1.1+ to 14.5+	1.2+ to 14.6+
Ongoing response — no. (%)	92 (57.1)	45 (41.7)	87 (56.9)	37 (41.6)
Best overall response — no. (%)				
Complete response	4 (1.4)	6 (2.1)	2 (0.7)	0
Partial response	157 (56.5)	102 (36.3)	151 (54.3)	89 (31.7)
Stable disease	78 (28.1)	104 (37.0)	80 (28.8)	124 (44.1)
Progressive disease	17 (6.1)	39 (13.9)	25 (9.0)	39 (13.9)
Not evaluable**	6 (2.2)	7 (2.5)	4 (1.4)	6 (2.1)
Not assessable††	16 (5.8)	23 (8.2)	16 (5.8)	23 (8.2)

* The intention-to-treat population included all patients who underwent randomization.
† Objective response was considered to be a confirmed complete or partial response, as assessed according to Response Evaluation Criteria in Solid Tumors, version 1.1.
‡ The estimated treatment difference was assessed with the use of the stratified method of Miettinen and Nurminen.
§ Time to response and duration of response were evaluated in the patients who had an objective response.
‖ Duration of response was calculated with the use of the Kaplan-Meier method for censored data. Plus signs in the range indicate the response was ongoing at the time of the last imaging assessment.

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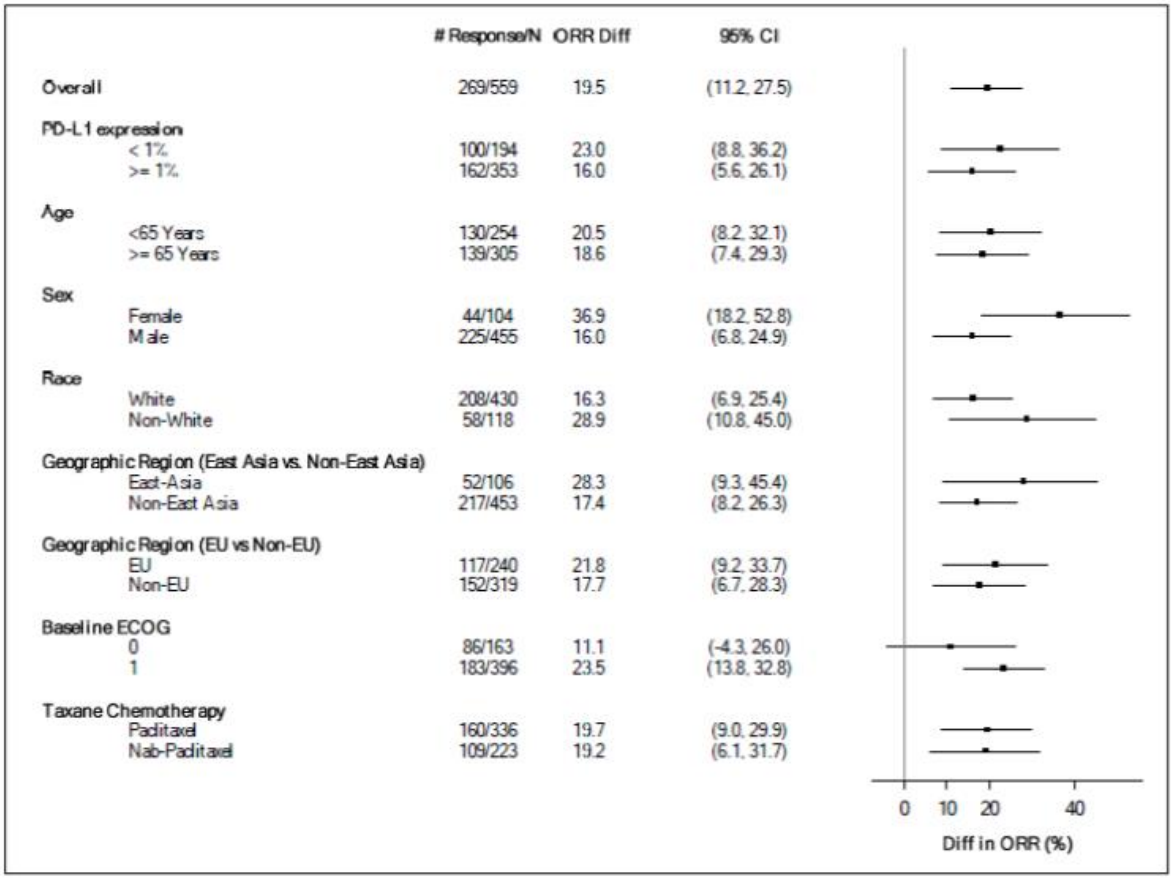
Figure 6.10: Subgroup analyses of objective response rate in the KEYNOTE-407 trial, ITT population



Analysis (ORR difference and 95% CI) for the overall population and the PD-L1 subgroup is based on the stratified Miettinen & Nurminen method; analysis for the other subgroups is based on the unstratified Miettinen & Nurminen method. If a subgroup variable has two levels and one level of the subgroup variable has fewer than 10% of the ITT population, then this subgroup is not displayed in the plot.
Subjects with PD-L1 not evaluable are not included in the analysis for PD-L1 subgroup variable.

Source: EMA Assessment Report, 2019; Figure 10, page 30/103[3]

Duration of Response (DOR)

The median DOR was 7.7 months (95% CI: 1.1, 14.7) in the BICR-assessed pembrolizumab combination arm compared to 4.8 months (95% CI: 1.3, 15.8), with participants experiencing ongoing response in both treatment arms. As shown in Table 6.13 (above), this was comparable to the investigator-assessed DOR. The median time to response was 1.4 months in both groups, ranging from 1.1 to 6.1 months in the pembrolizumab combination arm and 1.0 to 4.5 months in the placebo combination arm.[2]

Additional Analyses

A prespecified subgroup analysis with 106 (19.0% of global population) east Asian patients was conducted. This analysis included 54 patients in the pembrolizumab combination arm and 52 patients in the placebo combination arm, and the median

duration of follow-up was 6.7 months (range: 0.5-18.9 months). The median OS was 16.6 months (95% CI: 16.6, NR) in the pembrolizumab combination arm and 9.5 months (95% CI: 7.5, NR) in the placebo combination arm. There was a 56% reduction in the risk of death associated with the pembrolizumab combination arm compared to the placebo combination arm (HR: 0.44; 95% CI: 0.22, 0.89), which was consistent with the overall trial results. The median PFS was also longer in the pembrolizumab combination arm at 6.3 months (95% CI: 5.3, 10.2) compared to the placebo combination arm, which was 4.1 months (95% CI: 3.5, 5.2). Similar to OS, there was a 51% reduction in the risk of progression or death associated with the pembrolizumab combination compared to the placebo combination arm (HR: 0.49; 95% CI: 0.30, 0.82), which was also consistent with the overall trial results. The ORR was 63.0% in the pembrolizumab combination arm and 34.6% in the placebo combination arm, which was also consistent with the overall trial results. The proportion of grade ≥3 AEs were similar between treatment arms, however were higher in the east Asian subgroup than in the overall global population affecting 83.3% of patients in the pembrolizumab combination arm and 80.8% of patients in the placebo combination arm (~10% higher than in the overall trial).[25]

An additional prespecified analysis explored OS, PFS, and ORR, by investigator's choice of taxane (paclitaxel vs. nab-paclitaxel). Paclitaxel was the choice of taxane for 60.1% of patients compared to 39.9% of patients that received nab-paclitaxel. Patients who received pembrolizumab with carboplatin and nab-paclitaxel compared to patients who received placebo with carboplatin and nab-paclitaxel had a slightly higher reduction in the risk of death (HR: 0.59; 95% CI: 0.36, 0.98) compared to patients who received pembrolizumab with carboplatin and paclitaxel compared to placebo with carboplatin and paclitaxel (HR: 0.67; 95% CI: 0.48, 0.93). The opposite was true for PFS, where patients who received pembrolizumab with carboplatin and paclitaxel compared to patients who received placebo with carboplatin and paclitaxel had a greater reduction in the risk of progression or death (HR: 0.52; 95% CI: 0.40, 0.68) compared to patients who received pembrolizumab with carboplatin and nab-paclitaxel relative to placebo with carboplatin and nab-paclitaxel (HR: 0.65; 95% CI: 0.45, 0.94).ORR was similar across all treatment groups (Table 6.14).[24] Regardless of choice of taxane therapy, all results were consistent with the overall trial results.

Table 6.14. Subgroup analysis of OS, PFS, and ORR by choice of taxane therapy (paclitaxel versus nab-paclitaxel) in the KEYNOTE-407 trial

	Carboplatin plus Paclitaxel		Carboplatin plus Nab-Paclitaxel	
	Pembrolizumab + Chemo-therapy N = 169	Placebo + Chemo-therapy N = 167	Pembrolizumab + Chemo-therapy N = 109	Placebo + Chemo-therapy N = 114
OS, median (95% CI), mo	14.0 (12.6-16.6)	10.3 (8.2-14.8)	NR (NE-NE)	12.6 (9.6-NE)
HR (95% CI)[a]	0.67 (0.48-0.93)		0.59 (0.36-0.98)	
PFS, median (95% CI), mo	6.4 (6.0-8.3)	4.4 (4.2-5.1)	6.5 (6.2-8.5)	5.9 (4.4-6.9)
HR (95% CI)[a]	0.52 (0.40-0.68)		0.65 (0.45-0.94)	
ORR, % (95% CI)	57.4 (49.6-65.0)	37.7 (30.4-45.5)	58.7 (48.9-68.1)	39.5 (30.4-49.1)

[a]Based on a Cox regression model with treatment as a covariate.

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Quality of Life

At baseline, 92% of participants in the pembrolizumab combination arm, and 95% of patients in the placebo combination arm completed the EORTC QLQ-30 and QLQ-LC13 assessment. Compliance at week 9 and 18 was 80% and 88% in the pembrolizumab combination arm, and 88% and 87% in the placebo combination arm. Completion rates decreased at each time point as more participants discontinued from the trial.[4]

Mean EORTC QLQ-C30 global health status (GHS)/quality of life (QoL) score at baseline was were similar between the two treatment arms (63.9 vs. 62.7 in the pembrolizumab combination and placebo combination arms, respectively).[26] At week 9, there was a statistically significant difference in the mean GHS score based on the EORTC QLQ-C30 between treatment arms (LS mean diff: 3.6; 95% CI: 0.3, 6.9), as well as at week 18 (LS mean diff: 4.9; 95% CI: 1.4, 8.3), illustrated in Figure 6.11.[3,4] Evidence-based guidelines suggest that a mean difference in the global scale of the EORTC-QLQ-C30 of 0-4 is considered trivial, and 4-10 is considered small, and thus the clinical relevance of this finding is minimal.[5] Additionally, Figure 6.11 shows that by week 36, the small difference in QoL between treatment arms at week 9 and 18 is not retained, and QoL scores by week 36 are similar to baseline.

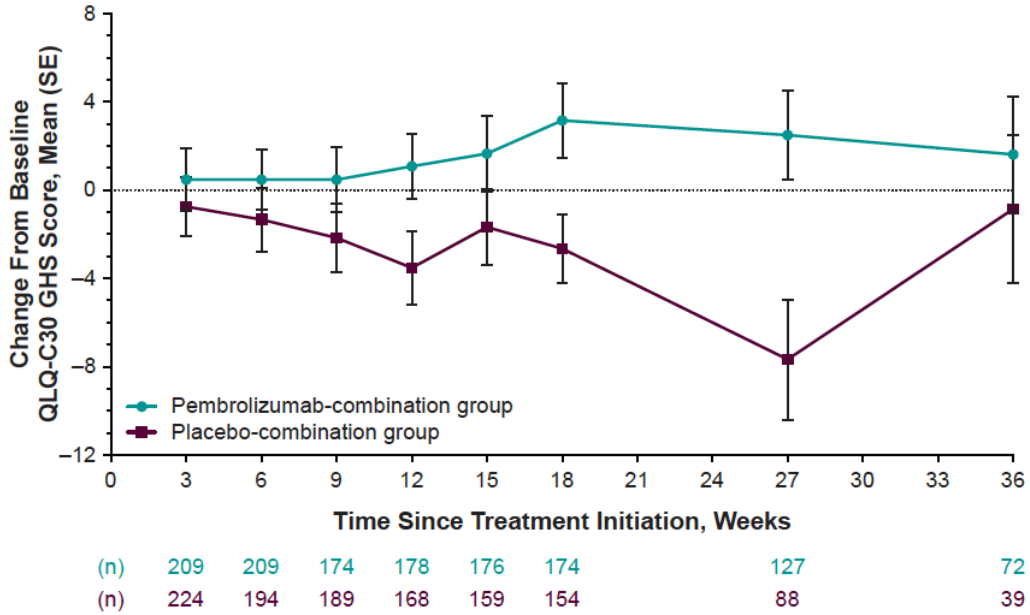
As shown in Figure 6.12, there was a significant improvement from baseline in emotional functioning in both treatment arms at both weeks 9 and 18. There was a significant improvement in the global health score in the pembrolizumab combination arm from baseline to week 18. At week 18, there was a significant

decrease in physical and role functioning in the chemotherapy combination arm from baseline. In reference to EORTC QLQ-C30 symptom subscales, from baseline to week 9, there was a significant improvement in both treatment arms for pain, insomnia, and appetite loss. At week 9 there was a significant worsening from baseline of diarrhea in the pembrolizumab combination arm that was not seen in the placebo combination arm, however this was no longer significant by week 18. In the pembrolizumab combination arm, from baseline to week 18, a significant improvement in pain, insomnia, and appetite loss was maintained, and additional significant improvements in fatigue, dyspnea, nausea and vomiting, and constipation were seen. In the placebo combination arm from baseline to week 18, significant improvements in insomnia and appetite loss were maintained, in addition significant improvements to nausea and vomiting, and constipation. Significant improvements in pain were not maintained in the placebo combination arm from week 9 to 18.[4]

Time to true deterioration of the composite endpoint consisting of the cough, chest pain, and dyspnea taken from the EORTC QLQ-LC13 questions 1 and 10, and the EORTC QLQ-C30 question 8, respectively, was explored. Median time to deterioration for the composite endpoint was not reached in either treatment arm.[26] As reported in Table 6.15, there was no significant difference between treatment arms in time to true deterioration of the composite endpoint (HR: 0.79; 95% CI: 0.58, 1.06).[3]

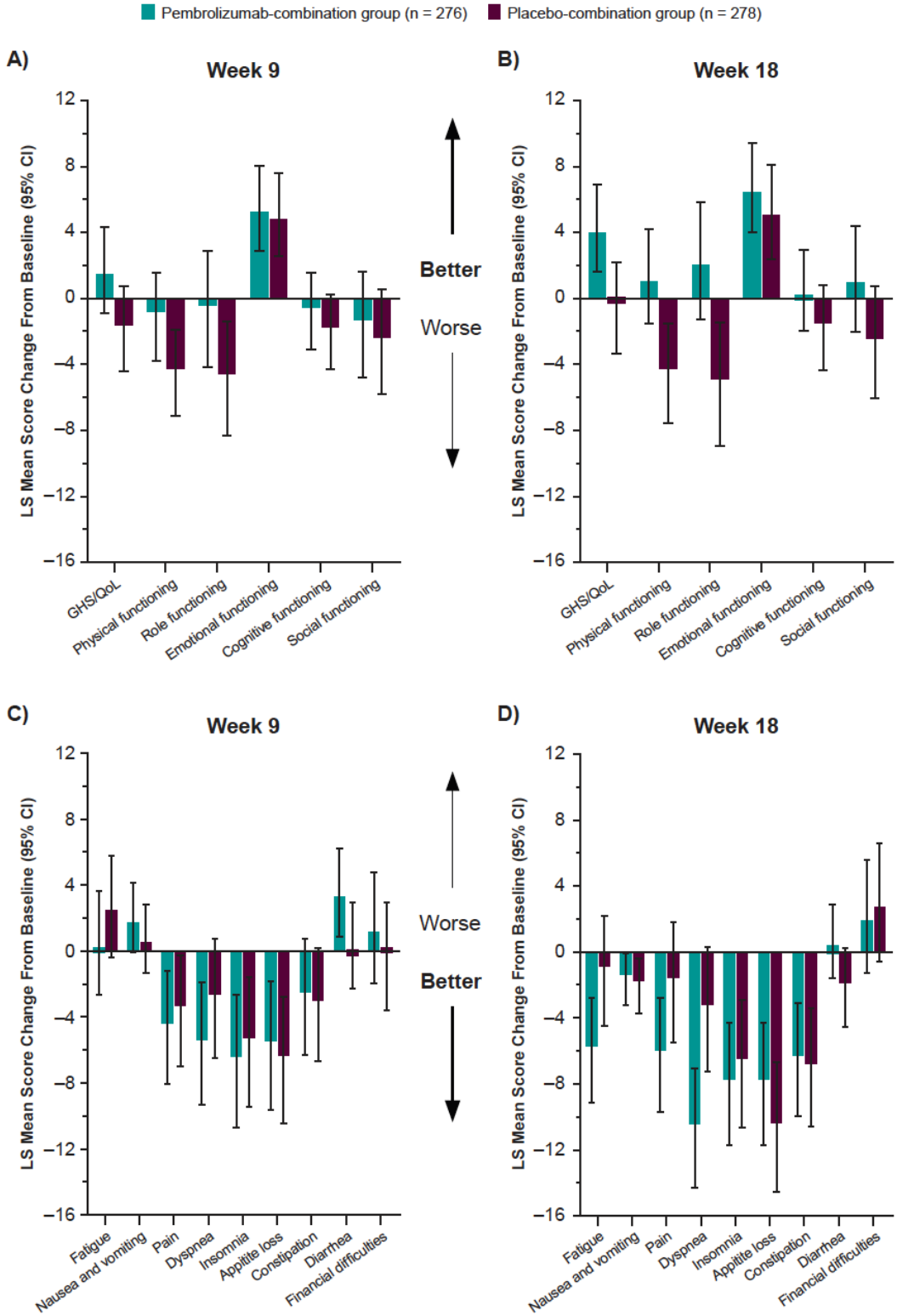
The results of the EQ-5D-3L were incorporated into the economic evaluation. Of note, there was no statistically significant difference in EQ-5D-3L VAS scores at week 9 between treatment arms, whereas by week 18 (when patients in the placebo group were no longer receiving chemotherapy) there was a statistically significant difference between arms.[6]

Figure 6.11: Mean change from baseline in EORTC QLQ-C30 global health status by visit



Source: Merck Canada Inc., 2018; Figure 14, page 29/43[37] Keytruda clinical rationale. For the first-line treatment of patients with metastatic squamous non-small cell lung cancer (NSCLC), in combination with carboplatin and either paclitaxel or nab-paclitaxel. In: pan-Canadian Oncology Drug Review manufacturer submission: Keytruda (pembrolizumab), powder for reconstitution for infusion - 50mg, solution for infusion 100mg/4mL vial. Kirkland (QC): Merck Canada Inc.; 2018 Feb 08. Accessed 2019 Sep 11.

Figure 6.12: Change from baseline in EORTC QLQ-C30 global health status and quality of life scores (A and B), and symptom subscale scores (C and D), at weeks 9 and 18



Source: Merck Canada Inc., 2018; Figure 16, page 31/43[37] Keytruda clinical rationale. For the first-line treatment of patients with metastatic squamous non-small cell lung cancer (NSCLC), in combination with carboplatin and either paclitaxel or nab-paclitaxel. In: pan-Canadian Oncology Drug Review manufacturer submission: Keytruda (pembrolizumab), powder for reconstitution for infusion - 50mg, solution for infusion 100mg/4mL vial. Kirkland (QC): Merck Canada Inc.; 2018 Feb 08. Accessed 2019 Sep 11.

Table 6.15: Time to true deterioration for the composite endpoint of cough, chest pain, or dyspnea in the KEYNOTE-407 trial, ITT population

Treatment	N	True Deterioration Events(%)	Pembrolizumab vs. Control	
			Hazard Ratio[†](95% CI)[‡]	p-Value[‡]
Pembro Combo	276	81 (29.3)	0.79 (0.58, 1.06)	0.125
Control	278	94 (33.8)	---	---

True deterioration is defined as the time to first onset of 10 or more increase from baseline with confirmation under right-censoring rule (the last observation).
[†] Based on Cox regression model with treatment as a covariate stratified by PD-L1 expression (tumor proportion score ≥ 1% vs. <1%), taxane chemotherapy (paclitaxel vs. nab-paclitaxel) and geographic region (East Asia vs. non-East Asia).
[‡] Two-sided p-value based on stratified log-rank test.
Database Cutoff Date: 03APR2018

Source: EMA Assessment Report, 2019; Table 16, page 27/103[3]

Harms Outcomes

Safety analyses were performed using the ASaT population, participants who received at least 1 dose of study treatment (n =558). AEs of any grade occurred in 98.2% and 97.9% of patients in the pembrolizumab combination arm and placebo combination arm, respectively. AEs of grade ≥ 3 or higher occurred in 69.8% and 68.2% of participants in the pembrolizumab combination arm and placebo combination arms, respectively.[2] There were a higher proportion of patients in the pembrolizumab combination arm (95.3%) with treatment-emergent AEs (TEAEs) compared to the placebo combination arm (88.9%). Participants with serious AEs (SAEs) were comparable between treatment arms (40.6% vs. 38.2% in the pembrolizumab combination arm and placebo combination arms, respectively); however a higher proportion of patients in the pembrolizumab combination arm experienced a serious TEAE (25.2% vs. 18.2%). Participants with grade ≥3 TEAEs were comparable between treatment arms (54.7% vs. 55.0% in the pembrolizumab combination arm and placebo combination arms, respectively).[3]

The 4 most commonly any cause (Table 6.16), any grade AEs in both treatment arms included anemia (53.2% vs. 51.8%, pembrolizumab combination arm vs. placebo combination arm, respectively); alopecia (46.0% and 36.4%, respectively); neutropenia (37.8% and 32.9%, respectively); and nausea (35.6% and 32.1%, respectively). In the pembrolizumab combination arm, this was followed by thrombocytopenia (30.6%), diarrhea (29.9%), and decreased appetite (24.5%), whereas in the placebo this was followed by decreased appetite (29.3%), fatigue (25.7%), thrombocytopenia (23.2%), and diarrhea (23.2%). As depicted in Figure 6.13, there was no significant risk difference between treatment arms for most AEs, with the exception of alopecia and pruritis (risk difference favoured placebo combination), and back pain (risk difference favoured pembrolizumab combination).

The top 3, any cause, grade ≥3 AEs (Table 6.17) in both treatment arms were neutropenia (22.7% vs. 24.6%, pembrolizumab combination arm vs. placebo

combination arm, respectively); anemia (15.5% vs. 20.4%, respectively); and thrombocytopenia (6.8% vs. 6.4%, respectively). This was followed by diarrhea (4.0%) and constipation (3.2%) in the pembrolizumab combination arm, where in the placebo combination arm, it was followed by fatigue (3.9%) and asthenia (3.6%). As depicted in Figure 6.13, there was no significant risk difference between treatment arms for most grade ≥3 AEs, with the exception of pneumonitis, and autoimmune hepatitis (placebo combination better).[2]

Illustrated in Figure 6.14, pneumonia (6.7% vs. 5.8%, pembrolizumab combination arm vs. placebo combination arm, respectively) and febrile neutropenia (3.6% vs. 5.4%) were the most commonly occurring SAEs in both treatment arms. This was followed by anaemia (2.9%) and neutropenia (2.5%) in the pembrolizumab combination arm, whereas in the placebo combination arm, the most common SAEs after pneumonia and febrile neutropenia were pneumonitis (2.5%) and diarrhea (2.5%). Overall, there was no significant risk difference between treatments arms for SAEs. In Table 6.17, the most common treatment-emergent SAE was febrile neutropenia in both treatment arms (5.0% and 3.2% in the pembrolizumab combination arm and placebo combination arm, respectively). This was followed by pneumonia (2.5%) in the pembrolizumab combination arm, and neutropenia (2.5%) in the placebo combination arm.

In Table 6.18, grade 3-5 TEAEs are presented. In both treatment arms, neutropenia was the most commonly occurring grade ≥3 TEAE (21.2% vs. 22.5%, pembrolizumab combination arm vs. placebo combination arm, respectively), followed by anaemia (13.7% vs. 15.4%, respectively).[3]

Any grade AEs of interest, defined as events of interest that are infusion reactions and events with an immune-related cause, were higher in the pembrolizumab combination arm (28.8% vs. 8.6% in the placebo combination arm). As shown in Table 6.19, hypothyroidism (7.9%), hyperthyroidism (7.2%), and pneumonitis (6.5%), was higher in the pembrolizumab combination arm than the placebo combination arm (1.8%, 0.7%, and 2.1% for hypothyroidism, hyperthyroidism, and pneumonitis, respectively). Grade ≥ 3 AEs of interest were higher in the pembrolizumab combination arm (10.8% vs. 3.2% in the placebo combination arm), with pneumonitis being the most common (2.5% vs. 1.1%, respectively).

A higher proportion of participants in the pembrolizumab combination discontinued all treatment components (13.3% vs. 6.4% in the placebo combination arm) and any treatment components (23.4% vs. 11.8% in the placebo combination arm) due to any grade AEs (Table 6.16). Discontinuation rates were similar for grade ≥ 3 AEs.[2]

There were a similar proportion of participants in the pembrolizumab combination arm that experienced an AE resulting in death (n=23; 8.3%) compared to the placebo combination arm (n=18; 6.4%), as shown in Table 6.20. In the pembrolizumab combination arm AEs leading to death included respiratory failure (n=3); sepsis (n=3), cardiac arrest (n=2), and pulmonary haemorrhage (n=2). In the placebo combination arm, AEs leading to death included septic shock (n=3), and cardio-respiratory arrest (n=2).[3] As per investigator assessment, 10 deaths in the pembrolizumab combination arm were treatment-related compared to 6 deaths in the placebo combination arm.[2]

Table 6.16: Adverse events of any cause in the KEYNOTE-407 trial, ASaT population

Event	Pembrolizumab Combination (N=278)		Placebo Combination (N=280)	
	Any Grade	Grade 3, 4, or 5	Any Grade	Grade 3, 4, or 5
	number of patients (percent)			
Any event	273 (98.2)	194 (69.8)	274 (97.9)	191 (68.2)
Event leading to discontinuation of all treatment components†	37 (13.3)	34 (12.2)	18 (6.4)	18 (6.4)
Event leading to discontinuation of any treatment component‡	65 (23.4)	54 (19.4)	33 (11.8)	29 (10.4)
Discontinuation of pembrolizumab or placebo	48 (17.3)	44 (15.8)	22 (7.9)	21 (7.5)
Discontinuation of carboplatin	31 (11.2)	28 (10.1)	21 (7.5)	19 (6.8)
Discontinuation of paclitaxel or nab-paclitaxel	44 (15.8)	33 (11.9)	28 (10.0)	24 (8.6)
Event leading to death§	23 (8.3)	23 (8.3)	18 (6.4)	18 (6.4)
Event leading to death that was attributed to a trial regimen by an investigator¶	10 (3.6)	10 (3.6)	6 (2.1)	6 (2.1)
Event occurring in ≥15% of patients in either group‖				
Anemia	148 (53.2)	43 (15.5)	145 (51.8)	57 (20.4)
Alopecia	128 (46.0)	1 (0.4)	102 (36.4)	3 (1.1)
Neutropenia	105 (37.8)	63 (22.7)	92 (32.9)	69 (24.6)
Nausea	99 (35.6)	3 (1.1)	90 (32.1)	4 (1.4)
Thrombocytopenia	85 (30.6)	19 (6.8)	65 (23.2)	18 (6.4)
Diarrhea	83 (29.9)	11 (4.0)	65 (23.2)	6 (2.1)
Decreased appetite	68 (24.5)	6 (2.2)	82 (29.3)	5 (1.8)
Constipation	64 (23.0)	2 (0.7)	61 (21.8)	3 (1.1)
Fatigue	63 (22.7)	9 (3.2)	72 (25.7)	11 (3.9)
Asthenia	60 (21.6)	6 (2.2)	59 (21.1)	10 (3.6)
Arthralgia	57 (20.5)	4 (1.4)	40 (14.3)	2 (0.7)
Peripheral neuropathy	57 (20.5)	3 (1.1)	45 (16.1)	2 (0.7)
Vomiting	45 (16.2)	1 (0.4)	33 (11.8)	6 (2.1)
Cough	37 (13.3)	2 (0.7)	47 (16.8)	3 (1.1)
Dyspnea	36 (12.9)	4 (1.4)	45 (16.1)	3 (1.1)

* Listed are all adverse events that occurred during the trial period or within the 30 days thereafter (within 90 days for serious events), regardless of attribution to any trial regimen by an investigator. Adverse events that occurred during crossover from the placebo-combination group to pembrolizumab monotherapy are excluded. The as-treated population included all patients who underwent randomization and received at least one dose of the assigned combination treatment.

† This category includes patients who discontinued pembrolizumab or placebo, carboplatin, and paclitaxel or nab-paclitaxel because of an adverse event at any time and patients who discontinued pembrolizumab or placebo for an adverse event after completing four cycles of carboplatin and either paclitaxel or nab-paclitaxel.

‡ Patients could have discontinued one, two, or all agents for a given adverse event.

§ The adverse events leading to death in the pembrolizumab-combination group were respiratory failure and sepsis in 3 patients each, cardiac arrest and pulmonary hemorrhage in 2 patients each, and cardiac failure, circulatory collapse, hepatic failure, intestinal perforation, lung abscess, necrotizing fasciitis, pneumonia, pneumonitis, and pulmonary sepsis in 1 patient each; 4 of the deaths in this group had an unspecified cause. The adverse events leading to death in the placebo-combination group were septic shock in 3 patients, cardiorespiratory arrest in 2 patients, and acute kidney injury, cardiac arrest, hemothorax, multiple organ dysfunction syndrome, pleural effusion, pneumonia, pneumonitis, pulmonary hemorrhage, pulmonary mycosis, and sepsis in 1 patient each; 3 of the deaths in this group had an unspecified cause.

¶ In the pembrolizumab-combination group, the adverse events leading to death that were attributed to one or more components of the trail regimen by an investigator were sepsis in 3 patients and hepatic failure, necrotizing fasciitis, pneumonitis, pulmonary hemorrhage, and respiratory failure in 1 patient each; 2 of the deaths that were attributed to one or more components of the trail regimen in this group had an unspecified cause. The adverse events leading to death that were attributed to a component of the trail regimen in the placebo-combination group were septic shock in 2 patients and acute kidney injury, multiple organ dysfunction syndrome, pneumonia, and pulmonary hemorrhage in 1 patient each.

‖ Events are listed in descending order of frequency in the pembrolizumab-combination group. None of these events were of grade 5 severity.

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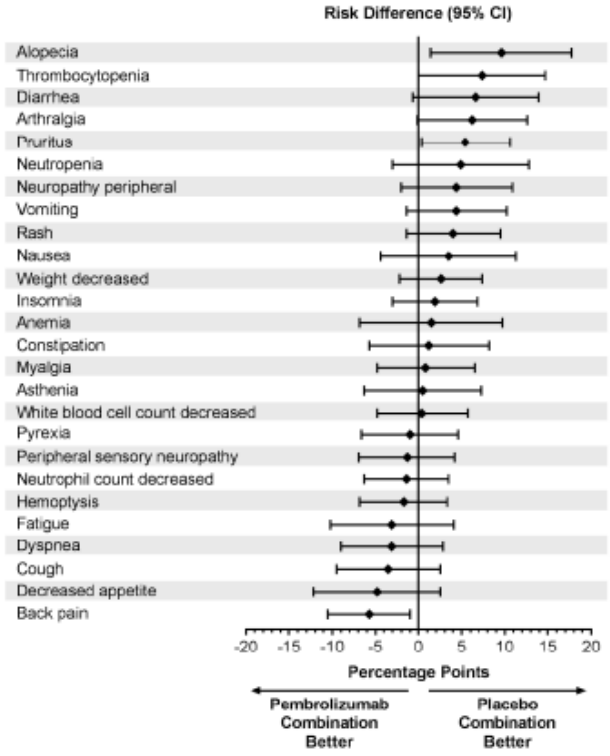
Figure 6.13: Risk difference between treatment groups for A) adverse events of any grade (occured in ≥10% patients) and B) adverse events grade 3-5 (occurred in ≥ 5 patients), ASaT population

(A)



(B)

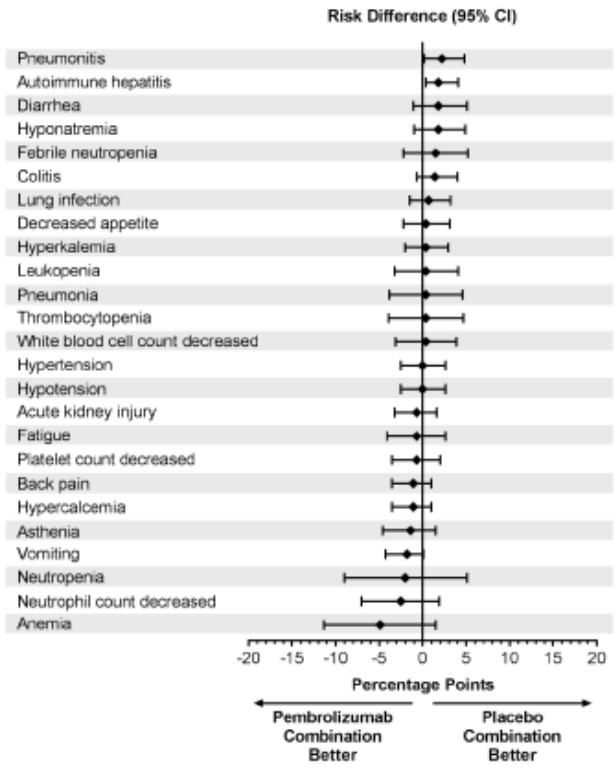


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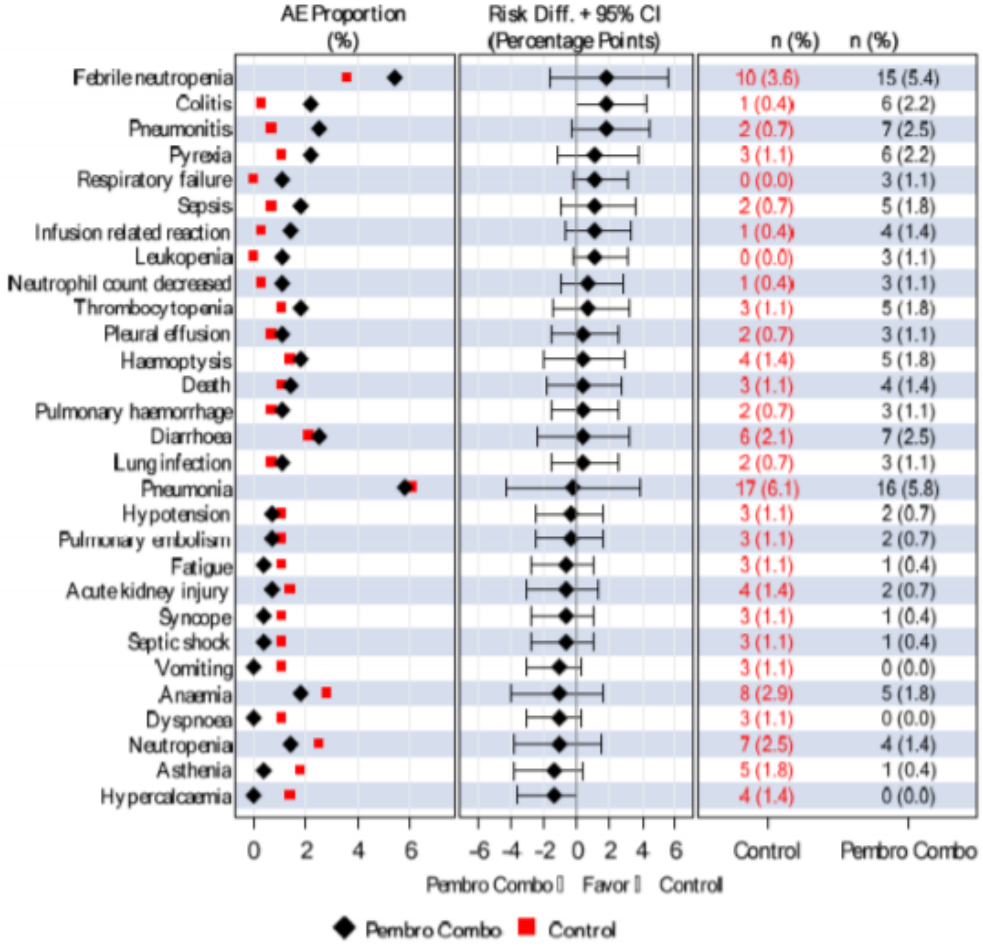
Figure 6.14: Serious adverse events in the KEYNOTE-407 trial, ASaT population



Source: EMA Assessment Report, 2019; Figure 16, page 60/103[3]

Table 6.17: Treatment-related serious adverse events in the KEYNOTE-407 trial, ASaT population

	Pembro Combo		Control	
	n	(%)	n	(%)
Subjects in population	278		280	
with one or more adverse events	70	(25.2)	51	(18.2)
with no adverse events	208	(74.8)	229	(81.8)
Febrile neutropenia	14	(5.0)	9	(3.2)
Pneumonia	7	(2.5)	3	(1.1)
Colitis	6	(2.2)	1	(0.4)
Anaemia	5	(1.8)	5	(1.8)
Pneumonitis	5	(1.8)	1	(0.4)
Thrombocytopenia	5	(1.8)	3	(1.1)
Diarrhoea	4	(1.4)	4	(1.4)
Infusion related reaction	4	(1.4)	1	(0.4)
Neutropenia	4	(1.4)	7	(2.5)
Sepsis	4	(1.4)	0	(0.0)
Leukopenia	3	(1.1)	0	(0.0)
Neutrophil count decreased	3	(1.1)	1	(0.4)
Pyrexia	3	(1.1)	0	(0.0)
Autoimmune hepatitis	2	(0.7)	0	(0.0)
Death	2	(0.7)	0	(0.0)
Duodenitis	2	(0.7)	0	(0.0)
Interstitial lung disease	2	(0.7)	2	(0.7)
Acute kidney injury	1	(0.4)	3	(1.1)
Asthenia	1	(0.4)	4	(1.4)
Atrial flutter	1	(0.4)	0	(0.0)
Autoimmune thyroiditis	1	(0.4)	0	(0.0)
Biliary tract infection	1	(0.4)	0	(0.0)
Cerebrovascular accident	1	(0.4)	0	(0.0)
Decreased appetite	1	(0.4)	1	(0.4)
Drug hypersensitivity	1	(0.4)	0	(0.0)
Fatigue	1	(0.4)	3	(1.1)
General physical health deterioration	1	(0.4)	0	(0.0)
Hepatic failure	1	(0.4)	0	(0.0)
Hyperthyroidism	1	(0.4)	0	(0.0)
Hyponatraemia	1	(0.4)	1	(0.4)
Hypopituitarism	1	(0.4)	0	(0.0)
Hypotension	1	(0.4)	2	(0.7)
Lung abscess	1	(0.4)	0	(0.0)

Lung infection	1	(0.4)	0	(0.0)
Myocardial infarction	1	(0.4)	0	(0.0)
Necrotising fasciitis	1	(0.4)	0	(0.0)
Nephritis	1	(0.4)	1	(0.4)
Neuropathy peripheral	1	(0.4)	0	(0.0)
Pericardial effusion	1	(0.4)	0	(0.0)
Platelet count decreased	1	(0.4)	0	(0.0)
Psoriasis	1	(0.4)	0	(0.0)
Pulmonary haemorrhage	1	(0.4)	1	(0.4)
Respiratory failure	1	(0.4)	0	(0.0)
Tubulointerstitial nephritis	1	(0.4)	0	(0.0)
Urosepsis	1	(0.4)	0	(0.0)
Vasculitis	1	(0.4)	0	(0.0)
White blood cell count decreased	1	(0.4)	0	(0.0)
Alanine aminotransferase increased	0	(0.0)	1	(0.4)
Arterial disorder	0	(0.0)	1	(0.4)
Candida infection	0	(0.0)	1	(0.4)
Cholangitis	0	(0.0)	1	(0.4)
Dehydration	0	(0.0)	1	(0.4)
Device related infection	0	(0.0)	1	(0.4)
Enterocolitis	0	(0.0)	1	(0.4)
Epistaxis	0	(0.0)	1	(0.4)
Gastric ulcer haemorrhage	0	(0.0)	1	(0.4)
Hyperkalaemia	0	(0.0)	1	(0.4)
Malaise	0	(0.0)	1	(0.4)
Multiple organ dysfunction syndrome	0	(0.0)	1	(0.4)
Myalgia	0	(0.0)	1	(0.4)
Nausea	0	(0.0)	1	(0.4)
Oedema peripheral	0	(0.0)	1	(0.4)
Pneumonia bacterial	0	(0.0)	1	(0.4)
Septic shock	0	(0.0)	2	(0.7)
Tumour necrosis	0	(0.0)	1	(0.4)
Uraemic encephalopathy	0	(0.0)	1	(0.4)
Vomiting	0	(0.0)	1	(0.4)

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
For subjects who crossed over to pembrolizumab from the Control Group, adverse events that occurred after the first dose of crossover phase are excluded.
Serious adverse events up to 90 days of last dose are included.
Database Cutoff Date: 03APR2018

Source: EMA Assessment Report, 2019; Table 45, page 62/103[3]

Table 6.18: Treatment-related grade 3-5 adverse events in the KEYNOTE-407 trial, ASaT population

	Pembro Combo		Control	
	n	(%)	n	(%)
Subjects in population	278		280	
with one or more adverse events	152	(54.7)	154	(55.0)
with no adverse events	126	(45.3)	126	(45.0)
Neutropenia	59	(21.2)	63	(22.5)
Anaemia	38	(13.7)	43	(15.4)
Thrombocytopenia	18	(6.5)	16	(5.7)
Neutrophil count decreased	17	(6.1)	24	(8.6)
Febrile neutropenia	14	(5.0)	10	(3.6)
Leukopenia	12	(4.3)	12	(4.3)
White blood cell count decreased	11	(4.0)	10	(3.6)
Diarrhoea	8	(2.9)	4	(1.4)
Pneumonia	8	(2.9)	3	(1.1)
Fatigue	7	(2.5)	7	(2.5)
Colitis	6	(2.2)	2	(0.7)
Autoimmune hepatitis	5	(1.8)	0	(0.0)
Decreased appetite	5	(1.8)	4	(1.4)
Hyponatraemia	5	(1.8)	1	(0.4)
Platelet count decreased	5	(1.8)	6	(2.1)
Pneumonitis	5	(1.8)	0	(0.0)
Asthenia	3	(1.1)	6	(2.1)
Infusion related reaction	3	(1.1)	1	(0.4)
Neuropathy peripheral	3	(1.1)	2	(0.7)
Sepsis	3	(1.1)	0	(0.0)
Hypotension	2	(0.7)	3	(1.1)
Nausea	2	(0.7)	3	(1.1)
Acute kidney injury	1	(0.4)	3	(1.1)
Alopecia	1	(0.4)	3	(1.1)
Vomiting	1	(0.4)	3	(1.1)
Gamma-glutamyltransferase increased	0	(0.0)	3	(1.1)

Every subject is counted a single time for each applicable row and column.

A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

For subjects who crossed over to pembrolizumab from the Control Group, adverse events that occurred after the first dose of crossover phase are excluded.

Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.

Grades are based on NCI CTCAE version 4.03.

Database Cutoff Date: 03APR2018

Source: [P407V01MK3475: adam-adsl; adae]

Source: EMA Assessment Report, 2019; Table 41, page 56/103[3]

Table 6.19: Adverse events of interest in the KEYNOTE-407 trial, ASaT population

Event	Pembrolizumab Combination (N=278)		Placebo Combination (N=280)	
	Any Grade	Grade 3, 4, or 5	Any Grade	Grade 3, 4, or 5
	number of patients (percent)			
Any event	80 (28.8)	30 (10.8)	24 (8.6)	9 (3.2)
Hypothyroidism	22 (7.9)	1 (0.4)	5 (1.8)	0
Hyperthyroidism	20 (7.2)	1 (0.4)	2 (0.7)	0
Pneumonitis	18 (6.5)	7 (2.5)†	6 (2.1)	3 (1.1)†
Infusion reaction	8 (2.9)	4 (1.4)	6 (2.1)	1 (0.4)
Colitis	7 (2.5)	6 (2.2)	4 (1.4)	3 (1.1)
Hepatitis	5 (1.8)	5 (1.8)	0	0
Severe skin reaction	5 (1.8)	3 (1.1)	1 (0.4)	1 (0.4)
Hypophysitis	3 (1.1)	2 (0.7)	0	0
Thyroiditis	3 (1.1)	1 (0.4)	0	0
Nephritis	2 (0.7)	2 (0.7)	2 (0.7)	2 (0.7)

* The adverse events of interest are infusion reactions and events with an immune-related cause; they are considered regardless of whether the investigator attributed the event to a trial regimen or considered the event to be immune-related. The events are listed in descending order of frequency in the pembrolizumab-combination group. In addition to the specific preferred terms that are listed, related terms were also included. The as-treated population included all patients who underwent randomization and received at least one dose of the assigned combination treatment.
† Data include 1 patient (0.4%) in each trial group who had grade 5 pneumonitis.

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Table 6.20: Participants with adverse events resulting in death in the KN-407 trial, ASaT population

	Pembro Combo		Control	
	n	(%)	n	(%)
Subjects in population	278		280	
with one or more adverse events	23	(8.3)	18	(6.4)
with no adverse events	255	(91.7)	262	(93.6)
Death	4	(1.4)	3	(1.1)
Respiratory failure	3	(1.1)	0	(0.0)
Sepsis	3	(1.1)	1	(0.4)
Cardiac arrest	2	(0.7)	1	(0.4)
Pulmonary haemorrhage	2	(0.7)	1	(0.4)
Cardiac failure	1	(0.4)	0	(0.0)
Circulatory collapse	1	(0.4)	0	(0.0)
Hepatic failure	1	(0.4)	0	(0.0)
Intestinal perforation	1	(0.4)	0	(0.0)
Lung abscess	1	(0.4)	0	(0.0)
Necrotising fasciitis	1	(0.4)	0	(0.0)
Pneumonia	1	(0.4)	1	(0.4)
Pneumonitis	1	(0.4)	1	(0.4)
Pulmonary sepsis	1	(0.4)	0	(0.0)
Acute kidney injury	0	(0.0)	1	(0.4)
Cardio-respiratory arrest	0	(0.0)	2	(0.7)
Haemothorax	0	(0.0)	1	(0.4)
Multiple organ dysfunction syndrome	0	(0.0)	1	(0.4)
Pleural effusion	0	(0.0)	1	(0.4)
Pulmonary mycosis	0	(0.0)	1	(0.4)
Septic shock	0	(0.0)	3	(1.1)

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
For subjects who crossed over to pembrolizumab from the Control Group, adverse events that occurred after the first dose of crossover phase are excluded.
Serious adverse events up to 90 days of last dose are included.
MedDRA 20.1 preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Database Cutoff Date: 03APR2018

Source: EMA Assessment Report, 2019; Table 47, page 65/103[3]

6.3 Ongoing Trials

There were three ongoing trials that met the eligibility criteria based on the systematic review protocol, of which one trial was specific to Sq NSCLC, and two trials included both Sq and non-squamous NSCLC patients.

Table 6.21: Ongoing trials of pembrolizumab in squamous, non-small cell lung cancer

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
Study:[42] NCT03875092 (China extension of KEYNOTE-407) **Characteristics:** Triple-blind, randomised placebo-controlled, phase III trial **Estimated enrolment:** n = 125 **Number of centres and number of countries:** China (number of sites unknown) **Patient Enrolment Dates:** June 9th, 2016 (completed) **Estimated primary study completion:** March 10th, 2020 **Estimated study completion:** February 15th, 2021 **Funding:** Merck Sharp & Dohme Corp.	Key Inclusion Criteria: • Stage IV Sq-NSCLC • Measurable disease as per RECIST 1.1 • No prior systemic therapy • ECOG PS 0-1 • Adequate organ function Key Exclusion Criteria: • NSq-NSCLC • Prior to first dose has investigational agent within 4 weeks; received prior systemic chemotherapy, targeted or biological antineoplastic therapy; major surgery within 3 weeks; or radiation to the lung >30 Gy • Live vaccine within 30 days of first dose • History of prior malignancy except if undergone curative therapy with no evidence of recurrence within 5 years • Active CNS metastases or carcinomatous meningitis • Pre-existing peripheral neuropathy • Active autoimmune disease that has required systemic treatment in past 2 years • On chronic systemic steroids • Active infection requiring therapy • Active infection with HBV, HCV, or HIV • Interstitial lung disease or history of pneumonitis • Severe hypersensitivity to mAbs	Interventions: Pembrolizumab (200 mg IV infusion once every 3 weeks) + carboplatin (AUC 6 by IV) + paclitaxel (200 mg/m^2 by IV) or nab-paclitaxel (100 mg/m^2 by IV) Comparators: Saline placebo (by IV) + carboplatin (AUC 6 by IV) + paclitaxel (200 mg/m^2 by IV) or nab-paclitaxel (100 mg/m^2 by IV)	Primary: • PFS by RECIST 1.1 • OS Secondary: • ORR by RECIST 1.1 • DOR by RECIST 1.1 • Safety
Study:[43] NCT03631199 **Characteristics:** Double-blind, randomised active-controlled, phase III trial **Estimated enrolment:** n = 627	Key Inclusion Criteria: • Stage IIIB or IV Sq- OR NSq-NSCLC • Measurable disease as per RECIST 1.1 • No prior systemic therapy • ECOG PS 0-1 • Archival tumor tissue or newly obtained biopsy to confirm PD-L1 status	Interventions: Canakinumab in combination with pembrolizumab and platinum-based doublet chemotherapy (options included carboplatin, cisplatin, paclitaxel, nab-paclitaxel, and/or pemetrexed)	Primary: • Safety • PFS • OS Secondary: • ORR • DCR • DOR • TTR • PKs

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
Number of centres and number of countries: 75 sites in 20 countries Canada, the United States, Argentina, Australia, Czechia, France, Germany, Iceland, Italy, Japan, Korea, Malaysia, Netherlands, Poland, Singapore, Spain, Switzerland, Taiwan, Thailand, and Vietnam **Patient Enrolment Dates:** December 21st, 2018 (ongoing) **Estimated primary study completion:** May 31st, 2021 **Estimated study completion:** October 21st, 2022 **Funding:** Novartis Pharmaceuticals	Key Exclusion Criteria: • Prior immunotherapy, mAb targeting T-cell co-stimulation, canakinumab or drug with similar mechanism of action • Active or untreated brain metastases or spinal cord compression • EGFR sensitizing mutations, ALK gene rearrangement • Suspected or proven immune-compromised infections • Received live vaccination ≤3 months; had major surgery ≤4 weeks prior to starting study drug; has thoracic radiotherapy: lung fields ≤ 4 weeks; other anatomic sites ≤ 2 weeks; palliative radiotherapy for bone lesions ≤ 2 weeks	Comparators: Canakinumab matching-placebo in combination with pembrolizumab and platinum-based doublet chemotherapy options included carboplatin, cisplatin, paclitaxel, nab-paclitaxel, and/or pemetrexed)	• HRQoL
Study:[44] NCT03322566 **Characteristics:** Quadruple-blind, randomised, active-controlled, phase II trial **Estimated enrolment:** n = 233 **Number of centres and number of countries:** 94 sites in Canada, the United States, Australia, Hungary, Ireland, Israel, Italy, Japan, Korea, Mexico, Russia, Spain, Taiwan, Turkey, United Kingdom **Patient Enrolment Dates:** December 21st, 2017 (not recruiting) **Estimated primary study completion:** December 13th, 2018	Key Inclusion Criteria: • Stage IV NSCLC without EGFR sensitizing mutation, ROS1 or ALK translocation • Measurable disease as per RECIST 1.1 • ECOG PS 0-1 • Adequate organ function • Provide tumor tissue sample Key Exclusion Criteria: • Known untreated CNS metastases and/or carcinomatous meningitis • History of pneumonitis • Symptomatic ascites or pleural effusion • Known history of additional malignancy unless no evidence of recurrence for 5 years curative treatment • Active autoimmune disease that has required systematic treatment in past 2 years • Had an allogeneic tissue/solid organ transplant • Known history of HIV infection, HBV or HCV • History or presence of clinically significant abnormal ECG	Interventions: Epacadostat (orally twice daily) + pembrolizumab (every 3 weeks) + platinum-based chemotherapy (options include pemetrexed + cisplatin; pemetrexed + carboplatin; paclitaxel + carboplatin) Comparators: Epacadostat-matching placebo (orally twice daily) + pembrolizumab (every 3 weeks) + platinum-based chemotherapy (options include pemetrexed + cisplatin; pemetrexed + carboplatin; paclitaxel + carboplatin)	Primary: • ORR Secondary: • PFS • OS • DOR • Safety

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
Estimated study completion: September 2021 **Funding:** Incyte Corporation			
Abbreviations: ALK = anaplastic lymphoma kinase; AUC = area under the curve; CNS = central nervous system; DCR = disease control rate; DOR = duration of response; ECOG PS= Eastern Cooperative Oncology Group performance score; EGFR = epidermal growth factor receptor; Gy = gray; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HRQoL = health related quality of life; IV = intravenous; mAb = monoclonal antibody; mg = milligram; mg/m2 = milligram per square meter of body surface; n = sample size; NSCLC = non-small cell lung cancer; NSq = non-squamous; ORR = objective response rate; OS= overall survival; PD-L1 = programmed death-ligand 1; PFS = progression-free survival; RECIST = response evaluation criteria in solid tumours; PK = pharmacokinetics; ROS1 = c-ros oncogene 1 receptor tyrosine kinase; Sq = squamous cell; TTR = time to response			

7 SUPPLEMENTAL QUESTIONS

The following supplemental issue was identified during development of the review protocol as relevant to the pCODR review of pembrolizumab in combination with chemotherapy (carboplatin and paclitaxel or nab-paclitaxel) for the first-line treatment of metastatic, Sq NSCLC:

- Context: Pembrolizumab monotherapy is currently approved and funded in most jurisdictions in Canada for patients with Sq NSCLC with PD-L1 TPS ≥50%. The economic evaluation includes a subgroup analysis that compares pembrolizumab in combination with chemotherapy to pembrolizumab monotherapy in patients with a PD-L1 ≥50% TPS.
- Issue: There are no RCTs comparing pembrolizumab + chemotherapy to pembrolizumab monotherapy.
- Supplemental item: As the submitter has individual patient data from the KEYNOTE trials, an indirect treatment comparison (ITC) was conducted to compare the two treatments and to inform the economic model. The Methods Team offered a summary and critical appraisal of the manufacturer-submitted ITC of pembrolizumab in combination with chemotherapy versus pembrolizumab monotherapy. Of note, PAG is seeking clarity on the most appropriate therapy in this setting (i.e., pembrolizumab in combination with platinum doublet therapies or single agent pembrolizumab); this ITC may offer PAG guidance on the most appropriate comparator.

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

7.1 Summary and critical appraisal of the manufacturer-submitted indirect treatment comparison of pembrolizumab in combination with chemotherapy versus pembrolizumab monotherapy

7.1.1 Objective

The submitter provided an indirect treatment comparison (ITC) to estimate the treatment difference in OS and PFS between pembrolizumab in combination with chemotherapy (carboplatin and paclitaxel or nab-paclitaxel) vs. pembrolizumab monotherapy in Sq-NSCLC patients with strong PD-L1 expression (TPS ≥50%).[45]

7.1.2 Methods

Data from two studies, the KEYNOTE-407 and KEYNOTE-042 trial were used for the ITC.[45] These studies are described below.

KEYNOTE-407

KEYNOTE-407 is described in detail in section 6 of this report. Briefly, KN-407 is an ongoing, international, phase III, superiority, double-blind, placebo-controlled, randomized (1:1 ratio) controlled trial (RCT). The objective of KN-407 was to compare the efficacy and safety of pembrolizumab in combination with carboplatin and paclitaxel or nab-paclitaxel versus saline placebo in combination with carboplatin and paclitaxel or nab-paclitaxel as first-line therapy in patients with metastatic Sq NSCLC. Choice of paclitaxel or nab-paclitaxel was pre-assigned by the investigator prior to randomization to pembrolizumab or placebo. Pembrolizumab was administered at a dose of 200mg every 3 weeks for up to 35 cycles (or saline placebo), carboplatin was administered for four cycles at a dose calculated to produce and area under the concentration-curve of 6mg per mL per minute. Based on the investigator's choice, paclitaxel was administered at 200mg per square meter of body-surface area, or nab-

paclitaxel was administered at 100 mg per square meter for 4 cycles. Crossover in the placebo + chemotherapy arm to pembrolizumab monotherapy (200 mg, once every 3 weeks) was allowed in this study after documented PD.[2]

KEYNOTE-042

KEYNOTE-042 is an international, phase III, superiority, open-label placebo-controlled, randomized (1:1 ratio), controlled trial (RCT). The objective of KN-042 was to compare the efficacy and safety of pembrolizumab monotherapy versus platinum-based chemotherapy in the first-line therapy in patients with PD-L1 expressing (≥1% TPS) NSCLC (squamous and non-squamous). Pembrolizumab was administered at a dose of 200mg every 3 weeks for up to 35 cycles. Platinum-based therapy selection was based on the investigator's choice, and was pre-assigned prior to randomization. Platinum-based regimens included carboplatin combined with pemetrexed or paclitaxel for 4 to 6 cycles. Carboplatin was administered at a dose calculated to produce an area under the concentration-curve of 5-6mg per mL per minute. Paclitaxel was administered at a dose of 200mg per square meter of body-surface area, and pemetrexed was administered at a dose of 500mg per square meter of body-surface area. Crossover to pembrolizumab monotherapy in the chemotherapy arm was not allowed in this study.[20]

Analysis Population

Only participants with squamous histology (all participants from KN-407 and select participants in KN-042) and PD-L1 TPS ≥50% (select participants in both trials) were included in the analysis. Participants pre-assigned to carboplatin and paclitaxel or nab-paclitaxel in the KN-407 trial, and participants assigned to carboplatin and paclitaxel in the KN-042 trial were selected. Nab-paclitaxel was not a comparator in the KN-042 trial, but participants assigned to nab-paclitaxel from the KN-407 trial were included because on findings from a previous trial where no statistical difference in OS or PFS between paclitaxel and nab-paclitaxel in combination with carboplatin, and to increase the sample size for analysis.[23] Thus, participants in the KN-042 trial assigned to carboplatin and pemetrexed were excluded from the ITC.[20,23] Data from KEYNOTE-024 (KN-024) was considered, since the first-line recommendation of pembrolizumab monotherapy for NSCLC patients with PD-L1 ≥50% was based on this trial, however, there were only 5 patients with Sq-NSCLC that received carboplatin + paclitaxel, with 5 patients pre-assigned to carboplatin + paclitaxel that received pembrolizumab monotherapy to compare to (and thus, a total of 10).[23,46,47] In addition, no patients in KN-024 received carboplatin + nab-paclitaxel, and thus data was limited to KN-042 for the efficacy of pembrolizumab monotherapy versus platinum-based chemotherapy.[23,46] To ensure similarity between study populations, patients with overall stage III cancer at screening were excluded from the KN-042 trial (KN-407 already excluded these patients), and patients with untreated brain metastases were excluded from KN-407 (KN-042 excluded these patients).[45]

Table 7.1. Indirect treatment comparison population selection criteria by trial

Trial	Treatment Arms	Population selection criteria
KN-407	Intervention: Pembrolizumab + Carboplatin + Paclitaxel or Nab-paclitaxel Comparator: Placebo + Carboplatin + Paclitaxel or Nab-paclitaxel	Inclusion: - Strong PD-L1 expression (TPS ≥50 %) Exclusion: - Low or no PD-L1 expression - Patients with untreated brain metastases*
KN-042	Intervention: Pembrolizumab monotherapy	Inclusion: - Squamous histology** - Stage IV cancer***

Trial	Treatment Arms	Population selection criteria
	Comparator: Investigator-choice of platinum-based chemotherapy	- Patients pre-assigned to carboplatin + paclitaxel Exclusion: - Non-squamous histology - Stage III cancer - All other chemotherapy regimens not stated in inclusion

Abbreviations: KN = Keynote; PD-L1 = programmed death-ligand 1; TPS = tumor proportion score
* KN-042 excluded these patients in the overall trial, and thus, these patients were excluded from KN-407
** KN-042 included both squamous and non-squamous histology
*** KN-407 only included stage IV patients in the overall trial, and thus, these patients were excluded from KN-042

Statistical Analyses

The primary analyses for treatment difference included OS and PFS. A sensitivity analysis adjusting OS for crossover to pembrolizumab monotherapy in the control arm (placebo and chemotherapy arm) of the KN-407 trial was also conducted.[45] All participants who were alive at the time of data cut-off were censored at the data cut-off date of their respective study protocol, April 3rd, 2018 for the KN-407 trial, and February 26th, 2018, for the KN-042 trial.[2,20,45]

Overall Survival – Primary Analysis

The ITT population is used for the primary analysis of OS. OS was defined as randomization to death due to any cause, and participants without documented death at the time of analysis were considered right censored at the day of last contact.[45]

Overall Survival Adjusted for Switch-Over – Sensitivity Analysis

OS was adjusted for switch-over of the control arm participants to pembrolizumab monotherapy (200 mg) or other anti-PD-1 or anti-PD-L1 therapies using a simplified two-stage survival analysis model, rank-preserving structure failure time (RPSFT), and inverse probability of censoring weighting (IPCW) models, which are described below.

- Simplified two-stage model: The survival time of the control arm of participants who switched to pembrolizumab monotherapy, or anti-PD-1 or anti-PD-L1 therapies, is adjusted, specifically, the time after discontinuing the control treatment.The survival time after the secondary baseline is adjusted multiplicatively by an acceleration factor determined in stage 1, using a regression model applied to post progression survival data.
- RPSFT model: The survival time of the control arm of participants who switched to pembrolizumab monotherapy, or anti-PD-1 or anti-PD-L1 therapies, is adjusted, specifically the time after discontinuing the control treatment and the switch occurs. The survival time is adjusted multiplicatively by an acceleration factor determined by the method called g-estimation in a first step, based on the common treatment assumption.
- IPCW model: The survival time of the control arm participants who switched over to pembrolizumab monotherapy, or anti-PD-1 or anti-PD-L1 therapies, is censored at the switching time. Individual observations are weighted in the final proportional hazards model using weights calculated in a first step.[45]

Progression-free Survival – Primary Analysis

The ITT population is used for the primary analysis of PFS. PFS was defined as the time, in days, from randomization to the first documented instance of PD per RECIST 1.1 evaluated by BICR, or death due to any cause, whichever occurred first. Participants without an event

(progression or death) at the time of last tumor assessment were considered right censored at the last disease assessment date.[45]

Indirect Treatment Comparison Estimation

The chemotherapy control arm was used as an anchor for the ITC comparison of the efficacy (OS and PFS) of pembrolizumab and chemotherapy compared to pembrolizumab monotherapy. The ITC was performed using the Bucher unadjusted and adjusted approach.

The Bucher unadjusted approach involves using individual-level data to estimate the treatment effect for each trial, which is then used to perform the ITC. The magnitude of the treatment effect of pembrolizumab + chemotherapy vs. chemotherapy (KN-407) and pembrolizumab monotherapy vs. chemotherapy (KN-042) was estimated using a stratified Cox proportional hazard model with Efron's method of tie handling for both OS and PFS. The models for the KN-407 trial were stratified by geographical region (East Asia vs. non-East Asia) and taxane chemotherapy (paclitaxel vs. nab-paclitaxel), and the models for the KN-042 trials were stratified by ECOG PS (0 vs. 1) and geographical region (East Asia vs. non-East Asia) in the KN-042 trial. Other stratification factors from the trials such as PD-L1 status in KN-407, and histology and PD-L1 status in the KN-042 trial were not considered as only squamous patients with PD-L1 TPS ≥50% were considered. The ITC to determine the treatment effect of pembrolizumab + chemotherapy vs. pembrolizumab monotherapy was then calculated by subtracting the calculated treatment effect estimated for the KN-407 trial from the treatment effect estimated for the KN-042 trial, which utilizes the control arms as an anchor for the ITC.

The adjusted Bucher method with IPTW methodology was used to balance covariates across treatment arms.[45] The IPTW methodology involves predicting the probability a study participant will receive a specific treatment (i.e. the propensity score) using all measured baseline characteristics, all baseline covariates that are associated with treatment assignment, all baseline characteristics that affect the outcome (i.e., potential confounders), and/or all covariates that affect both treatment assignment and the outcome (i.e., the true confounders) in a propensity score model.[48] Covariates identified as potential confounders (effect modifiers) included ECOG PS (0 vs.1), smoking status (never vs. former/current), age, sex, and baseline tumor size, and were considered in the model for the ITC.[45] The inverse of the propensity score (i.e., probability of receiving the treatment the participant actually received) represents the weight for that participant, and regression models can be weighted using the inverse of the propensity score to estimate treatment effects. In RCTs, propensity score methods allow for the estimation of the marginal treatment effect, which is the average effect on the population. To assess whether the propensity score model has been adequately specified when the IPTW methodology is used, the treated and untreated participants are compared to determine if the distribution of covariates is similar across treatment arms.[48,49] The adjusted analyses were conducted as described in the unadjusted Bucher approach as above, with IPTW weighting of the model for each of the studies separately.[23,45]

7.1.2 Findings

Patient Population

A total of 137 participants with squamous histology and strong PD-L1 (TPS ≥50%) who were assigned by the local investigator to carboplatin and paclitaxel or nab-paclitaxel were selected from KN-407, with 69 participants in the pembrolizumab + chemotherapy arm and 68 participants in the placebo + chemotherapy arm. A total of 181 participants with squamous histology and strong PD-L1 who were

assigned by the local investigator to carboplatin and paclitaxel were selected from KN-042, with 89 participants in the pembrolizumab monotherapy arm and 92 participants in the chemotherapy arm.[45]

Population Characteristics and IPTW Weighting

Baseline characteristics of participants prior to weighting as well as after weighting were compared. All selected effect modifiers (ECOG PS, smoking status, sex, baseline tumor size, and age) were imbalanced, and baseline tumor size was the most imbalanced covariate. Following weighting, the covariates were balanced and the weights used to the IPTW population adjusted models were stable.[45]

Summary of Primary Indirect Treatment Comparison Analyses for Overall Survival and Progression-Free Survival

The primary analysis of the ITT population for OS yielded no significant statistical difference between pembrolizumab + chemotherapy and pembrolizumab monotherapy in both unadjusted and adjusted models (HR: 1.03; 95% CI: 0.53, 2.00). Similarly, there was no statistically significant difference in PFS between pembrolizumab + chemotherapy and pembrolizumab monotherapy in both unadjusted and adjusted (HR: 1.72; 95% CI; 0.99, 3.03). The PFS of the adjusted model of the ITC may suggest clinical significance in increasing the risk of PD or death associated with pembrolizumab monotherapy compared to pembrolizumab + chemotherapy.[23]

Summary of Sensitivity Analyses of Overall Survival Adjusting for Cross-Over

All approaches to adjusting for cross-over for sensitivity OS analyses were consistent with the unadjusted and adjusted primary analyses for OS.[45]

Summary

The quality of the ITC provided by the Manufacturer was assessed according to the recommendations made by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force on Indirect Treatment Comparisons.[48] Details of the critical appraisal are presented in Table 7.5.

Table 7.5: Adapted ISPOR questionnaire to assess the credibility of the network meta-analysis pembrolizumab + carboplatin + paclitaxel or nab-paclitaxel vs. pembrolizumab monotherapy for the 1st line treatment of EGFR and ALK negative metastatic squamous non-small cell lung cancer patients†

ISPOR Questions		Details and Comments
1.	Is the population relevant?	**Yes, in part**. The study populations of the studies included in the submitted NMA aligned with the indication under review. Only participants with squamous, Stage IV, and those receiving carboplatin and paclitaxel from the KN-042 study were included to be comparable to the population in the KN-407 trial. Of note, KN-407 included participants with asymptomatic brain metastases that were excluded from the ITC, as these patients in the KN-042 trial were excluded and this ensured comparability of the trial.
2.	Are any critical interventions missing?	**No, in part.** The Submitter included a commonly used platinum doublet in this patient population as a comparator intervention, however in clinical practice other platinum doublets may be used (gemcitabine, cisplatin, etc.).
3.	Are any relevant outcomes missing?	**Yes, in part.** The Submitter included PFS and OS as the key efficacy outcomes in the ITC. Other outcomes such as ORR, HRQoL, and safety, were not considered, and additional

Table 7.5: Adapted ISPOR questionnaire to assess the credibility of the network meta-analysis pembrolizumab + carboplatin + paclitaxel or nab-paclitaxel vs. pembrolizumab monotherapy for the 1st line treatment of EGFR and ALK negative metastatic squamous non-small cell lung cancer patients†		
ISPOR Questions		**Details and Comments**
		information on these relevant outcomes may have been informative to the review.
4.	Is the context (e.g., settings and circumstances) applicable to your population?	**Yes**. The settings of the included trials were relevant to this pCODR review.
5.	Did the researchers attempt to identify and include all relevant randomized controlled trials?	**No.** The Submitter specified in the objective the ITC would only include data from the KN-407 and KN-042 trials.
6.	Do the trials for the interventions of interest form one connected network of randomized controlled trials?	**Yes**. The included RCTs form a connected network where the treatment comparison of interest can be compared indirectly through the common comparator of the control arm.
7.	Is it apparent that poor quality studies were included thereby leading to bias?	**No, in part.** The Submitter did not formally assess the methodological quality of the included clinical trials. However, the included trials have similar methodology, which are generally of high quality. One key difference between the trials was that the KN-407 trial was double-blind and the KN-042 trial was open-label, which may influence outcomes such as PFS.
8.	Is it likely that bias was induced by selective reporting of outcomes in the studies?	**No.** There was no selective reporting of outcomes.
9.	Are there systematic differences in treatment effect modifiers (i.e. baseline patient or study characteristics that impact the treatment effects) across the different treatment comparisons in the network?	**Yes**. The Submitter highlighted imbalances in key effect modifiers and absolute differences between the different treatment comparisons in the network. The Submitter also performed population adjusted ITCs for the efficacy outcomes of interest (OS and PFS) using IPTW methodology to balance out the covariates.
10.	If yes (i.e. there are such systematic differences in treatment effect modifiers), were these imbalances in effect modifiers across the different treatment comparisons identified prior to comparing individual study results?	**Yes**. Based on the submitted ITC report, the study design identified potential effect modifiers prior to comparing individual study results. Imbalances were identified between studies and minimized through applying IPTW methodology for a population adjusted analyses.
11.	Were statistical methods used that preserve within-study randomization? (No naïve comparisons)	**Yes**. The Submitter used the Bucher method to compare treatments indirectly, while preserving within-study randomization.
12.	If both direct and indirect comparisons are available for pairwise contrasts (i.e. closed loops), was agreement in treatment effects (i.e. consistency) evaluated or discussed?	**Not applicable.** The network contained no closed loops.
13.	In the presence of consistency between direct and indirect comparisons, were both direct and indirect evidence included in the network meta-analysis?	**Not applicable.**
14.	With inconsistency or an imbalance in the distribution of treatment effect modifiers across the different types of comparisons in the network	**Yes.** The submitter used IPTW methodology to calculate weights, called propensity scores, using patient level data to reduce imbalances between trials, as well as within trials between treatment arms.

Table 7.5: Adapted ISPOR questionnaire to assess the credibility of the network meta-analysis pembrolizumab + carboplatin + paclitaxel or nab-paclitaxel vs. pembrolizumab monotherapy for the 1st line treatment of EGFR and ALK negative metastatic squamous non-small cell lung cancer patients†		
ISPOR Questions		**Details and Comments**
	of trials, did the researchers attempt to minimize this bias with the analysis?	
15.	Was a valid rationale provided for the use of random effects or fixed effect models?	**Not applicable.**
16.	If a random effects model was used, were assumptions about heterogeneity explored or discussed?	**Not applicable.**
17.	If there are indications of heterogeneity, were subgroup analyses or meta-regression analysis with pre-specified covariates performed?	**Not applicable.**
18.	Is a graphical or tabular representation of the evidence network provided with information on the number of RCTs per direct comparison?	**Yes, in part**. The Submitter provided a tabular representation of the 2 trials, which included the treatment arms, but not the observed results. Those are presented later in individual tables per analysis (summary trial data is not used, and instead individual study data is used to estimate treatment effects for the populations of interest from each of the trials). The Submitter did not provide a graphical representation of the evidence network. Due to the simple nature of the ITC with only 2 included studies, this may not have been necessary.
19.	Are the individual study results reported?	**Yes**. The effect estimates of all outcomes used in the NMA were provided in the submitted report.
20.	Are results of direct comparisons reported separately from results of the indirect comparisons or network meta-analysis?	**Not applicable.** There were no closed loops in the network.
21.	Are all pairwise contrasts between interventions as obtained with the network meta-analysis reported along with measures of uncertainty?	**Yes.** The Submitter's report provided the ITC results for pembrolizumab + chemotherapy versus pembrolizumab monotherapy. Measures of uncertainty (95% CI) were reported for estimates of effect.
22.	Is a ranking of interventions provided given the reported treatment effects and its uncertainty by outcome?	**Not applicable.**
23.	Is the impact of important patient characteristics on treatment effects reported?	**No.** Patient characteristics considered effect modifiers were adjusted for in the ITC analyses.
24.	Are the conclusions fair and balanced?	**Yes. In part.** The submitted ITC's conclusion that in the patient population of interest, pembrolizumab + chemotherapy was not superior to pembrolizumab monotherapy in terms of OS. Though the Submitter suggested there may be benefit in terms of PFS for pembrolizumab + chemotherapy compared to pembrolizumab monotherapy, the Submitter did not include that these results were not statistically significant. However, it was acknowledged that the limited sample size contributed to wide CIs around the HRs.
25.	Were there any potential conflicts of interest?	**Not reported.**
26.	If yes, were steps taken to address these?	**Not applicable.**
Abbreviations:		

Table 7.5: Adapted ISPOR questionnaire to assess the credibility of the network meta-analysis pembrolizumab + carboplatin + paclitaxel or nab-paclitaxel vs. pembrolizumab monotherapy for the 1st line treatment of EGFR and ALK negative metastatic squamous non-small cell lung cancer patients†

ISPOR Questions	Details and Comments

CI = confidence interval; HR= hazard ration; **HRQoL** = health-related quality of life; **ISPOR** = International Society For Pharmacoeconomics and Outcomes Research; **ITC** = indirect treatment comparison; **OS** = overall survival **PFS** = progression-free survival

† Adapted from Jansen, Value Health. 2014;17(2):157-73[48]

7.1.3 Conclusions

The Submitter provided an ITC utilizing the Bucher method and individual level data from the KN-407 and KN-042 trials to estimate the unadjusted and adjusted treatment difference of pembrolizumab in combination with platinum-based chemotherapy vs. pembrolizumab monotherapy in the 1st line treatment of patients with metastatic, Sq-NSCLC, and strong PD-L1 expression (TPS ≥50%). There was no statistically significant difference in OS between pembrolizumab and chemotherapy vs. pembrolizumab monotherapy in both unadjusted and adjusted models. The unadjusted and adjusted models for OS adjusting for cross-over were consistent with the primary analyses for OS. There was no statistically significant difference in PFS between pembrolizumab + chemotherapy vs. pembrolizumab monotherapy, however the results may suggest a clinical benefit in PFS associated with pembrolizumab + chemotherapy. The adjusted models for PFS showed a trend towards significance, which may be limited by the small, restricted sample size. The small sample size may also contribute to instability of the estimates, as CIs for reported HRs were wide, and as such, the results should be interpreted with caution. In addition, the proportional hazards assumption was not met for OS and PFS for the KN-042 study, suggesting results should be interpreted with caution.

It was requested the submitter repeat the analyses using the patients included in the KEYNOTE-024 (KN-024) study, however the submitter reported this to only increase the data by 6% and predicted to not change the outcome for the comparison, and thus the submitter did not repeat the analyses using patients from KN-024. Additionally, the submitter opted to only include patients pre-assigned to a similar control arm as KN-407 to reduce the risk of potential bias and have a truly common anchor, as a rationale for excluding patients pre-assigned to other chemotherapy regimens in the KN-024 trial. In clinical practice, alternate chemotherapy regimens may be used with pembrolizumab, and thus, the exclusion of patients from KN-024 is a limitation as the inclusion of these patients in the ITC may have provided a more realistic estimate of the comparative efficacy of pembrolizumab + chemotherapy vs. pembrolizumab monotherapy. Furthermore, for a truly common anchor, patients from KN-407 who received pembrolizumab in combination with nab-paclitaxel should have been excluded, despite the rationale of similar efficacy between carboplatin + paclitaxel and carboplatin + nab-paclitaxel. The study conducted by Socinski et al., 2012, did not find a statistically significant difference between paclitaxel and nab-paclitaxel in combination with carboplatin with regards to OS and PFS, however the direction of the treatment effect was favourable to nab-paclitaxel suggesting a 10% improvement in PFS and 8% in OS, as well a statistically significant ORR associated with nab-paclitaxel.[49] Furthermore, a subgroup analysis of OS and PFS of the sub-population selected from KN-407 for the ITC by taxane group was requested from the submitter, although the sample sizes were limited. This analysis showed more enhanced treatment effect for OS, though not statistically significant in either taxane subgroup, in the pembrolizumab + carboplatin + nab-paclitaxel group vs. placebo + carboplatin + nab-paclitaxel compared to the pembrolizumab + carboplatin + paclitaxel group vs. placebo + carboplatin + paclitaxel group. Similarly, PFS showed a more enhanced effect for PFS, which was statistically significant in both taxane groups, in the pembrolizumab + carboplatin + nab-paclitaxel group vs. placebo + carboplatin + nab-paclitaxel compared to the pembrolizumab +

carboplatin + paclitaxel group vs. placebo + carboplatin + paclitaxel group . It is possible the treatment effect of pembrolizumab in combination with carboplatin and taxane therapy may vary based on the type of taxane therapy, which may have confounded the estimated treatment effect. It is important to note that although there was suggestion of enhanced treatment effect based on taxane group, there was no statistically significant difference between subgroups by taxane therapy for OS or PFS (p-value for interaction >0.05), which is limited by a highly selected and small sample size for this analysis. Nonetheless, controlling for taxane therapy in adjusted analyses or excluding nab-paclitaxel for a truly common comparator would have been preferred to reduce the risk of potential confounding. This could have supplemented an analysis including all chemotherapy regimens from all available trials (KN-407, KN-042, and KN-024) for the patient population included in the ITC to provide a treatment effect of pembrolizumab + chemotherapy vs. pembrolizumab monotherapy that may be reflective of clinical practice, where variety of standard chemotherapy regimens are used.

In consideration of the submitted ITC and possible limitations, a head-to-head trial would be required to definitively confirm the results reported in the ITC, and the relative efficacy of pembrolizumab + chemotherapy vs. pembrolizumab monotherapy remains uncertain in the patient population of interest.

8 COMPARISON WITH OTHER LITERATURE

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

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 Sq 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.

This Final Clinical Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Clinical Guidance Report supersedes the Initial Clinical Guidance Report.

The 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 AND DETAILED METHODOLOGY

1. Literature search via OVID platform

Database(s): **EBM Reviews - Cochrane Central Register of Controlled Trials** February 2019**, Embase** 1974 to 2019 April 01**, Ovid MEDLINE(R) ALL** 1946 to April 01, 2019
Search Strategy:

#	Searches	Results
1	(Keytruda* or Pembrolizumab* or Lambrolizumab* or HSDB 8257 or HSDB8257 or Merck 3475 or Merck3475 or MK 3475 or MK3475 or Sch 900475 or Sch900475 or DPT0O3T46P).ti,ab,ot,kf,kw,hw,rn,nm.	12272
2	Carcinoma, Non-Small-Cell Lung/	57359
3	Carcinoma, Squamous Cell/ and (exp Lung/ or lung.ti,ab.)	18606
4	(SqCLC? or NSCLC?).ti,ab,kf,kw.	112967
5	((non small cell* or nonsmall cell* or squamous* or epidermoid*) adj5 (lung* or bronch* or pulmonar*) adj5 (cancer* or tumor* or tumour* or carcinoma* or neoplasm*)).ti,ab,kf,kw.	169481
6	or/2-5	201987
7	1 and 6	2802
8	7 use medall	547
9	7 use cctr	164
10	*pembrolizumab/	2506
11	(Keytruda* or Pembrolizumab* or Lambrolizumab* or HSDB 8257 or HSDB8257 or Merck 3475 or Merck3475 or MK 3475 or MK3475 or Sch 900475 or Sch900475).ti,ab,kw,dq.	7743
12	or/10-11	8079
13	non small cell lung cancer/ or squamous cell lung carcinoma/	97622
14	squamous cell carcinoma/ and (exp lung/ or lung.ti,ab.)	32551
15	(SqCLC? or NSCLC?).ti,ab,kw,dq.	112757
16	((non small cell* or nonsmall cell* or squamous* or epidermoid*) adj5 (lung* or bronch* or pulmonar*) adj5 (cancer* or tumor* or tumour* or carcinoma* or neoplasm*)).ti,ab,kw,dq.	168916
17	or/13-16	214634
18	12 and 17	2312

19	18 use oemezd	1633
20	19 and conference abstract.pt.	839
21	limit 20 to yr=2014-current	836
22	19 not conference abstract.pt.	794
23	(Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or Equivalence Trial or Clinical Trial, Phase III).pt.	1122849
24	Randomized Controlled Trial/	1019547
25	exp Randomized Controlled Trials as Topic/	289204
26	"Randomized Controlled Trial (topic)"/	156821
27	Controlled Clinical Trial/	554610
28	exp Controlled Clinical Trials as Topic/	300810
29	"Controlled Clinical Trial (topic)"/	9929
30	Randomization/	179910
31	Random Allocation/	196765
32	Double-Blind Method/	404612
33	Double Blind Procedure/	158684
34	Double-Blind Studies/	266623
35	Single-Blind Method/	77978
36	Single Blind Procedure/	34447
37	Single-Blind Studies/	79921
38	Placebos/	332090
39	Placebo/	331278
40	Control Groups/	112430
41	Control Group/	112337
42	(random* or sham or placebo*).ti,ab,hw,kf,kw.	4086152
43	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.	790294
44	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.	3079
45	(control* adj3 (study or studies or trial* or group*)).ti,ab,kf,kw.	2698759
46	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf,kw.	95716
47	allocated.ti,ab,hw.	175722
48	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf,kw.	114941

49	((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.	25228
50	(pragmatic study or pragmatic studies).ti,ab,hw,kf,kw.	960
51	((pragmatic or practical) adj3 trial*).ti,ab,hw,kf,kw.	11368
52	((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.	18288
53	(phase adj3 (III or "3") adj3 (study or studies or trial*)).ti,hw,kf,kw.	132275
54	or/23-53	5839274
55	21 and 54	310
56	8 or 22	1341
57	54 and 56	374
58	9 or 57	538
59	remove duplicates from 58	426
60	55 or 59	736
61	limit 60 to english	683

2. Literature search via PubMed

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

Search	Query	Items found
#11	Search #9 AND publisher[sb] Filters: English	36
#10	Search #9 AND publisher[sb]	36
#9	Search (#3 AND #8)	558
#8	Search (#4 OR #5 OR #6 OR #7)	86217
#7	Search ((nonsmall cell*[tiab] OR non small cell*[tiab] OR squamous*[tiab] OR epidermoid* [tiab]) AND (lung*[tiab] OR bronchus*[tiab] OR brochiole*[tiab] OR pulmonar*[tiab]) AND (cancer*[tiab] OR tumor[tiab] OR tumors[tiab] OR tumorous[tiab] OR tumour*[tiab] OR carcinoma*[tiab] OR neoplasm*[tiab]))	71276
#6	Search (SqCLC[tiab] OR SqCLCs[tiab] OR NSCLC[tiab] OR NSCLCs[tiab])	37425
#5	Search Carcinoma, Squamous Cell[mh] AND (lung[mh] OR lung[tiab])	15741
#4	Search "Carcinoma, Non-Small-Cell Lung"[Mesh]	47355
#3	Search (#1 OR #2)	2364
#2	Search Keytruda*[tiab] OR Pembrolizumab*[tiab] OR Lambrolizumab*[tiab] OR HSDB 8257[tiab] OR HSDB8257[tiab] OR Merck 3475[tiab] OR Merck3475[tiab] OR MK 3475[tiab] OR MK3475[tiab] OR Sch 900475[tiab] OR Sch900475[tiab] OR DPT0O3T46P[rn]	2364
#1	Search "pembrolizumab" [Supplementary Concept]	873

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/

World Health Organization
http://apps.who.int/trialsearch/

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

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

Conference abstracts:

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

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

Search: Keytruda/pembrolizumab, squamous non-small cell lung cancer – last 5 years

Literature Search Methods

The literature search for clinical studies was performed by an information specialist from the pCODR Methods Team using the abovementioned search strategy, which was peer-reviewed according to the *PRESS Peer Review of Electronic Search Strategies* checklist (https://www.cadth.ca/resources/finding-evidence/press).[50]

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946–) via Ovid, Embase (1974–) via Ovid, the Cochrane Central Register of Controlled Trials (CENTRAL) 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 squamous non-small cell lung cancer.

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

The search is considered up to date as of September 16, 2019.

Grey literature (literature that is not commercially published) was identified by searching websites from relevant sections of the *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature* checklist (https://www.cadth.ca/grey-matters).[51] Included in this search were the websites of regulatory agencies (US Food and Drug Administration and European Medicines Agency), clinical trial registries (US National Institutes of Health's clinicaltrials.gov and Canadian Partnership Against Cancer Corporation's Canadian Cancer Trials), and relevant conference abstracts. Conference abstracts were retrieved through a search of the Embase database limited to the last five years. Abstracts from the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) were searched manually for conference years not available in Embase. Searches were supplemented by reviewing the bibliographies of key papers and through contacts with the CADTH Clinical Guidance Panel. As well, the manufacturer of the drug was contacted for additional information, as required by the pCODR Review Team.

Study Selection

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

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

Quality Assessment

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

Data Analysis

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

Writing of the Review Report

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

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

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