CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Initial Clinical Guidance Report

Pembrolizumab (Keytruda) for Nonsquamous Non-small Cell Lung Cancer

April 4, 2019

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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 non-squamous 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 non-squamous 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 non-squamous NSCLC. A summary of submitted Provincial Advisory Group Input on pembrolizumab non-squamous NSCLC and a summary of submitted Registered Clinician Input on pembrolizumab non-squamous 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 pemetrexed and platinum chemotherapy, for the treatment of metastatic non-squamous NSCLC, in adults with no EGFR or ALK genomic tumor aberrations, and no prior systemic chemotherapy treatment for metastatic NSCLC.

The Health Canada indication is in line with the reimbursement request. Pembrolizumab (Keytruda) for metastatic non-squamous NSCLC in combination with pemetrexed and platinum chemotherapy, in adults with no EGFR or ALK genomic tumour aberrations, and no prior systemic chemotherapy treatment for metastatic NSCLC was issued marketing authorization without conditions in March 2019.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

The pCODR systematic review included two randomized controlled trial. The results of KN-189 (N = 616) and KN-021 (N= 123) trials will be presented below:

KEYNOTE-189 (KN-189)[1,2]

KN-189 is an ongoing phase III, international, multicentre, randomized, double-blind, placebo-controlled trial of combination therapy with pembrolizumab plus pemetrexed and a platinum-based drug as first-line therapy in patients with metastatic non-squamous (NSQ) non-small cell lung cancer (NSCLC) in whom there were no EGFR or ALK mutations. Eligible patients were randomized (2:1 ratio) to receive pembrolizumab in combination with pemetrexed-platinum chemotherapy (pembrolizumab combination arm; n=410) or placebo plus pemetrexed-platinum chemotherapy per investigator's choice (placebo combination arm; n=206) on Day 1 of each 3-week dosing cycle. Treatment was continued until the completion of 35 cycles with pembrolizumab (or placebo), radiographic disease

progression, unacceptable toxicities, investigator's decision to stop the treatment, or patient withdrawal of consent. Patients who attained a complete response could consider stopping trial treatment. In the pembrolizumab arm, initial responders with a disease progression at any time during the 2-year follow-up period were eligible to receive up to 12 months of pembrolizumab monotherapy in the Second Course Phase. In the Placebo arm, patients who experienced documented disease progression during the Treatment Phase could continue on open-label pembrolizumab monotherapy in the Crossover Phase.

KN-189 has two primary end points: overall survival (OS), and progression-free survival (PFS) as assessed by blinded, independent central radiologic review (BICR). The secondary endpoints included overall response rate (ORR); duration of response (DOR), and safety. Patient-reported outcomes were also evaluated using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30), Lung Cancer 13 (QLQ-LC13), and the EuroQoL 5 Dimension (EQ-5D).

The majority of study participants were White (94%) and current or former smokers (88%). A PD-L1 tumor proportion score of ≥1% was reported in 63.4% of the patients in the pembrolizumab combination arm and in 62.1% of those in the placebo combination arm. Carboplatin was selected as the platinum-based chemotherapy agent in 72.4% of the patients in the pembrolizumab combination arm and 71.8% of patients in the placebo combination arm. Overall, the baseline characteristics were generally well balanced between the two study arms; except, in the placebo combination arm there was a higher proportion of patients who were female (47.1% versus 38.0% in the pembrolizumab combination arm; p=0.04).

Efficacy

The key efficacy outcomes of the KN-189 trial (as of the 08-NOV-2017data cut-off date) are presented in Table 1.1.

Overall survival: After a median follow-up duration of 10.5 months, a total of 235 deaths were reported in the KN-189 trial (127 [31.0%] in the pembrolizumab combination arm and 108 [52.4%] in the placebo combination arm). The median OS was not reached in the pembrolizumab combination arm, and was 11.3 months (95% CI 8.7, 15.1) for the placebo combination arm (HR = 0.49; 95% CI 0.38, 0.64; P<0.00001). OS rate at 12 months was 69.2% (95% CI 64.1, 73.8) in the pembrolizumab combination arm and 49.4% (95% CI 42.1, 56.2) in the placebo combination arm. The OS subgroup analyses results were consistent with those of the original OS analysis [1,2]

Progression-free-survival: A total of 410 PFS events were reported in the KN=189 trial (244 [59.5%] in the pembrolizumab combination arm and 166 [80.6%] in the placebo combination arm). The median PFS was 8.8 months (95% CI 7.6, 9.2) in the pembrolizumab combination arm, and was 4.9 months (95% CI 4.7, 5.5) in the placebo combination arm (HR = 0.52; 95% CI 0.43, 0.64; P<0.00001). PFS rate at 12 months was 34.1% (95% CI 28.8, 39.5) in the pembrolizumab combination arm and 17.3% (95% CI 12.0, 23.5) in the placebo combination arm. The PFS subgroup analyses results were generally consistent with those of the original PFS analysis [1,2]

Objective response rate: the BICR-assessed ORR was 47.6% (95% CI 42.6, 52.5) in the pembrolizumab combination arm and 18.9% (95% CI 13.8, 25.0) in the placebo combination arm (estimated treatment difference = 28.5%; 95% CI 21.1, 35.5; p<0.0001) The median DOR was 11.2 months (range 1.1 to 18.0) in the pembrolizumab combination arm and 7.8 months (range 2.1 to 16.4) in the placebo combination arm.[1,2]

Quality of Life

At the time of data cut-off, more than 99% of the study participants (in either of the study arms) had completed ≥1 patient-reported outcome assessment. At week 12, no statistically significant differences were found in EORTC QLQ-C30 global health status/QoL change from baseline between the pembrolizumab and the placebo combination arms (mean difference = 3.58 points ; 95% CI -0.05, 7.22; p=0.053). At Week 21, however, a statistically significant improvement was observed with the pembrolizumab combination (mean difference= 5.27 points; 95% CI 1.07, 9.74; p=0.014).[2]

AT both Week 12 and Week 21, statistically significant changes from the baseline in the EQ-5D visual analog scale (VAS) scores were observed between the two study arms, favouring the pembrolizumab combination.[3]

Harm outcomes

Adverse events (AEs): AEs of any grade were reported in 99.8% of patients in the pembrolizumab combination arm and 99.0% of those in the placebo combination arm. The most common AEs reported in both groups included Nausea, anemia, and fatigue (see section 6.3.22 for more details). Acute kidney injury occurred more frequently in the pembrolizumab combination arm (5.2%) than in the placebo-combination group (0.5%).[1] Treatment related AEs were reported in 91.9% of patients in the pembrolizumab combination arm.[2]

Grade 3 or higher AEs: Grade 3+ were reported in 67.2% of patients in the pembrolizumab combination arm and 65.8% of those in the placebo combination arm, with the most commonly reported Grade 3+ AEs being anemia and neutropenia (see section 6.3.22 for more details). The AE rates were reported to be similar in patients who received carboplatin and those who received cisplatin.[1]

Withdrawal due to AEs: Overall, 27.7% of the patients in the pembrolizumab combination arm and 14.9% of those in the placebo-combination arm discontinued all trial drugs due to an AE; with discontinuation rates of pembrolizumab and placebo being 20.2% and 10.4%, respectively.

Death: There were 27 cases of fatality due to AEs in the pembrolizumab combination arm (6.7%) versus 12 cases in the placebo combination arm (5.9%). [1]

Immune-mediated AEs occurred in 22.7% in the pembrolizumab combination arm and in 11.9% of those in the placebo combination arm. The rates of Grade 3+ immune-related AEs were 8.9% in the pembrolizumab arm and 4.5% in the placebo arm. In the pembrolizumab combination arm, three patients died due to immune-mediated AEs (all pneumonitis).[1]

Table 1.1: Highlights of Key Outcomes in the KN-189 trial

	KN-189	
	Pembrolizumab + Chemotherapy (N= 410)	**Placebo + Chemotherapy (N= 206)**
Primary Outcomes		
OS		
OS events (%)	127 (31.0)	108 (52.4)
Median, months (95% CI)	NE (NE, NE)	11.3 (8.7, 15.1
HR (95%CI)	0.49 (0.38, 0.64)	
p-value	<0.00001	
OS at 12 months, % (95% CI)	69.2 (64.1, 73.8)	49.4 (42.1, 56.2)
PFS		
PFS events (%)	244 (59.5)	166 (80.6)
Median, months (95% CI)	8.8 (7.6, 9.2)	4.9 (4.7, 5.5)
HR (95%CI)	0.52 (0.43, 0.64)	
p-value	P<0.00001	
PFS at 12 months, % (95% CI)	34.1% (28.8, 39.5)	17.3% (12.0, 23.5)
Key Secondary Outcomes		
ORR		
Best response rate, % (95% CI)	47.6 (42.6, 52.5)	18.9 (13.8, 25.0)
Difference vs control	28.5 (21.1, 35.4)	
p-value	<0.0001	
DOR, months (range)	11.2 (1.1 to 18.0)	7.8 (range 2.1 to 16.4)
HrQoL	**Pembrolizumab + Chemotherapy (N= 359)**	**Placebo + Chemotherapy (N= 180)**
EORTC QLQ-C30 global health status (Week 21)		
Change from baseline, mean (SD)	66.97 (19.43)	62.55 (24.07)
Difference vs control	5.27 (1.07, 9.47)	
p-value	0.014	
Harms Outcome, n (%)	**Pembrolizumab + Chemotherapy (N= 405)**	**Placebo + Chemotherapy (N= 202)**
Grade ≥3 AEs	272 (67.2)	133 (65.8)
AEs (any grade)	404 (99.8)	200 (99.0)
WDAE (all treatments)	56 (13.8)	16 (7.9)
WDAE (pembrolizumab/placebo)	82 (20.2)	21 (10.4)
Death due to AEs (any grade)	27 (6.7)	12 (5.9)

AE = adverse event, **CI =** confidence interval, DOR = duration of treatment; **HR =** hazard ratio; **HRQoL =** health-related quality of life; **NE**= not estimable; **ORR** = objective response rate; **OS** = overall survival; **PFS** = progression-free survival; **SD** = standard deviation; **WDAE** = withdrawal due to adverse event
HR < 1 favours pembrolizumab + chemotherapy

Sources:
[EMA Assessment Report (EMEA/H/C/003820/II/0043);page 21/89][2]
[Gandhi, N Engl J Med 2018;378:2078-92; Figure 1][1]
[Garassino, ASCO Annual Meeting June 1–5, 20189021 Chicago, Illinois; poster#9021][4]

KEYNOTE-021 Cohort G (KN-021G)[2,5,6]

KN-021 is ongoing Phase I/II, multi-centre, multi-cohort randomized controlled trial to compare the efficacy and safety carboplatin-pemetrexed chemotherapy with and without

pembrolizumab as first-line therapy in patients with metastatic NSQ NSCLC in whom there were no EGFR or ALK mutations. KN-021 trial included multiple cohorts. Cohort G, (N=123) that is relevant to the submission under review enrolled chemotherapy naïve patients to receive pembrolizumab plus pemetrexed and carboplatin chemotherapy versus chemotherapy with pemetrexed and carboplatin.

Eligible patients were randomized (1:1 ratio) to receive pembrolizumab + pemetrexed-carboplatin chemotherapy (pembrolizumab combination arm; n=60) or pemetrexed-corboplatin chemotherapy alone (chemotherapy arm; n=63). Treatment was to be continued until disease progression or protocol-defined unacceptable toxicities. In the chemotherapy arm, patients who experienced documented disease progression could crossed over to pembrolizumab monotherapy.

The primary efficacy endpoint in the KN-021 trial was ORR, where ORR was defined as the proportion of patients with CR or PR according to RECIST 1.1 by BICR. The key secondary endpoint included BICR-assessed PFS, OS, DOR, and safety. The majority of patients were female (63% and 59% in the pembrolizumab combination arm and chemotherapy arms, respectively, White (82% and 92%, respectively), current or former smoker (86% and 75%, respectively), with adenocarcinoma histology (92% and 82%, respectively).

Efficacy

The key efficacy outcomes of the KN-021G trial are presented in Table 1.2. The primary analysis of KN-021G trial was performed after a minimum 6 months (10.6 months median duration of follow up); the analysis was updated two times with median follow up durations of 18.7 months and 23.9 months.[2,6]

Results of the longest term follow-up (01-DEC-2017 data cu-off; median follow-up 23.9 months) are as follows:

Objective Response Rate: the BICR-assessed ORR was 56.7% in the pembrolizumab combination arm and 30.2% in the chemotherapy arm (estimated treatment difference = 26.4%; 95% CI 8.9, 42.4; p=0.0016). The median DOR was 11.2 months (range 1.1 to 18.0) in the pembrolizumab combination arm and 7.8 months (range 2.1 to 16.4) in the placebo combination arm.[2,6]

Progression-Free-Survival: A total of 71 PFS events were reported (28 [47%] in the pembrolizumab combination arm and 43 [68%] in the chemotherapy arm. The median PFS was 24.0 months (95% CI 8.5, not estimable) with the pembrolizumab combination and 9.3 months (95% CI 6.2, 14.9) with chemotherapy alone. The PFS benefit was statistically higher in the pembrolizumab combination arm than that in the chemotherapy arm (HR = 0.53; 95% CI, 0.33–0.86; P=0.0049).[6]

Overall Survival: After a median follow-up duration of approximately 24 months, 22 (37%) patients in the pembrolizumab combination group and 35 (56%) patients in the chemotherapy arm had died. The OS benefit with the pembrolizumab combination was statistically higher than with chemotherapy alone (HR = 0.56; 95% CI 0.32, 0.95; P=0.0151). The median OS was not reached in the pembrolizumab combination arm (95% CI 24.5 months, not estimable) and 21.1 months (95% CI 14.9, not estimable) in the chemotherapy arm.[6]

Quality of Life

Patient- reported/ quality of life outcomes were not measured in the KN-021G trial.

Harm outcomes[6]

Adverse events (AEs): AEs of any grade were reported in 93.2% of patients in the pembrolizumab combination arm and 91.9% of patients in the chemotherapy arm. The most common AEs reported in both groups included fatigue, nausea, anemia, vomiting, rash, and diarrhea. Anemia was reported more frequently in the chemotherapy arm.

Grade 3 or higher AEs: Grade 3+ were reported in 41% of patients treated in the pembrolizumab combination arm and 27% of those treated with chemotherapy alone. Anemia was the most common Grade 3 or 4 AE that was reported in 12% of patients in the pembrolizumab combination arm and 13% of those in the chemotherapy arm.

Withdrawal due to AEs: Treatment-related AEs that led to discontinuation of any component of study medication were reported 16.9% of patients in the pembrolizumab combination arm and 12.9% of those in the chemotherapy arm.

Death: Treatment-related fatal AEs occurred in one (1.7%) patient in the pembrolizumab combination arm (due to sepsis) and two (3.2%) patients in chemotherapy arm (due to pancytopenia and sepsis).

Immune-mediated AEs occurred in 17 (28.8%) patients in the pembrolizumab combination arm and 7 (11.3%) patients in the chemotherapy arm.

Table 1.2: Highlights of Key Outcomes in the KN-021G trial

	KN-021G	
	Pembrolizumab + Chemotherapy (N= 60)	**Chemotherapy alone (N= 63)**
Primary Outcome		
ORR		
Primary analysis (med follow up :10.6 m)		
Best response rate, % (95% CI)	55 (42, 68)	29 (18, 41)
Difference vs control, % (95% CI)	26 (9, 42)	
p-value	0.0016	
Time to response[months], median (IQR)	1.5 (1.4, 2.8)	.7.0 (1.4, 2.8)
1st updated analysis (med follow up :18.7 m)		
Best response rate, % (95% CI)	56.7 (43.2, 69.4)	31.7 (20.6, 44.7)
Difference vs control, % (95% CI)	24.8 (7.2, 40.9)	
p-value	0.0029	
Time to response[months], median (IQR)	1.6 (1.2, 12.3)	2.8 (1.1, 10.3)
2nd updated analysis (med follow up :23.9 m)		
Best response rate, % (95% CI)	56.7 (NR)	30.2 (NR)
Difference vs control	26.4 (8.9, 42.4)	
p-value	0.0016	
Time to response[months], median (IQR)	NR	NR
Key Secondary Outcomes		
PFS		
Primary analysis (med follow up :10.6 m)		
PFS events (%)	23 (38)	33 (52)
Median, months (95% CI)	13·0 (8.3, NE)	8·9 (4.4, 10.3)
HR (95%CI)	0·53; 95% CI 0.31, 0.91	
p-value	0.010	
PFS at 6 months, % (95% CI)	77 (64, 86)	63 (49, 74)
2nd updated analysis (med follow up :23.9 m)		
PFS events (%)	28 (47)	43 (68)
Median, months (95% CI)	24.0 (8.5, NE)	9.3 (6.2, 14.9)
HR (95%CI)	0.53 (0.33–0.86)	
p-value	0.0049	

	KN-021G	
OS		
Primary analysis (med follow up :10.6 m)		
OS events (%)	13 (22)	14 (22)
Median, months (95% CI)	NR	NR
HR (95%CI)	0.90 (0.42, 1.91)	
p-value	0.39	
OS at 6 months, % (95% CI)	34.1% (28.8, 39.5)	17.3% (12.0, 23.5)
2nd updated analysis (med follow up :23.9 m)		
OS events (%)	22 (37)	35 (56)
Median, months (95% CI)	NE (24.5, NE)	21.1 (14.9, NE)
HR (95%CI)	0.56 (0.32, 0.95)	
p-value	0.0151	
HrQoL	NR	

Harms Outcome, n (%)	**Pembrolizumab + Chemotherapy (N= 59)**	**Chemotherapy alone (N= 62)**
Grade ≥3 AEs	24 (41)	17 (27)
AEs (any grade)	55 (93)	57 (92)
WDAE	10 (17)	8 (13)
Death due to AEs (any grade)	1 (2)	2 (3)

AE = adverse event, **CI** = confidence interval, **HR** = hazard ratio; **HRQoL** = health-related quality of life; **NE**= not estimable; **NR** = not reported; **ORR** = objective response rate; **OS** = overall survival; **PFS** = progression-free survival; **WDAE** = withdrawal due to adverse event
HR < 1 favours pembrolizumab + chemotherapy

Sources:
[EMA Assessment Report (EMEA/H/C/003820/II/0043);page 21/89][2]
[Langer CJ, Lancet Oncol. 2016 Nov;17(11):1497-1508; Table 1][5]

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 perspective, lung cancer impacts many aspects of day-to-day life. Specifically, it affects the respondents' ability to work, travel, socialize and participate in leisure and physical activities. It also affects their relationships with family and friends, emotional well-being and may cause financial hardship. It was reported by both patient and caregiver respondents that high symptom burden of lung cancer is difficult to manage. LCC indicated that symptoms may include: loss of appetite, cough, pain, and shortness of breath. Moreover, one of the most common symptom burdens for patients with lung cancer is fatigue or lack of energy. Chemotherapy is seen as a persistent psychological and physical burden, with health ill effects that limit personal independent and quality of life, although some can tolerate it and do see improvement in tumour size. Patients with experience with immunotherapy reported much milder side effects that did not significantly interfere with daily life, although pneumonitis, a less frequent but severe side effect, was noted in one patient who needed hospitalization.

Respondents reported that, from their perspective, the following key treatment outcomes were the most important areas to be addressed by this new drug combination: to stop or slow the progression of the disease, to reduce or eliminate side effects (e.g., reduce pain, fatigue, cough and shortness of breath), and to improve appetite and energy. Respondents additionally indicated that they would value improved independence and requiring less assistance from others. They would also like there to be less or no cost burden associated with new treatments.

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

The clinicians providing input noted that the combination of pembrolizumab and pemetrexed/platinum-based chemotherapy would be a suitable first line option for all non-squamous NSCLC patients with low expression of PD-L1, as well as for those with high expression of PD-L1 who are eligible for pembrolizumab monotherapy but may benefit from a rapid therapeutic response. According to the clinicians, the combined use of chemotherapy and immunotherapy addresses a therapeutic gap whereby one would usually have to risk a worsening condition after progression on one therapy before trying the other. It is felt that the availability of first line immunotherapy independent of PD-L1 expression increases equity in patients who have no PD-L1 results and those unfit for

second line therapy. Safety and tolerability were not seen as major issues by clinicians. They maintained that both combination and monotherapy options should remain available for NSQ NSCLC patients, but agreed that the sequence of therapies should favour first line pembrolizumab therapy (alone or combined with chemotherapy, as determined by PD-L1 status and patient preference) moving forward.

Summary of Supplemental Questions

The following supplemental issues were identified during development of the review protocol as relevant to the pCODR review of pembrolizumab plus platinum-doublet chemotherapy, for the treatment of metastatic non-squamous (NSQ) non-small cell lung cancer (NSCLC) in adults with no EGFR or ALK genomic tumour aberrations and no prior systemic treatment for metastatic NSQ NSCLC:

- Issue 1: Summary and critical appraisal of the manufacturer-submitted indirect treatment comparison of pembrolizumab in combination with chemotherapy versus pembrolizumab monotherapy

Indirect treatment comparisons (ITC) were performed using Bucher method after weighted adjustment of the treatment arms from the KN-189 and KN-024 trials. Point estimates of the effect from the ITC suggested that pembrolizumab + chemotherapy was superior to pembrolizumab monotherapy, in terms of PFS and OS, in patients with metastatic, NSQ NSCLC with strong PD-L1 (TPS ≥50%). However, the corresponding confidence intervals crossed the null hypothesis value, indicating a statistical non-significance. Therefore, the relative efficacy of pembrolizumab + chemotherapy over pembrolizumab monotherapy remains uncertain in the patient population of interest.

See section 7.1 for more information.

- Issue 2: Summary and critical appraisal of the manufacturer-submitted network meta-analysis of pembrolizumab + platinum + pemetrexed for the 1st line treatment of metastatic NSQ NSCLC patients whose tumors are sensitizing EGFR mutation and ALK translocation negative

The submitter conducted a systematic review of literature and NMA to provide indirect comparisons between pembrolizumab + platinum-pemetrexed chemotherapy and competing interventions for the 1st line treatment of metastatic NSCLC in patients with non-squamous histology who are EGFR mutation and ALK translocation negative.

The submitted NMA s concluded that in the patient population of interest, pembrolizumab + chemotherapy could be superior to most competing interventions in terms of OS and PFS except for atezolizumab regimen and other pembrolizumab regimens. Some levels of heterogeneity in effect modifiers between trials. However, these results should be interpreted with caution due to limitations that may arise from between-study differences in some covariates; and lack of sufficient evidence to minimize heterogeneity and inconsistency (e.g., by performing meta-regression analysis).

See section 7.2 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).

<table>
<tr><th>Domain</th><th>Factor</th><th>Evidence from the KEYNOTE-189 Trial</th><th>Generalizability Question</th><th>CGP Assessment of Generalizability</th></tr>
<tr><td rowspan="4">Population</td><td>Histological Subtype</td><td>The KN-189 trial eligibility criteria required that patients have histologically or cytologically confirmed stage IV non-squamous NSCLC.</td><td>Do the trial results apply to patients with other histological types of NSCLC?
Why (why not)?</td><td>These results are not generalizable to patients with squamous NSCLC. However, this patient population has been studied in Keynote 407</td></tr>
<tr><td>ALK and EGR mutations</td><td>The KN-189 trial eligibility criteria required that patients have no EGFR or ALK mutations.</td><td>Do the trial results apply to patients with EGFR, ALK mutations?</td><td>These results are not generalizable to patients with molecular abnormalities such as EGFR, ALK and ROS1</td></tr>
<tr><td>ECOG Performance Status</td><td>The KN-189 trial limited eligibility to patients with an ECOG performance status of 0-1. Only one patient with ECOG >1 was included in the pembrolizumab combination arm.
<table>
<tr><th>ECOG PS</th><th>Pembrolizumab + chemotherapy (n=410)</th><th>Chemotherapy (n=206)</th></tr>
<tr><td>0</td><td>186 (45.4%)</td><td>80 (38.8%)</td></tr>
<tr><td>1</td><td>221 (53.9%)</td><td>125 (60.7%)</td></tr>
<tr><td>2</td><td>1 (0.2%)</td><td>0 (0%)</td></tr>
<tr><td>missing</td><td>2 (0.5%)</td><td>1 (0.5%)</td></tr>
</table></td><td>Do the trial results (efficacy and toxicity) apply to patients with an ECOG PS of 2 or greater?
Why (why not)?</td><td>It would be reasonable to extrapolate the results to patients with ECOG 2. The results do not apply to patients with ECOG 3 and 4 who would not normally be offered chemotherapy</td></tr>
<tr><td>Brain metastases</td><td>The KN-189 trial excluded patients with active brain metastases and/or carcinomatous meningitis.</td><td>Do the trial results apply to patients with brain metastases?</td><td>Other trials of immunotherapy agents have included patients with treated stable brain metastases off steroids, so it would be reasonable to apply the results to those patients</td></tr>
</table>

Domain	Factor	Evidence from the KEYNOTE-189 Trial	Generalizability Question	CGP Assessment of Generalizability
Intervention	Line of therapy	The KN-189 trial included patients who had not received prior systemic treatment for their advanced/metastatic NSCLC. However, patients who received adjuvant or neoadjuvant therapy would be eligible if the adjuvant/neoadjuvant therapy was completed at least 12 months prior to the development of metastatic disease.	Do the trial results apply to patients who have previously been treated in the advanced/ metastatic setting? Why (why not)?	These results would not apply to patients who have been previously treated in the metastatic setting. Most patients with non squamous NSCLC will have been treated with platinum-pemetrexed and maintenance pemetrexed, so it is unlikely to have a patient treated with advanced disease with a prolonged period of time off therapy. If such a patient had more than 12 months off therapy since first line platinum therapy, one might consider individual cases for this therapy
Comparator	Pemetrexed + platinum-based chemotherapy	The comparator in the KN-189 trial was pemetrexed + platinum doublet: pemetrexed 500 mg/m^2 + the investigators' choice of cisplatin 75 mg/m^2 or carboplatin AUC 5 Currently funded treatments in 1st line treatment of advanced or metastatic NSCLC include platinum doublet therapies and single agent pembrolizumab (for patients with PD-L1 ≥50%). The submitter provided ITCs that included indirect comparisons of pembrolizumab plus chemotherapy with pembrolizumab monotherapy and other relevant comparators. Please refer to the ITC assessment section 7 for more information.	Are the findings of the KN-189 trial generalizable to patients who may receive other available treatments for first-line NSCLC (including single agent pembrolizumab)?	Pembrolizumab and chemotherapy, as well as single agent pembrolizumab are both superior to platinum pemetrexed chemotherapy in patients with PD-L1 positive tumors. Both represent an option for first-line therapy of advanced disease. It is not clear whether one of these therapies is superior to another. There is insufficient evidence to generalize the results to all platinum-based

Domain	Factor	Evidence from the KEYNOTE-189 Trial	Generalizability Question	CGP Assessment of Generalizability
				chemotherapy regimens.
Outcomes	Appropriateness of Primary and Secondary Outcomes	Primary outcomes: Overall survival (OS) and BICR-assessed progression free survival (PFS) Secondary outcomes: objective response rate (ORR), duration of response (DoR), and safety.	Were the primary and secondary outcomes appropriate for the trial design?	OS and PFS are the most relevant outcomes for efficacy and both were improved.
Setting	Countries participating in the Trial	The trial was conducted in at 126 sites in 16 countries, including Australia, multiple countries in Europe, Israel, Japan, the United States, and 6 sites in Canada.	Are there any known potential differences in the practice patterns between other countries that the trial was conducted in and Canada?	No.

1.2.4 Interpretation

The introduction of immune checkpoint inhibitors (ICI) in the treatment of advanced NSCLC represents a major advancement in treatment. This has the potential to impact on the survival and quality of life of large numbers of patients with advanced NSCLC. Nivolumab,[7,8] pembrolizumab[9] and atezolizumab[10,11] have all demonstrated improvements in OS for NSCLC patients receiving second-line therapy. Earlier use of pembrolizumab, in first-line therapy of NSCLC has also shown superior OS for patients with tumors expressing high levels of PD-L1 (≥ 50%).[12] Median OS in this group of NSCLC is now exceeding 18 months, in comparison to the 12 months expected from platinum-based chemotherapy. ICI have also improved OS in stage III NSCLC patients undergoing chemoradiation.[13,14] One year of therapy with durvalumab, a PD-L1 inhibitor, significantly reduced the risk of progression (HR 0.52, 95%CI 0.42-0.65) and death (HR 0.68, 95%CI 0.47-0.997), supporting the use of ICI earlier in treatment algorithms for NSCLC.

Currently ICI are only offered routinely as initial therapy for advanced and metastatic NSCLC to those patients with tumors expressing high levels of PD-L1 (≥ 50%). This represents only about 30% of patients. Some evidence exists of additive efficacy from the concurrent administration of ICI and chemotherapy. The KEYNOTE-21G trial was a randomized phase II trial evaluating the addition of pembrolizumab to platinum-based chemotherapy in patients with non-squamous NSCLC.[5] This trial demonstrated significantly higher ORR for the combination of pembrolizumab, carboplatin and pemetrexed, compared with carboplatin and pemetrexed alone (55% vs 29%, p=0.00016). The benefits were observed in patients with tumors both PD-L1 positive and negative. Secondary outcomes were also improved in the pembrolizumab plus chemotherapy arm. PFS was significantly longer (HR 0.53, 95%CI 0.31-0.91), although OS was not significantly improved at the time of the initial analysis (HR 0.90, 95%CI 0.42 – 1.91).

KEYNOTE-189 was a randomized phase III trial performed to confirm the results of KEYNOTE -21G.[1] Good performance status patients (ECOG 0-1), with non-squamous NSCLC without an *EGFR* mutation or *ALK* translocation, measurable disease and a tumor sample available for PD-L1 assessment were randomized 2 to 1 to pembrolizumab, platinum and pemetrexed (n=410) versus placebo, platinum and pemetrexed (n=206). Patients with symptomatic 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. It is unclear from current data if any patients have discontinued and then been retreated to date. 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, toxicity and PROs. There were no major issues with the clinical trial design.

The patient population of KEYNOTE -189 were typical for large randomized trials in NSCLC. The median age was around 63, there were slightly more men than women and the population was mostly white. They were mostly current or former smokers and approximately 17% had brain metastases. Only 30% of participants had PD-L1 negative tumors, which is slightly less than expected. The majority of patients were treated with carboplatin, rather than cisplatin based chemotherapy. Standard doses of chemotherapy were used and 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 10.5 months, so the OS results are still immature.

KEYNOTE -189 met both its primary study outcomes. OS was significantly improved for patients randomized to pembrolizumab, platinum and pemetrexed compared with placebo, platinum and pemetrexed (median OS NR vs 11.3 months, HR 0.49, 95%CI 0.38-0.64). Similarly, PFS was significantly improved (median PFS 8.8 vs 4.9 months, HR 0.52, 95%CI 0.43-0.64). The ORR was higher in patients randomized to pembrolizumab and chemotherapy versus chemotherapy alone (47.6% vs 18.9%). The higher ORR was seen in patients with PD-L1 positive and negative tumors. Benefit was seen in favour of pembrolizumab plus chemotherapy in all planned subgroup analyses. There was a significant improvement in global quality of life health scores at week 21 favouring the pembrolizumab and chemotherapy group.

The overall profile of adverse effects (AEs) was similar in both groups, with a similar incidence of grade 3 and 4 AEs. The AE profile was driven by expected chemotherapy AEs. More patients discontinued therapy due to an AE in the pembrolizumab arm than the control arm (27.7% vs 14.9%). Not surprisingly, the incidence of immune related AEs was higher in the pembrolizumab arm than control (22.7% vs 11.9%). Oncologists are familiar with identification and management of these AEs.

The results of the KEYNOTE-189 trial support the implementation of pembrolizumab in combination with platinum and pemetrexed chemotherapy, as initial therapy or advanced and metastatic NSCLC. The data on efficacy favour pembrolizumab and chemotherapy across all outcomes and reinforces the results of the KEYNOTE-21G trial. The magnitude of the improvements in OS and PFS are large. There is a modest improvement in quality of life observed at week 21. This improved efficacy is associated with some increase in the incidence of immune related AEs and some increased risk of discontinuation of therapy. These appear acceptable in the setting of a large improvement in the primary outcomes. Given the burden of illness from lung cancer across the Canadian population, there is potential to improve health outcomes in a large number of Canadians living with NSCLC.

The findings from KEYNOTE-189 are generalizable to the large majority of patients with advanced and metastatic NSCLC. Patients with targetable molecular abnormalities such as *EGFR* mutations, *ALK* and *ROS1* translocations were not included in this trial and would not be candidates for first-line pembrolizumab, platinum and pemetrexed therapy. These patients are best treated with molecularly targeted therapy and appear less likely to benefit from ICI therapy. These data only apply to patients with non-squamous NSCLC and would not be generalized to patients with squamous cancers. However, the KEYNOTE-407 trial evaluated pembrolizumab in combination with chemotherapy, in patients with squamous NSCLC.[15] Similar outcomes were observed and these data will likely form a future submission to pCODR. Keynote 189 included only patients with ECOG 0-1. Most treatment algorithms, including ASCO guidelines for advanced NSCLC recommend treatment be considered in patients with a performance status of ECOG 2 as well. These patients are currently offered ICI as second-line therapy. It would be reasonable to generalize the findings of KEYNOTE-189 to NSCLC with performance status of ECOG 2 as well. The trial included only patients with measurable disease, but would be applicable to patients with evaluable disease as well. While the trial excluded patients who received thoracic radiation within six months of study entry, data from the PACIFIC trial of consolidation durvalumab after concurrent chemoradiation demonstrated safety of ICI following thoracic radiation.[13] Given these data, patients who received recent thoracic radiation should also be considered for pembrolizumab plus chemotherapy. Patients who receive pembrolizumab plus chemotherapy in the first-line setting would not be eligible for second-line ICI.

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

- The original KEYNOTE-10 trial used weight based dosing for pembrolizumab, at a dose of 2mg/kg.[9] Subsequent trials of pembrolizumab have adopted a fixed dose of pembrolizumab

at 200mg. The clinical guidance panel would strongly recommend pembrolizumab be used as per the evidence i.e. 200mg flat dosing. There is some evidence that higher doses of pembrolizumab may be associated with better efficacy. KEYNOTE-10 also evaluated pembrolizumab 10mg/kg and the best OS numerically, was seen in this arm. There are also some retrospective data from patients with metastatic melanoma treated with ICI demonstrated better survival in patients with obesity compared to normal or low body weight.[16] However, the CGP recognize that prior decisions regarding pembrolizumab have recommended pembrolizumab dosing at 2mg/kg up to a maximum of 200mg.

- KEYNOTE-189 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, or how many patients were retreated. However, in the second-line setting continuation of nivolumab until disease progression was shown to be superior to discontinuation after one year of therapy.[17] Therefore the CGP believes patients who complete two years of pembrolizumab and discontinue therapy without progression, should have the option for retreatment with pembrolizumab, if there is at least six months between completion of therapy and documented disease progression.

- Currently, patients with tumors with high PD-L1 expression (≥ 50%) would receive pembrolizumab monotherapy in the first line setting. Pembrolizumab plus chemotherapy provides another option for the treatment of this population of patients. There are no randomized trials to address the question of pembrolizumab alone versus pembrolizumab plus chemotherapy in this patient group. An indirect treatment comparison (ITC) was provided suggesting improved efficacy for the combination of pembrolizumab plus chemotherapy. The clinical guidance panel believes there are sufficient limitations to the ITC to leave uncertainty about this question. Both treatments are superior to chemotherapy alone and should be available to clinicians to choose based on individual patient needs and preferences as outlined in the physician input to this review. The CGP notes that routine testing for PD-L1 expression will still be required in order to facilitate treatment decisions between pembrolizumab plus chemotherapy and pembrolizumab alone in patients with PD-L1 positive tumors.

- Additionally, a NMA was provided comparing pembrolizumab plus chemotherapy, with other published first-line therapies in NSCLC. The combination of carboplatin, paclitaxel, bevacizumab and atezolizumab was identified as another treatment strategy with similar efficacy.[18] Given that bevacizumab containing regimens have not impacted greatly in Canadian NSCLC treatment algorithms, the CGP believes this regimen to have less potential impact on NSCLC treatment options.

- Treatment algorithms for earlier stage NSCLC are also evolving. Patients with locally advanced NSCLC treated by concurrent chemoradiation are now being offered one year of consolidation durvalumab therapy. Some patients with resected NSCLC have taken part in trials evaluating ICI. KEYNOTE-189 does not help answer the question if these patients should receive pembrolizumab plus chemotherapy as initial therapy for recurrent / metastatic disease. The CGP believes it is reasonable to consider pembrolizumab plus chemotherapy for metastatic disease in patients who have had at least one year since receiving adjuvant or consolidation ICI therapy. These patients would be considered for platinum-based chemotherapy and so should be eligible for pembrolizumab plus platinum and pemetrexed.

- There will be patients who have recently commenced treatment with platinum-pemetrexed therapy who could benefit from the addition of pembrolizumab therapy. Patients who are still receiving platinum and pemetrexed should be allowed to commence pembrolizumab as well. The CGP felt there was too much uncertainty to generalize this to patients who have already commenced maintenance pemetrexed, or who were not candidates for platinum-doublet therapy.

1.3 Conclusions

The Clinical Guidance Panel members believe there is a net overall clinical benefit from the addition of pembrolizumab to platinum-pemetrexed chemotherapy in patients with advanced / metastatic non squamous NSCLC. The OS survival data are still immature. However, the KEYNOTE - 189 trial demonstrates clear improvement in both OS (median OS NR vs 11.3 months, HR 0.49, 95%CI 0.38-0.64) and PFS (median PFS 8.8 vs 4.9 months, HR 0.52, 95%CI 0.43-0.64) for pembrolizumab plus chemotherapy, versus platinum-pemetrexed chemotherapy alone. Secondary efficacy parameters including ORR and quality of life were significantly improved for patients receiving the combination of pembrolizumab plus chemotherapy. These improved efficacy outcomes have an acceptable safety profile. The AE profile is largely driven by expected chemotherapy AEs, which are similar between the two groups. There are expected immune related AEs that oncologists are already familiar with managing. Non squamous NSCLC represents are significant health burden. Estimates are that over 4000 patients annually across Canada might benefit from the addition of pembrolizumab to platinum and pemetrexed chemotherapy. Therefore this new option for treatment has the potential to improve on a significant unmet need.

Pembrolizumab, platinum and pemetrexed would insert into the existing NSCLC treatment algorithm as initial therapy patients with advanced / metastatic non squamous NSCLC, performance status ECOG 0-2, no *EGFR* mutations, *ALK* or *ROS1* translocations and no contraindications to ICI therapy. 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 12 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 cancer represents the second most common cause of cancer among both men and women in Canada, but the largest cause of death from cancer. In 2016, there were approximately 28,400 new cases of lung cancer and 20,800 deaths from lung cancer.[19] About 85% of these cases would be classified as Non-Small Cell Lung Cancer (NSCLC). Approximately 50% of NSCLC patients have stage IV disease at the time of presentation, with another 25-30% presenting with locally advanced stage III disease.[20] Only 20-25% of patients present with early stage disease amenable to surgical resection. The incidence of NSCLC rises with age and the median age at diagnosis is 70 years. Given the high proportion of patients presenting with advanced stage, it is not surprising that the expected five year survival is only 18%.[19]

2.2 Accepted Clinical Practice

Treatment algorithms for advanced NSCLC have changed substantially over the last decade. In past years, one algorithm was applicable to all patients. Initial therapy consisted of a platinum-doublet with cisplatin or carboplatin in combination with gemcitabine, vinorelbine, paclitaxel, or docetaxel.[21] Maintenance therapy was not routinely recommended and patients well enough to receive further therapy at the time of disease progression would be offered docetaxel,[22] pemetrexed[23] and/ or erlotinib.[24] Histology emerged as a predictive marker for some systemic agents, including pemetrexed and bevacizumab, resulting in different treatment algorithms for squamous and non squamous NSCLC.[25-27] More recent advances have arisen as a result of the identification of molecular abnormalities driving lung cancer growth and development. To date therapeutic options for these groups of NSCLC have been primarily identified in patients with non squamous histology. A study conducted by the Lung Cancer Mutation Consortium (LCMC) reported on the results of molecular profiling in 1007 lung adenocarcinomas.[28] Oncogenic drivers were found in 64% of cases. Commonly observed gene mutations included *KRAS* (25%), *EGFR* (17%) and *ALK* (8%). Mutations occurring in 1-2% of patients included *ERBB2*, *BRAF*, *MET*, *NRAS*, *MEK* and *ROS1*. Data from randomized trials have established that oral tyrosine kinase inhibitors (TKIs) targeting the *EGFR* or *ALK* genes have superior objective response rates (ORR) and progression free survival (PFS) than platinum-based chemotherapy. Molecularly targeted therapies such as gefitinib,[29,30] afatinib,[31,32] crizotinib[33] and alectinib[34] are now the preferred initial therapy in NSCLC patients with these molecular abnormalities. Similar findings from phase II trials have established high efficacy of molecularly targeted therapies in patients with tumors containing less common molecular abnormalities of *ROS1*[35 36] and *BRAF* genes.[37,38] Nevertheless, available data would suggest that only one in three patients receive systemic therapy and the rate of treatment declines with advancing age.[20,39]

The development of immune checkpoint inhibitors represents the most significant recent change in the treatment algorithm for advanced NSCLC. The interaction between the Programmed Cell Death–1 (PD-1) receptor and its ligand (PD-L1) represents an inhibitory signal to T-cell activation. It is one of the mechanisms by which cancers are thought to escape immune surveillance. Monoclonal antibodies directed against the PD-1 receptor, or its ligand are now approved therapy in the treatment of advanced NSCLC.

RCTs comparing second line therapy with nivolumab,[7,8] pembrolizumab[9] and atezolizumab,[10,11] to docetaxel chemotherapy, have all demonstrated superior overall survival (OS) for the immune checkpoint (IC) inhibitors (Table 1). These trials consistently demonstrate a 30-40% reduction in the hazard for death, among patients receiving a PD-1/PD-L1 inhibitor compared with docetaxel. Fatigue is a commonly observed adverse effect. Novel toxicities are associated with the use of immune checkpoint inhibitors including autoimmune adverse effects including pneumonitis, hepatitis, colitis, diarrhea, skin toxicities such as rash and pruritus, as well as endocrine dysfunction involving the thyroid, pituitary, adrenal and pancreas glands. These agents have changed treatment algorithms and would now be considered routinely in second-line therapy of advanced NSCLC. Many patients do not appear to benefit from second-line IC therapy, with relatively short median PFS observed in many of these trials.

Therefore, predictive biomarkers would be of value, to better identify patients for IC therapy. PD-L1 expression[7,8,11] and tumor mutation burden (TMB)[40] have both been identified as potential predictive biomarkers. In Checkmate 017, conducted in patients with squamous NSCLC, PD-L1 status was neither prognostic, nor predictive for OS.[8] However, in the Checkmate 057 trial, in patients with non-squamous NSCLC, PD-L1 status appeared to be predictive of improved OS in patients receiving nivolumab. PD-L1 expression ≥ 1%, 5%, or 10% was associated with higher OS in patients randomized to nivolumab. The Keynote 10 trial did not include NSCLC patients with tumours not expressing PD-L1. Higher ORR and improved OS were observed in patients with tumours expressing PD-L1 in 50% of greater of cells. Improvement in OS was observed in patients with PD-L1 positive and negative tumors in the OAK trial evaluating atezolizumab.[11]

Given the activity observed from IC therapy in the second-line setting, multiple trials have evaluated single agent pembrolizumab[12,41] and nivolumab[42] in the first-line setting. Both the Keynote 24 trial,[12] conducted in NSCLC patients (all histologies) with tumours expressing high levels of PD-L1 (TPS ≥ 50%) and Keynote 42,[41]conducted in NSCLC patients (all histologies) with any PD-L1 positive tumours (TPS ≥ 1%), demonstrated improved OS for patients randomized to single agent pembrolizumab compared with platinum-based chemotherapy. Subset analysis of Keynote 42 suggested greater benefit in patients with tumours with high PD-L1 expression. Interestingly, the Checkmate 26 trial, which randomized patients with PD-L1 positive tumours to nivolumab versus platinum-based chemotherapy, failed to demonstrate improved OS.[42] Post hoc analysis of this trial suggested that patients with high TMB and high PD-L1 expression may have better OS from nivolumab than chemotherapy. Therefore single agent pembrolizumab is currently offered as initial therapy to patients with advanced NSCLC with high PD-L1 expression (TPS ≥ 50%). These trials did not include patients with underlying molecular abnormalities such as *EGFR* mutations and *ALK* translocations.

More recently trials have evaluated the efficacy of pembrolizumab in combination with platinum-based chemotherapy, compared with platinum-based chemotherapy alone.[1,5,15] KEYNOTE- 21G was a randomized phase II trial of carboplatin and pemetrexed alone or in combination with pembrolizumab in patients with non-squamous NSCLC. The primary outcome, ORR, was significantly improved in patients randomized to chemotherapy plus pembrolizumab (55% vs 29%, p=0.0016). The benefit was present in all levels of PD-L1 expression (PD-L1 negative – 57%, PD-L1 ≥ 1% - 54%, PD-L1 ≥ 50% - 80%). PFS was also significantly greater in patients randomized to chemotherapy plus pembrolizumab (13.0 months vs 8.9 months, HR 0.53, 0.31-0.91). The results were confirmed in KEYNOTE-189, a similarly designed phase III trial in patients with non-squamous NSCLC. ORR was significantly greater in the pembrolizumab group (47.6% vs 18.9%, p<0.001). Significant improvements in PFS (8.8 months vs 4.9 months, HR 0.52, 0.43-0.64) and OS (not reached vs 11.3 months, HR 0.49, 0.38-0.64) were also reported. Improved OS was observed in patients with all levels of PD-L1 expression. Similar findings were also observed in the KEYNOTE-407 trial, which randomized patients with squamous NSCLC to carboplatin and either paclitaxel or nab-paclitaxel alone, or in combination with pembrolizumab. Significant improvements were seen

in ORR, PFS and OS for patients randomized to chemotherapy plus pembrolizumab. Similar to the findings of KEYNOTE- 21G and 189, these improvements were observed in all patients regardless of PD-L1 expression.

These data support the addition of pembrolizumab to platinum-based chemotherapy in both squamous and non-squamous NSCLC. Competing treatment strategies exist for patients with tumours expressing high levels of PD-L1 (TPS ≥ 50%). Single agent pembrolizumab has also been shown to be superior to platinum-based chemotherapy and there are no data comparing single agent pembrolizumab with chemotherapy plus pembrolizumab. At present single agent pembrolizumab would appear to be the preferred treatment approach in patients with high levels of PD-L1 expression. Sub group analyses in the KEYNOTE- 42 trial do not demonstrate a significant improvement in OS for patients with lower levels of PD-L1 expression (TPS 1-49%). Given the consistency of findings across KEYNOTE-21G, 189 and 407 studies, based on PD-L1 expression, chemotherapy plus pembrolizumab is the preferred treatment strategy in patients with PD-L1 negative tumours, as well as tumours with PD-L1 expression 1-49%.

Patients with advanced NSCLC		
Line of Therapy	[Current algorithm]	[Proposed algorithm]
1st-Line	Pembrolizumab (TPS ≥ 50%), or platinum-based chemotherapy	Pembrolizumab (TPS ≥ 50%), or platinum-based chemotherapy plus pembrolizumab
Maintenance	Pembrolizumab, or maintenance chemotherapy	Platinum-based chemotherapy, or docetaxel
2nd-Line	Platinum-based chemotherapy if prior pembrolizumab, or nivolumab, pembrolizumab (if PD-L1 ≥ 1%), or atezolizumab	Docetaxel or erlotinib
3rd Line	Docetaxel	Erlotinib
4th Line	Erlotinib	

Summary of trials of immune checkpoint inhibitors in NSCLC				
Trial	**Intervention**	**ORR**	**PFS**	**OS**
Checkmate 17[8]	Docetaxel	9%	2.8m	6.0m
	Nivolumab	20%	3.5m HR 0.62	9.6m HR 0.59
Checkmate 57[7]	Docetaxel	12%	4.2m	9.4m
	Nivolumab	19%	2.3m HR 0.92	12.2m HR 0.73
KEYNOTE 10[9]	Docetaxel	9%	4.0m	9.5m
	Pembrolizumab 2mg	18%	3.9m HR 0.88	10.4m HR 0.71
	Pembrolizumab 10mg	18%	4.0m HR 0.79	12.7m HR 0.61

Summary of trials of immune checkpoint inhibitors in NSCLC				
Trial	**Intervention**	**ORR**	**PFS**	**OS**
OAK[11]	Docetaxel Atezolizumab	13% 14%	4.0m 2.8m HR 0.95	9.6m 13.8m HR 0.73
Poplar[10]	Docetaxel Atezolizumab	15% 17%	3.0m 2.7m HR 0.94	9.7m 12.6m HR 0.73
Keynote 24[12]	Platinum-pemetrexed Pembrolizumab	22.7% 44.8%	6.0m 10.3m HR 0.50	HR 0.60 (median not reached)
KEYNOTE 42[41]	Platinum-pemetrexed Pembrolizumab	26.5% 27.3%	5.4m 6.5m HR 1.07	12.1m 16.7m HR 0.81
Checkmate 26[42]	Platinum-pemetrexed Nivolumab	33.5% 26.2%	5.9m 4.2m HR 1.15	13.2m 14.4m HR 1.02
KEYNOTE 21G[5]	Platinum-pemetrexed Platinum-pemetrexed + pembrolizumab	29% 55%	8.9m 13.0m HR 0.53	HR 0.90
KEYNOTE 189[1]	Platinum-pemetrexed Platinum-pemetrexed + pembrolizumab	18.9% 47.6%	4.9m 8.8m HR 0.52	11.3m NR HR 0.49
KEYNOTE 407[15]	Platinum-taxane Platinum-taxane + pembrolizumab	38.4% 57.9%	4.8m 6.4m HR 0.56	11.3m 15.9m HR 0.64

2.3 Evidence-Based Considerations for a Funding Population

There are approximately 28,800 new cases of lung cancer annually in Canada.

- Proportion of NSCLC (85%) 24,480
- Proportion with locally advanced or metastatic disease (75%) 18,360
- Proportion with non-squamous histology (75%) 13,770
- Proportion receiving treatment (30%) 4,131
- Proportion with PD-L1 expression <50% (70%) 2,890

Based on the above assumptions, if 30% of patients receive some systemic therapy for advanced or metastatic NSCLC, there are approximately 4131 patients with non-squamous histology who receive systemic therapy. Approximately 30% are PD-L1 strongly positive who already receive first-line pembrolizumab. As many as 2890 patients with either PD-L1 expression < 1%, or 1-49%, who would be eligible for pembrolizumab in combination with platinum-pemetrexed chemotherapy. The number treated will likely be lower, as some of these patients may have contraindications to the use of pembrolizumab.

2.4 Other Patient Populations in Whom the Drug May Be Used

Pembrolizumab is currently indicated as first-line therapy in patients with advanced NSCLC and tumours with high expression of PD-L1 (TPS ≥ 50%), or as second-line therapy in NSCLC patients with PD-L1 positive tumours, previously treated with platinum-based chemotherapy. The latest indication would further expand the population of NSCLC patients that might benefit from therapy with pembrolizumab.

The KEYNOTE trials included patients with performance status ECOG 0-1. However, physicians are likely to extrapolate the data to patients with ECOG 2, as well. Given the broad population of patients that would be eligible for pembrolizumab in combination with platinum-based chemotherapy, there is less scope to expand to other populations of patients with advanced NSCLC.

3 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

Patient input regarding pembrolizumab (Keytruda) in combination with pemetrexed and platinum chemotherapy for the treatment of patients with metastatic non-squamous (mNSQ) non-small cell carcinoma (NSCLC) was provided by three patient advocacy groups: Lung Cancer Canada (LCC), the Ontario Lung Association (OLA) and the British Columbia Lung Association (BCLA). The latter two provided a joint submission to the pCODR program. Their input is summarized below.

LCC used three sources of information for its submission. The organization conducted a national survey of lung cancer patients and caregivers in August 2015. There were 91 patient and 72 caregiver respondents who completed the survey. All of the patient respondents had or survived lung cancer, and all of the caregiver respondents were current or previous caregivers for patients with lung cancer. LCC also performed an environmental scan of online forums where discussions on pembrolizumab in combination with pemetrexed and platinum chemotherapy occurred, resulting in the collection of thoughts from nine patients and eight caregivers. Finally, to provide context around patients' experiences with lung cancer and their treatments, LCC included focus group discussions and individual interviews from a recent submission to the pCODR program in 2017 regarding pembrolizumab for metastatic NSCLC whose tumours express PDL-1. A total of 23 patient and 14 caregiver respondents with experience with pembrolizumab were gathered from this submission.

In September 2018, OLA obtained feedback from a Toronto-based lung health support group comprised of six members and conducted a phone interview with a patient with lung cancer. Patients were living with COPD (4), idiopathic pulmonary fibrosis (1) or lung cancer (2). OLA also reported feedback for previous submissions to CADTH over the past three years in addition to input from one caregiver. No patients within this group submission have experience with pembrolizumab.

The information provided from the BCLA was obtained from phone interviews with five patients living with lung cancer and three caregivers who completed an online survey developed through Fluid Survey over the past three months. Two patients in this group had experience with pembrolizumab.

From a patient perspective, lung cancer impacts many aspects of day-to-day life. Specifically, it affects the respondents' ability to work, travel, socialize and participate in leisure and physical activities. It also affects their relationships with family and friends, emotional well-being and may cause financial hardship. It was reported by both patient and caregiver respondents that high symptom burden of lung cancer is difficult to manage. LCC indicated that symptoms may include: loss of appetite, cough, pain, and shortness of breath. Moreover, one of the most common symptom burdens for patients with lung cancer is fatigue or lack of energy. BCLA noted that symptoms are not fixed or consistent, but rather change frequently, which can be difficult to manage. For the vast majority of this patient population, the current standards of care are chemotherapy or radiation. According to LCC, chemotherapy is viewed as a necessary, but feared, treatment. The infusions presented challenges with respect to travel time and hospital visits. Chemotherapy is seen as a persistent psychological and physical burden, with health ill effects that limit personal independent and quality of life, although some can tolerate it and do see improvement in tumour size. Patients with experience with immunotherapy reported much milder side effects that did not significantly interfere with daily life, although pneumonitis, a less frequent but severe side effect, was noted in one patient who needed hospitalization.

Respondents reported that, from their perspective, the following key treatment outcomes were the most important areas to be addressed by this new drug combination: to stop or slow the progression of the disease, to reduce or eliminate side effects (e.g., reduce pain, fatigue, cough

and shortness of breath), and to improve appetite and energy. Respondents additionally indicated that they would value improved independence and requiring less assistance from others. They would also like there to be less or no cost burden associated with new treatments.

For respondents who had experience with pembrolizumab plus chemotherapy, fatigue and nausea were common undesirable effects, with pneumonitis and itchy skin being prominent side effects of the immunotherapy component. Patients saw significant and encouraging clinical (tumour size) and symptomatic (breathing, cough, etc.) improvements during and after treatment with this drug combination, and some were able to resume normal, pleasurable and fulfilling life activities.

Pembrolizumab in combination with chemotherapy was seen as an aggressive therapeutic approach for a variety of clinical presentations. It was mentioned that it may be an attractive option for patients wishing to benefit from first line immunotherapy without being limited by tumour PD-L1 expression, and that anticipated side effects would be acceptable to many in view of the promises of gains in length and quality of life.

Summary of the patient and caregiver input data sources

Patient Advocacy Groups	Source of Data	# Patients	# Caregivers
Lung Cancer Canada (LCC)	Survey (2015)	91	72
	environmental scan	9	8
	Focus group discussions ; individual interviews (from previous CATH submission)	23	14
Ontario Lung Association (OLA)	Support group consultation	6	-
	Phone interview	1	-
British Columbia Lung Association (BCLA)	Phone interview	5	-
	Online survey	-	3

3.1 Condition and Current Therapy Information

3.1.1 Experiences Patients have with Lung Cancer

LCC did not provide information on the specific symptoms patients in the sample experienced with their cancer.

At the stage of lung cancer diagnosis, both OLA and BCLA reported issues of heightened anxiety, depression and frustrations with delays. The most common symptoms described included: chronic cough, coughing up blood, chest pain, shortness of breath, repeated pneumonia or chronic bronchitis, hoarseness of voice, loss of appetite or weight and extreme tiredness. Both BCLA and OLA indicated that symptoms are not fixed or consistent, but rather change frequently, which can also be difficult to manage.

BCLA and OLA reported that lung cancer impacts many aspects of day-to-day life for people living with it. Specifically, it affects: the respondents' ability to work, travel, socialize and participate in leisure and physical activities. It also affects their relationships with family and friends, independence, emotional well-being and their financial situation. For some, it was reported that it strips them of their ability to do anything on their own. One respondent stated: "*this disease has affected all parts of my life. I am not able to go outside on cold days, I am no longer able to drive, and must use volunteer drivers to get to my appointments, I am dependent on my neighbours to get my mail each day and take my weekly trash out. I have lost a significant amount of weight and am tired, weak and without energy. I am no longer able to do the activities I enjoy. It is very hard to be positive and hopeful.*"

3.1.2 Patients' Experiences with Current Therapy for Lung Cancer

LCC highlighted that patients with NSCLC who are not candidates for oncogene targeting therapy are currently being treated with chemotherapy, with the subset of patients with high PD-L1 expression being treated with pembrolizumab. Patient experiences with these two treatments have been documented in previous LCC submissions and were provided again.

For chemotherapy, LCC asserted that it is still a viable option for many lung cancer patients, but is associated with significant negative effects, including the following:

- Even before treatment begins, chemotherapy carries a psychological burden with perceptions that it is a "cytotoxic killer" and a "poison". In addition, recovery time is needed after each chemotherapy infusion. Patients recounted the experience as "*two bad weeks and one good week*" and "*I was so, so sick on infusion chemo, I wasn't functional*". Chemotherapy also limits personal activities, with one patient maintaining that "*when you are on chemotherapy you can be at home but there is no difference to being in the hospital. You still can't do things.*"
- The impact of chemotherapy is persistent, with one patient feeling that "*you never recover*". Four years after chemotherapy, the patient still experiences fatigue and had not yet been able to return to work.
- Memory and clarity issues ("chemo-fog") have also been reported by patients.
- The issue of physical appearance: not only did patients feel sick on chemotherapy, they felt they also looked sick. As a result, they tended to stay at home.

Nonetheless, a patient conceded that the treatments were acceptable and appeared effective: "*They are no fun, but they are tolerable. I just had my first cat scan after 2 treatments and there was good shrinkage of all tumours in my lungs*"

For immunotherapy, LCC reported that a majority of patients experienced zero to mild side effects that were easily managed, with some more severe cases requiring OTC or prescription drugs. Of those, most found that the management was tolerable and did not interfere with day-to-day life, however, one patient was taken off pembrolizumab due to pneumonitis. Two of the patients reported some fatigue that went away "with a nap during the day". At the beginning, one of the patients had bloody stools that were managed through steroids. Three of the patients reported a rash that was managed through corticosteroids.

Immunotherapy allowed patients to resume normal daily activities, such as "*put on clothes like a normal person*" and "*fix my hair*". In contrast to chemotherapy, immunotherapy gave patients and their families a new, "good" quality of life by giving them a chance to keep performing activities they were able to do before a lung cancer diagnosis, such as "*[being] back playing golf*", allowing "*playtime with grandchildren*" or being a parent to young children. Immunotherapy established a "*new normal*". Lastly, immunotherapy offered the possibility of returning to work and feel productive. One patient was happy that treatments allowed him to continue to teach at a Canadian University, coach Little League, and play hockey. From a practicality standpoint, immunotherapy patients are able to go to the infusions by themselves and feel well enough that they can leave the hospital by themselves.

The OLA provided the experience of patients who had used various medications for managing symptoms of lung disease including Spiriva, Seebri, Advair, Symbicort, Daxas, Prednisone, Ventolin, Atrovent, Serevent, Onbrez, Tudorza and Ventolin. Only one patient was undergoing radiation and chemotherapy. It was mentioned that treatments provide some relief for fatigue, shortness of breath, cough, appetite loss and low energy, but the side effects such as:

palpitations, dry mouth, mouth sores, vision and urinary problems and impact on mood need to be better managed. The submission was not clear on which medication related to which effect. Radiation left one patient with an extremely sore and painful throat, making it difficult to swallow food.

Patients interviewed by OLA mentioned the burden of medical appointments and costs. They hope that treatments provide enough help that they will experience improved independence and require less assistance from others. The desire for improved energy was noted many times.

Training for general practitioners (GPs) was also mentioned as a need, as these patients felt their GPs needed to know more about lung diseases to avoid delays in diagnosis and treatment. The relevance of this need in the context of lung cancer is unclear. Improved communications was a recurrent theme for OLA interviewees, with many stating the importance of understanding treatment options and their implications.

3.1.3 Impact of Lung Cancer and Current Therapy on Caregivers

According to OLA, caregivers of those living with lung cancer mentioned the negative impact that this role had on multiple aspects of their lives, including work, finances, relationships with family and friends, physical and leisure activities, and the ability to travel and socialize. The emotional toll of watching patients suffer without the ability to alleviate their discomfort was an overarching theme.

3.2 Information about the Drug Being Reviewed

3.2.1 Patient Expectations for and Experiences To Date with Pembrolizumab plus Chemotherapy

Nine patients and 8 caregivers identified by LCC had experience with pembrolizumab plus chemotherapy. These patients experienced a spectrum of side effects including fatigue and nausea. One patient experienced extreme fatigue, loss of appetite and had to be hospitalized for severe dehydration. These effects may have been caused by chemotherapy since carboplatin had to be stopped in this patient.

According to a caregiver, one patient had a thyroid issue, a common side effect that was subsequently controlled by medication. Pneumonitis was attributed to immunotherapy in several of the patients and one patient was taken off the treatment. According to a caregiver, a patient had severe itchy skin that “drove her crazy, especially at night”. For some patients, side effects were minimal and manageable: “Except for fatigue, I feel pretty close to normal”.

Despite the side effects, this new treatment was a chance for some patients to aggressively treat their lung cancer. One patient stated: “Side effects of carboplatin were difficult to manage, but the scan showed a decrease in the size of the tumor”. This patient was off work for a few days a month while on treatment. Another patient also experienced a balance of side effects and clinical improvements, and was happy to have persisted through the treatment. Post-treatment pemetrexed maintenance was better tolerated by some patients.

According to a caregiver, recommendation for the pembrolizumab combination felt “like a lifeline” and allowed the patient to stay “stable”. Another patient saw her tumour size reduced by almost 75%, and she was grateful that the cancer was treatable. Other patients experienced significant improvements in their condition with reduced symptoms including resolved pleural effusion, tumor shrinkage and stable metastases. A patient returned to working, gardening and playing with grandkids after treatment, and another was able to go to back to work full time.

Another patient failed first line pembrolizumab, but responded well to the pembrolizumab/carboplatin/pemetrexed combination with 30-40% tumour size reduction, loss of visible metastases, improvements in breathing and coughing, and resolution of pleural effusion. A patient had few side effects on pembrolizumab alone and the addition of chemotherapy led to "more fatigue and some nausea but I was able to work full time". Finally, a caregiver reported that a patient had his tumours "shrunken by 60-80% before he had to have a break" which allowed him to "[get] 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". The LCC concluded that pembrolizumab in combination with chemotherapy is a more aggressive type of treatment that does carry additional side effects, but that should nonetheless be offered to patients who are seeking access to first line immunotherapy and are willing to go down that path.

The OLA submission did not include patients who had experience with pembrolizumab. Two out of five patients, described by the BCLA, who had experience with pembrolizumab reported lesser symptoms, little impact on normal life, and no side effects from the medication(s), contrary to their experience prior to treatment. However, it was not clear whether these patients were treated with pembrolizumab alone or in combination with chemotherapy.

3.2.2 Patient Expectations for and Experiences To Date with Pembrolizumab plus Chemotherapy

LCC noted that this new treatment combination presents patients with an opportunity to experience first line immunotherapy, regardless of their PD-L1 status. Patients expect to live longer on this treatment compared with monotherapy.

According to OLA, patients and caregivers expect that certain outcomes will be addressed, including: to stop or slow the progression of the disease, to reduce pain, fatigue, cough and shortness of breath, and to improve appetite and energy. The following current side effects are expected to be reduced or eliminated: pain, fatigue, nausea, shortness of breath, appetite loss, low energy, inability to fight infection, burning of skin and impact to mood. They would also like there to be less or no cost burden associated with new treatments. Cost was also identified as a concern for BCLA patients.

OLA patients would like the ability to do treatments at home and thus minimize time off of work and the disruption of daily routine. The importance of quality of life was a common theme, as one declares "if I have less than three years to live, I would like to be able to enjoy that time with my family."

3.3 Additional Information

LCC stated that while data are considered in aggregate form, patients have distinct characteristics that may impact decisions. Some will have particularly large tumours, and some may be very aggressive and progress quickly. Some patients will be very functional at time of diagnosis. Some may have young families. While this option does not replace pembrolizumab alone in the first line setting, these patients may choose, and should be given the opportunity, to access more aggressive treatment. This is a choice that is made based on individual situation in consultation with their families. Depending on individual patient circumstances, some may still want to delay chemotherapy. According to LCC, the research data supports both pembrolizumab monotherapy and in combination with chemotherapy in the first line, enabling patient choice in order to improve outcomes.

4 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

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

Overall Summary

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

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 and single agent pembrolizumab (for patients with PD-L1 ≥50%) are standard of care for first-line treatment of advanced NSCLC. Pemetrexed in combination with platinum would be specific for non-squamous histology. For patients not eligible for platinum-based therapies, they may receive single agent pemetrexed.

4.2 Eligible Patient Population

In the KEYNOTE-189 trial, patients were excluded if they had EGFR or ALK mutations. PAG is seeking confirmation that eligibility for pembrolizumab in this setting would not include patients with EGFR, ALK, or ROS-1 mutations. PAG noted there may be interest to use pembrolizumab for these patients and thus risk of indication creep. PAG is seeking clarity that patients would be eligible for pembrolizumab in this setting irrespective of PD-L1 TPS.

PAG noted that the reimbursement request is for pembrolizumab in combination with pemetrexed and platinum chemotherapy. Although out of scope of the review, PAG is seeking information on the use of pembrolizumab in combination with other chemotherapy regimen (e.g., non-platinum based regimens).

If recommended for reimbursement, PAG noted the following groups of patients would need to be addressed on a time-limited basis:

- Patients recently treated or currently treated with a platinum-based drug plus pemetrexed
- Patients currently treated with pemetrexed
- Patients currently treated with single agent pembrolizumab

4.3 Implementation Factors

The dose is 200mg for NSCLC in the funding request and KEYNOTE-189 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).

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 identified that the continued availability of the 50 mg vial and 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.

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 2 years, 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).

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.
- 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.
- Appropriateness of re-treatment with single-agent pembrolizumab (i.e., after 35 cycles or earlier) or pemetrexed maintenance therapy.
- For patients who are unable to tolerate pemetrexed, whether single-agent pembrolizumab would be appropriate to continue up to 35 cycles.

With respect to treatment sequencing, PAG is seeking guidance on whether patients with mutations (EGFR, ALK, or ROS-1) should be treated with targeted treatment first and if it would be reasonable to subsequently treat with pembrolizumab.

At the time of this PAG input, durvalumab for locally advanced, unresectable NSCLC whose disease has not progressed following platinum-based chemoradiation therapy is being reviewed by pCODR. PAG is seeking data on whether pembrolizumab or other PD-1/PD-L1 inhibitors would be used for treating metastatic disease after progression on durvalumab as well as the appropriate time frame between treatments.

For patients with PD-L1 ≥50%, single agent pembrolizumab is available in jurisdictions, PAG is seeking clarity whether these patients should receive single agent pembrolizumab or the combination of pembrolizumab with pemetrexed and platinum chemotherapy.

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

Three clinician inputs were received from clinicians from the following organizations: Lung Cancer Canada (six clinicians), Cancer Care Ontario (two clinicians), London Regional Cancer Program (one clinician), for a total of nine clinicians providing input.

The clinicians providing input generally agreed that the combination of pembrolizumab and pemetrexed/platinum-based chemotherapy would be a suitable first line option for all non-squamous (NSQ) NSCLC patients with low expression of PD-L1, as well as for those with high expression of PD-L1 who are eligible for pembrolizumab monotherapy but may benefit from a rapid therapeutic response. According to the clinicians, the combined use of chemotherapy and immunotherapy addresses a therapeutic gap whereby one would usually have to risk a worsening condition after progression on one therapy before trying the other. It is felt that the availability of first line immunotherapy independent of PD-L1 expression increases equity in patients who have no PD-L1 results and those unfit for second line therapy. Safety and tolerability were not seen as major issues by clinicians. They maintained that both combination and monotherapy options should remain available for NSQ NSCLC patients, but agreed that the sequence of therapies should favour first line pembrolizumab therapy (alone or combined with chemotherapy, as determined by PD-L1 status and patient preference) moving forward.

Please see below for details from the clinician input.

5.1 Current Treatment(s) for this NSQ-NSCLC

The clinicians providing input agreed that platinum doublet therapies and single agent pembrolizumab (for patients with PD-L1 ≥50% and where publically available) are standard of care for first-line treatment of advanced NSCLC. Pemetrexed in combination with platinum would be specific for non-squamous (NSQ) histology. Patients not eligible for platinum-based therapies may receive single agent pemetrexed.

5.2 Eligible Patient Population

The clinicians providing input indicated that clinicians could use pembrolizumab combined with chemotherapy (pemetrexed and platinum) for almost all patients with advanced NSQ NSCLC, with the notable exception of a minority of cases who harbour a targetable mutation in EGFR or ALK. Clinicians agreed that trial criteria from the pivotal trial are applicable in clinical practice. They would use the combination of platinum-pemetrexed with pembrolizumab in patients with PD-L1 < 50% and might either use pembrolizumab alone or platinum–pemetrexed with pembrolizumab in patients with PD-L1 ≥ 50%; depending on various factors such as patient preference, need for rapid response (bulky or aggressive disease), and need to minimize toxicity.

According to Canadian statistics from 2017, there were over 28,000 new cases of lung cancer diagnosed in Canada and over 21,000 lung cancer related deaths. About 50% of lung cancers at presentation have incurable stage IV disease, and many of those with earlier stage disease managed with curative intent ultimately have disease recurrence or relapse. As the non-squamous subset represents the majority of new diagnoses, it is the opinion of clinicians that the latest evidence has the potential to impact best care practices for the great majority of lung cancer patients with incurable disease.

According to clinician input, the patterns of failure with current best available first line therapy, be it platinum/pemetrexed or single agent pembrolizumab, leave a large area of

unmet need. All patients ultimately progress after first line therapy, and many patients are not candidates for second line systemic therapy, although there are options that have known survival benefits (e.g. single agent immunotherapy after progression on platinum doublet chemotherapy). Thus, combining platinum doublet with immunotherapy in first line helps meet this need by providing a treatment strategy in which a patient with incurable lung cancer is guaranteed access to both chemotherapy and immunotherapy and is no longer at risk of having clinical progression before they had an opportunity to receive the other.

Further, in current practice, first line pembrolizumab as a single agent is reserved for those patients who have a documented PD-L1 TPS ≥ 50%. There are some patients for whom the PD-L1 TPS is unknown at the time of starting first line systemic therapy. Reflex testing for PD-L1 status is not standard across Canada, and many centres must refer tissue to outside labs for testing, including out of province, which translates into delays in getting results. Other patients do not have adequate tissue for a valid PD-L1 TPS status to be determined, as current testing requires a minimum of 100 viable tumour cells for analysis. Those patients who have been diagnosed via a procedure that does not provide adequate tissue for that analysis, especially those who have been diagnosed via fine needle aspirate (FNA) or cytology from a malignant pleural effusion, are most likely to fall into this category.

Currently, without a known PD-L1 status, patients have to be treated with platinum and pemetrexed. According to clinicians providing input, this is a disservice to that group of patients, as upwards of one third would be expected to have a PD-L1 TPS ≥50%, and chemotherapy has been proven to be an inferior strategy compared to first line immunotherapy in Keynote 024 when the PD-L1 TPS is ≥50%. Hence, access to pembrolizumab given with first line chemotherapy would prevent this group of patients from missing out on the best therapy by removing the requirement of having biomarker results available.

The clinicians submitting input indicated that the Keynote 189 trial design was very straightforward, and the inclusion and exclusion criteria are reflective of the information that clinicians have readily available in the real world situation. Notably, EGFR and ALK mutations are exclusion criteria for eligibility in the trials. Such criteria can be implemented in practice given that reflex pathologic testing for these mutations has been widely adopted throughout Canada, and in jurisdictions where it has not, testing is standardly available in a timely manner.

5.3 Relevance to Clinical Practice

All clinicians declared that they had experience with using the treatment under review, for instance through clinical trials, manufacturer's access program, or private drug insurance.

Clinicians providing input reiterated that they would use pembrolizumab in combination with pemtrexed and platinum chemotherapy for first line treatment in any patients who are PD-L1 negative or with < 50% expression. Clinicians clarified that the combination of pembrolizumab and platinum/pemetrexed is not a new therapy, but rather a new strategy. Currently, immunotherapy can be accessed upon progression on chemotherapy, and platinum/pemetrexed can be given to those who have progressed on first line pembrolizumab monotherapy. The novelty is in combining these therapies in the first line setting, thus mitigating the risks of progression and clinical deterioration on individual treatments. The assurance that patients receive all of the most effective therapies up front may in part account for the significant survival benefit seen in Keynote 189, along

with the possibility that there is a synergistic effect between chemotherapy and immunotherapy when delivered together.

According to clinicians, the new treatment offers superior efficacy to currently available options (especially in the no/low PD-L1 subgroup), albeit with some decrease in tolerability. For patients with a large tumour burden or rapid progression of clinical symptoms, the use of combination immunotherapy and chemotherapy may quickly provide significant tumour response and thus would be the preferred treatment option.

For the patient group with a PD-L1 TPS <50%, the ability to treat patients with combined chemotherapy and immunotherapy in first line reduces the risk that a given patient would clinically deteriorate before they had the option to receive immunotherapy. Clinicians stressed that the combination of chemotherapy and immunotherapy would not replace platinum/pemetrexed alone as an option in this group, but rather allow for more strategies to best meet an individual patient's needs.

For the patient population with PD-L1 TPS ≥50%, having access to combination immunotherapy and platinum/pemetrexed would not mean that use of single agent pembrolizumab would no longer be employed. Instead, single agent pembrolizumab would be an option that would be best suited for a patient who wished to delay/avoid chemotherapy. Having access to both approaches allows the clinician to work with the patient to best tailor a treatment plan for that individual's cancer in the context of the patient's own personal goals and clinical status.

From the clinician perspective, safety and tolerability of the combination therapy are within acceptable range, and the scientific information does not indicate that there is a compounded risk for any particular adverse effect in patients receiving pembrolizumab with platinum/pemetrexed. Contraindications for this treatment would be active autoimmune inflammatory diseases and poor performance status. Clinicians did not identify subgroups with contraindications to current standard chemotherapy that would be eligible to the new combination.

5.4 Sequencing and Priority of Treatments with Pembrolizumab

The clinicians providing input indicated that the combination treatment is likely to replace the current standard of chemotherapy followed by immunotherapy. It would also replace the reverse sequence (pembrolizumab then platinum/pemetrexed) for high PD-L1 expressers opting for the combination instead of first line pembrolizumab monotherapy. According to the clinicians, there is currently no evidence to support a benefit for second line immunotherapy in patients who have received immunotherapy in first line. Thus, after progression on chemotherapy and pembrolizumab in first line, one would expect patients to be offered standard treatment with second line single agent chemotherapy (e.g. docetaxel) or enrollment in clinical trials.

Clinicians noted that the cost impact per lifetime of treatment of a single patient on the health care budget would be much less than introducing a whole new line of therapy or a new agent into the treatment algorithm.

5.5 Companion Diagnostic Testing

The oncologists providing input noted that companion diagnostic testing for PD-L1 would not be required for this indication, but it may still be desirable to enable the option of pembrolizumab monotherapy in high PD-L1 expressers. EGFR and ALK testing is already routinely reflexively done, so no practice change is required.

5.6 Additional Information

No additional information was provided.

5.7 Implementation Questions

5.1.1 For patients with PD-L1 ≥50%, is there a preference to provide these patients with single agent pembrolizumab or the combination of pembrolizumab with pemetrexed and platinum chemotherapy?

Some clinicians providing input explained that if the options of single agent pembrolizumab or platinum/pemetrexed plus pembrolizumab were both available for a patient with PD-L1 TPS ≥50%, treatment would be based on the patient's own preferences and disease characteristics, and both options should be available. They predict that the majority of these patients will still be treated with single agent pembrolizumab as an effective treatment that allows deferring exposure to chemotherapy. There will be patients with PD-L1 TPS ≥50% for whom combination chemotherapy and immunotherapy would be the most appropriate treatment choice, such as those with a large tumour burden or rapid progression of clinical symptoms, in whom getting a significant tumour response quickly is important. Conversely, other clinicians noted that in the absence of data comparing pembrolizumab alone to chemotherapy/pembrolizumab in the PD-L1 population, they would use pembrolizumab alone.

5.1.2 For patients currently on first-line single-agent pembrolizumab, should pemetrexed be added to their treatment? If so, at what point in their treatment? For patients currently on first-line pemetrexed, should pembrolizumab be added to their treatment? If so, at what point in their treatment?

Clinicians providing input responded that for patients currently on therapy, they would not suggest adding to what they are already on. For those already on platinum/pemetrexed, a PD-L1/PD-1 inhibitor should be offered in second line as per the current standard of care. Clinicians believe that patients currently on single agent pembrolizumab should have access to platinum/pemetrexed in second line. One responding clinician was open to discussing with patients on chemotherapy the possibility of adding pembrolizumab.

5.1.3 Would you use pembrolizumab in this setting for treating metastatic disease after progression on durvalumab? If yes, what would be the appropriate time frame between treatments?

One clinician was inclined to agree with this approach, but admitted that there are no good data to support or refute it. The clinician explained that the mechanism of action is slightly different between durvalumab and pembrolizumab, and the addition of chemotherapy to the pembrolizumab might also make a difference. While the clinician was ready to proceed immediately after durvalumab, another group of clinicians noted that the approach would be valid for patients having developed metastatic disease more than 6 months after stopping durvalumab.

The other clinicians providing input believed that patients who have developed metastatic disease after receiving any immunotherapy given with curative intent, should be considered for therapy with pembrolizumab in conjunction with platinum/pemetrexed. This would extend beyond patients who have received durvalumab after curative intent chemo-radiation for stage III NSCLC, to include other patients who may have received

immunotherapy in the adjuvant setting as part of a clinical trial after curative intent resection of a NSCLC.

Clinicians noted evidence of response in the metastatic setting on re-challenge with immunotherapy (e.g. Checkmate 153), which would suggest that clinical benefit could be seen for patients who progress after having completed a course of adjuvant immunotherapy post surgery or chemo-radiation. According to a group of clinicians, the synergy between chemotherapy and immunotherapy could allow patients who progressed on adjuvant immunotherapy to benefit in this setting. In the absence of a proven lack of efficacy of chemotherapy plus immunotherapy in the metastatic setting after curative intent immunotherapy, it was felt that those patients should not be prevented from receiving potentially beneficial, evidence-based therapy.

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the effect of pembrolizumab in combination with pemetrexed and a platinum-based drug, followed by maintenance pemetrexed, for the treatment of metastatic non-squamous (NSQ) NSCLC in adults with no EGFR or ALK genomic tumour aberrations and no prior systemic treatment for metastatic NSQ NSCLC.

Note: A supplemental issue most relevant to the pCODR review and to the Provincial Advisory Group were identified while developing the review protocol and is outlined in section 7.

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

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the CGP and the pCODR Methods Team. Studies were chosen for inclusion in the review based on the criteria in the table below. The literature search strategy and detailed methodology used by the from patient advocacy groups are those in bold.

Table 6.1: Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Published or unpublished RCTs	Adult patients with metastatic NSQ NSCLC with no EGFR or ALK genomic tumor aberrations, and no prior systemic chemotherapy treatment for metastatic NSCLC <u>Subgroups:</u> • Histologic type (adenocarcinoma vs. unspecified NSCLC) • ECOG PS (0 vs 1 vs. ≥2) • PD-L1 TPS (<1% vs ≥1%) • Type of platinum-based chemotherapy (cisplatin vs carboplatin) • Previous	• Pembrolizumab plus platinum-doublet chemotherapy KN-189 Trial protocol: Pembrolizumab (200 mg) + IV cisplatin (75mg/m^2) or carboplatin (AUC, 5) + pemetrexed (500mg/m^2) every 3 weeks followed by maintenance pemetrexed (500mg/m2) every 3 weeks	• Pembrolizumab monotherapy • Placebo plus chemotherapy KN-189 Trial protocol: Placebo + IV cisplatin (75mg/m^2) or carboplatin (AUC, 5) + pemetrexed (500mg/m^2) every 3 weeks followed by maintenance pemetrexed (500mg/m2) every 3 weeks	• **OS** • **PFS** • **QOL** • Time to progression • Tumor response rate (ORR, CR, PR) • Duration of response • Time to deterioration of symptoms Safety • AEs • SAEs • WDAEs

Table 6.1: Selection Criteria				
Clinical Trial Design	**Patient Population**	**Intervention**	**Appropriate Comparators***	**Outcomes**
	treatments for non-metastatic cancer (radiotherapy vs neoadjuvant therapy vs adjuvant therapy) • Smoking status (smoker vs. non-smokers • Gender (male vs. female) • Age (<65 vs ≥65 years)			

AE = adverse events; **AUC** = target area under the curve (desired carboplatin exposure); **CR** = complete response; **ECOG PS** = Eastern Cooperative Oncology Group Performance Status Scale; **IV** = intravenous; **NSQ** = Non-Squamous cell; **NSCLC**= Non-small Cell Lung Cancer; **ORR** = overall response rate; OS=overall survival; **PFS** = progression-free survival; **PR** = partial response; **QOL** = quality of life; **RCT** = randomized controlled trial; **SAE** = serious adverse events; **TPS** = tumour proportion score; **WDAE** = withdrawals due to adverse events

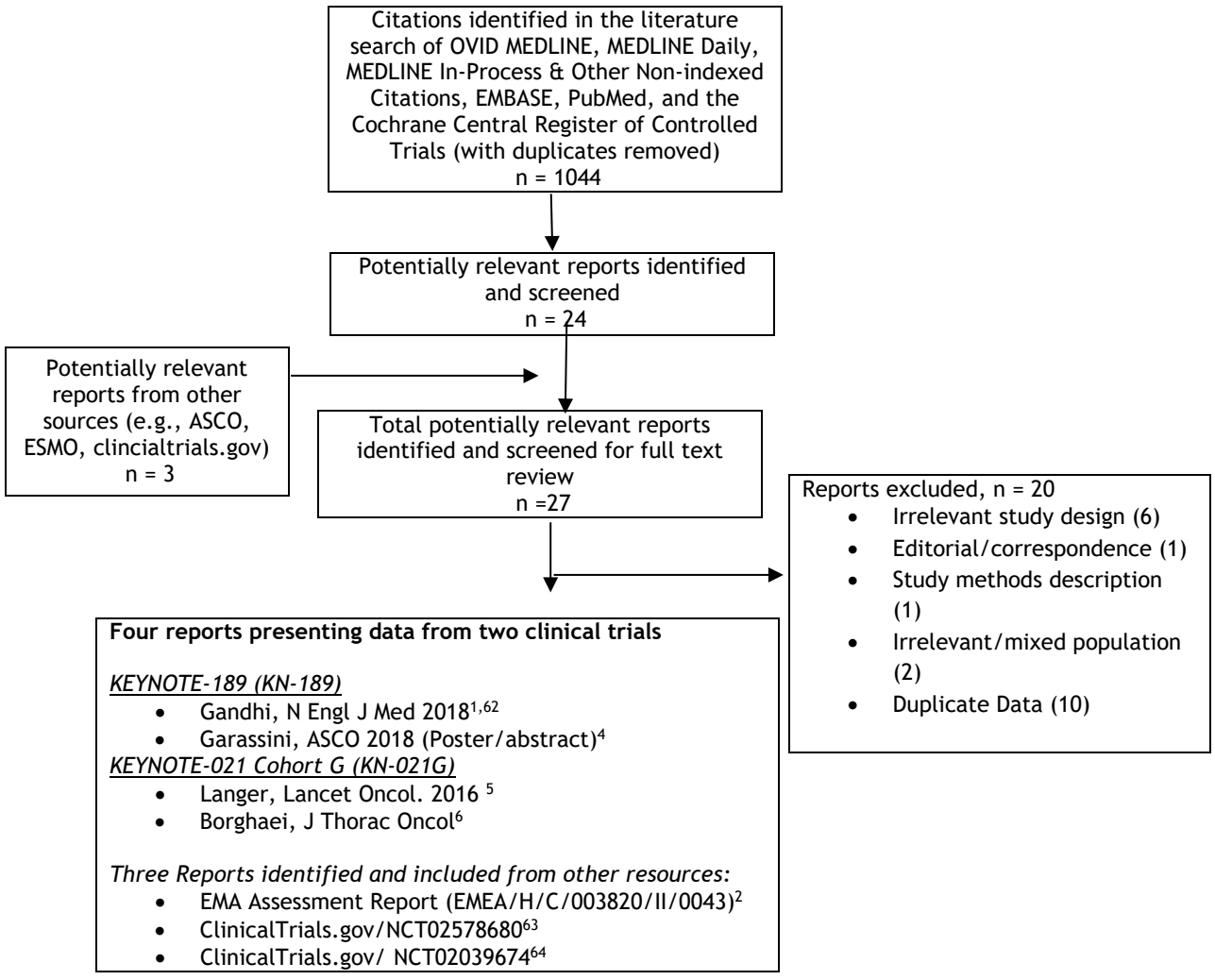
** Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions)*

6.3 Results

6.3.1 Literature Search Results

Of the 27 potentially relevant citations identified, seven citations, reporting data from two clinical trials, were included in the pCODR systematic review, and 20 citations were excluded. Studies were excluded because they were irrelevant study types,[43-48] only described study design,[49] or included mixed or irrelevant study population,[50,51] Comments or editorials,[52] as well as conference abstracts and journal articles reporting duplicate data from the included full articles[53-61] were also excluded. Figure 6.1 illustrates the PRISMA flow Diagram for the study selection process.

Figure 6.1. PRISMA Flow Diagram for Inclusion and Exclusion of studies



Note: Additional data related to the KN-189 and KN-021G trials were also obtained through requests to the Submitter by pCODR [65]

6.3.2 Summary of Included Studies

6.3.2.1 Detailed Trial Characteristics

Table 6.2: Summary of Trial Characteristics of the Included Studies

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
Study: KN-189[1,2] NCT02578680[63] Characteristics: ongoing phase III, international, multi-center, randomized (2:1 ratio), double-blind, placebo-controlled trial N randomized = 616 n treated = 607 Number of centres and number of countries: 126 sites in 16 countries Patient Enrolment Dates 26-FEB-2016 to 06-MAR-2017 Data cut-off First interim analysis: 08_NOV-2017 Final Analysis Date (Estimated Study Completion Date: 15-APR-2019)[63] Funding: Merck	Key Inclusion Criteria: – ≥18 years of age – Untreated stage IV NSQ NSCLC – No sensitising EGFR or ALK alterations – ECOG PS 0 or 1 – Provision of sample for PD-L1 assessment Key Exclusion Criteria: – Active CNS metastases and/or carcinomatous meningitis – Pneumonitis requiring steroid therapy – -Prior systemic cytotoxic chemotherapy for metastatic disease prior to the first dose of the study treatment – Radiation therapy to the lung (> 30 Gy) within 6 months of the first dose of trial treatment	Intervention: Pembrolizumab (200 mg) + IV cisplatin (75mg/m^2) or carboplatin (AUC 5) + pemetrexed (500mg/m^2) every 3 weeks followed by maintenance pemetrexed (500mg/m2) every 3 weeks Comparator: Placebo + IV cisplatin (75mg/m^2) or carboplatin (AUC 5) + pemetrexed (500mg/m^2) every 3 weeks followed by maintenance pemetrexed (500mg/m2) every 3 weeks	Primary: – OS – PFS Secondary: – ORR – DOR – Safety – Exploratory: – PROs – effect of PD-L1 expression on efficacy
Study: KN-021[2,5,6] NCT02039674[64] Characteristics: ongoing phase I/II, multi-centre, randomized (1:1 ratio) controlled trial N randomized = 616 n treated = 607 Number of centres and number of countries: 26 sites in the United States and Taiwan Patient Enrolment Dates 25-NOV-2014 to 25-JAN-2016	Key Inclusion Criteria: – ≥18 years of age – Untreated stage IV NSQ NSCLC – No sensitising EGFR or ALK alterations – ECOG PS 0 or 1 – Provision of sample for PD-L1 assessment Key Exclusion Criteria: – Active CNS metastases – Active interstitial lung disease pneumonitis requiring steroid therapy – Radiation therapy to	Intervention: Pembrolizumab (200 mg) + IV carboplatin (AUC 5) + pemetrexed (500mg/m^2) every 3 weeks followed by maintenance pemetrexed (500mg/m2) every 3 weeks Comparator: IV carboplatin (AUC 5) + pemetrexed (500mg/m^2)	Primary: – ORR Secondary: – PFS – OS – DOR – Safety

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
Data cut-off First interim analysis: 31-December-2016 Updated analysis: 31- MAY-2017 01-DEC-2017 Final Analysis Date ?? Funding: Merck	the lung (> 30 Gy) within 6 months of the first dose of trial treatment – Ongoing use of systemic corticosteroids or other immunosuppressive treatment	every 3 weeks followed by maintenance pemetrexed (500mg/m2) every 3 weeks	

ALK = anaplastic large-cell lymphoma kinase; **CNS** = central nervous system; **DOR** = duration of response; **ECOG PS**= Eastern Cooperative Oncology Group performance score; **EGFR =** epidermal growth factor receptor; **IV** = intravenous; **mg =** milligram**; mg/m^2** = milligram per square meter of body surface; **NSCLC**= non-small cell lung cancer; **NSQ** = non squamous; **ORR** = objective response rate; **OS**= overall survival; **PD-L1** = programmed death-ligand1; **PFS** = progression-free survival

[Table 6.3]: Select quality characteristics of included studies of pembrolizumab in patients with non-squamous 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-189	Pembrolizumab vs. placebo Both in combination with platinum-pemetrexed chemotherapy	PFS and OS	570	616	Yes central computer based randomization; 2:1 ratio	Yes I VRS/IWRS	Yes, partially pembrolizumab/ placebo: double blind chemotherapy: open-label	Yes	No Anticipated in April-2019[63]	No	Yes
KN-021G	Pembrolizumab in combination with carboplatin-pemetrexed chemotherapy vs. carboplatin-pemetrexed chemotherapy	ORR	108	123	Yes central computer based randomization; 2:1 ratio	Yes I VRS/IWRS	No Open-label	Yes	No Anticipated in April 2020[2]	No	Yes

IVRS/IWRS: interactive voice-response /and Web response system; **OS**= overall survival; **PFS** = progression-free survival

a) Trials

KEYNOTE-189 (KN-189) is an ongoing phase III, international, multi-center, randomized, double-blind, placebo-controlled trial to compare the efficacy and safety of combination therapy with pembrolizumab plus pemetrexed and a platinum-based drug (hereafter referred to as the pembrolizumab combination arm) versus saline placebo plus pemetrexed and a platinum-based drug (hereafter referred to as the placebo combination arm) as first-line therapy in patients with metastatic NSQ NSCLC in whom there were no EGFR or ALK mutations.[1] The trial was conducted in at 126 sites in 16 countries, including 6 sites in Canada.[1]

Trial design

The KN-189 study design is illustrated in Figure 6.2. The trial consisted of the following phases:[62]

Screening Phase: During a 28 days assessment period prior to randomization, potential study participants were screened for eligibility; informed consent was obtained; and tumor assessment and clinical/laboratory examinations were performed.

Treatment Phase: Eligible patients were randomized to receive the pembrolizumab plus pemetrexed-platinum chemotherapy combination (n=410) or placebo plus pemetrexed-platinum chemotherapy (n=206) on Day 1 of each 3-week (Q3W) dosing cycle. Treatment was to be continued until the completion of 35 treatments (approximately two years) with pembrolizumab/placebo, radiographic disease progression, unacceptable toxicities, investigator's decision to stop the treatment, or patient withdrawal of consent.

Post-Treatment (follow-up) Phase: Patients were followed for up to two years. Response to treatment was assessed, using radiographic imaging and according to the Response Evaluation Criteria in Solid Tumors (RECIST; version 1.1), at 6 weeks (42 ± 7 days) and 12 weeks (84 ± 7 days) and then every 9 weeks (63 ± 7 days) for the first 48 weeks, and every 12 weeks (84 ± 7 days)

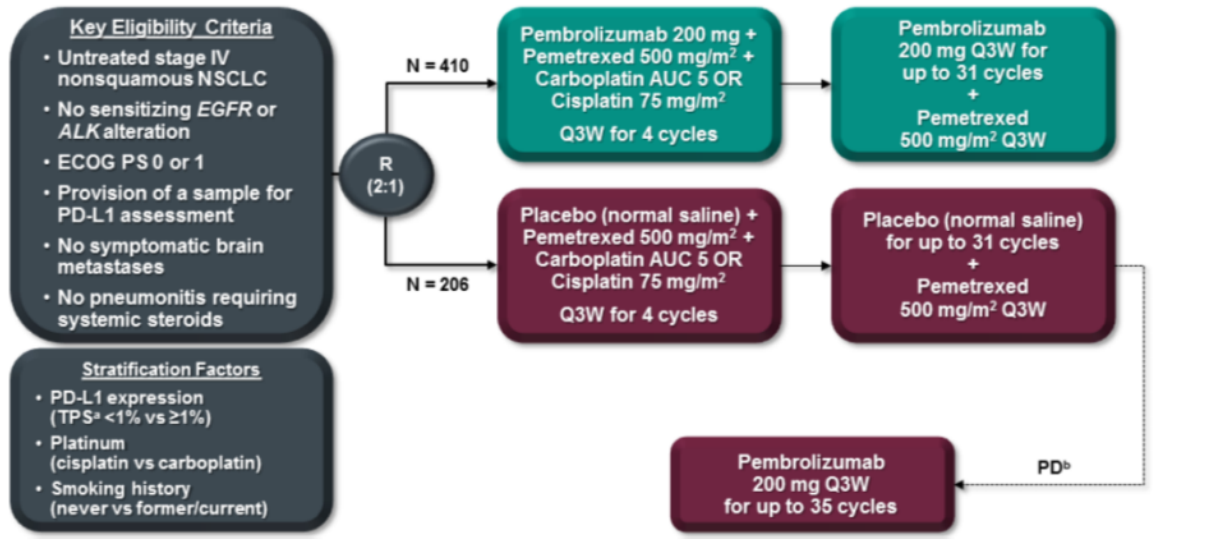
thereafter. Post-treatment follow-up visits continued until initiating a non-study cancer treatment, experiencing disease progression, death, withdrawing consent, or becoming lost to follow-up. Patients who discontinued trial treatment for a reason other than disease progression were continued with regularly scheduled assessments for disease progression, death, or initiation of a new antineoplastic therapy.

AEs were monitored for a minimum of 30 days, even if the patient started new anti-cancer treatment. Data on serious AEs was collected for up to 90 days following cessation of the study treatment, or 30 days after cessation of treatment if the patient initiated new anticancer therapy, whichever occurred earlier. Patients were contacted every 12 weeks to assess survival during follow-up.

Second Course (retreatment) Phase: Patients who attained a complete response could consider stopping trial treatment. Initial responders (complete response [CR], partial response [PR], or stable disease [SD]) during the Treatment Phase on pembrolizumab, who had a disease progression at any time during the 2-year follow-up period, were eligible to receive up to 12 months of pembrolizumab monotherapy in the Second Course Phase. After the Second Course Phase, patients were followed for up to two years, with no option for retreatment with on-study pembrolizumab.

Crossover Phase: Patients who experienced documented disease progression during the Treatment Phase had their treatment assignment un-blinded and could continue on open-label pembrolizumab monotherapy in the Crossover Phase. Crossover to pembrolizumab was not permitted earlier than 21 days after the patient's last dose of chemotherapy (regardless of the time of progression).

Figure 6.2: KN-189 Study Design



[a]Percentage of tumor cells with membranous PD-L1 staining assessed using IHC 22C3 pharmDx assay. [b]Patients could crossover during the induction or maintenance phase. To be eligible for crossover, PD must have been verified by blinded, independent central radiologic review and all safety criteria had to be met

AUC: area under the concentration-time curve; ECOG: Eastern Cooperative Oncology Group NSCLC: non-small cell lung cancer; TPS: tumour proportion score; PS: performance status; Q3W: every 3 weeks

Source: Gandhi et al. AACR 2018[16]

Source: [Merck Oncology KEYTRUDA® Clinical Rationale, Figure 4][65]

Randomization and treatment concealment

Randomization was performed centrally using an integrated interactive voice-response and Web response system (IVRS/IWRS). Patients were assigned randomly in a 2:1 ratio to the pembrolizumab combination arm and placebo combination arm, respectively. The choice of cisplatin or carboplatin treatment was determined by the investigators prior to randomization and documented in the IVRS/IWRS.[62]

Randomization was stratified according to the following factors:[62]

- PD-L1 expression (tumor proportion score, ≥1% vs. <1%)
- Choice of platinum-based drug (cisplatin vs. carboplatin)
- Smoking history (never vs. former or current)

Study participants, investigators, and Sponsor personnel or delegate(s) who were involved in the treatment administration or clinical evaluation of patients were blinded to the treatment assignment (i.e., pembrolizumab or saline placebo); however, the chemotherapy agents were administered on an open-label basis. The study site's un-blinded pharmacist obtained each patient's study identification number and study drug assignment from IVRS/IWRS, prepared the assigned solution (pembrolizumab/saline placebo), and provided the researchers with identically-packaged ready to-use blinded infusion solutions.[62]

Study endpoints and disease assessment

KN-189 has two primary end points:

- Overall survival (OS), defined as time from randomization to death from any cause; and
- Progression-free survival (PFS), defined as time from randomization to disease progression (per RECIST version 1.1), as assessed by blinded, independent central radiologic review (BICR), or death from any cause, whichever occurred first.

The secondary end points included overall response rate (ORR; as per RECIST version 1.1), duration of response (DOR), and safety. ORR was defined as the proportion of subjects who have a CR or a PR.DOR was defined as time from first documented CR or PR to disease progression or death. Both ORR and DOR were assessed by BICR. Exploratory end points included the effect of PD-L1 expression on efficacy, and patient-reported outcomes (PROs).[62]

Response to treatment was assessed, using radiographic imaging. Treatment-based decisions were based on the immune-related RECIST criteria (irRECIST).

Adverse Events (AEs) were graded in severity according to the guidelines outlined in the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.[62]

PROs were evaluated using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30), Lung Cancer 13 (QLQ-LC13), and the EuroQoL 5 Dimension (EQ-5D). EORTC QLQ-C30 and QLQ-LC13 were administered by trained site personnel and completed electronically by patients at cycles 1–5; then every third cycle (every 9 weeks) through the remainder of year 1; every fourth cycle (every 12 weeks) during years 2 and 3 until disease progression (while on study treatment); and at the treatment discontinuation and the 30-day safety follow-up visits. Patients completed the EORTC QLQ-C30 prior to the EORTC QLQ-LC13. The questionnaires were completed before study treatment administration, AE assessment, and disease status notification.

Statistical analysis

Interim analyses and adjustment for multiplicity[1,62]

One interim analysis of PFS and two interim analyses of OS were planned in addition to the respective final analyses (Table 6.4).

The first interim analysis was planned to be performed after enrollment was complete and after incidence of approximately 370 PFS events and 242 deaths. The analysis was performed at the data cut-off date of 08_NOV-2017, when 410 PFS events and 235 deaths had been observed.

KN-189 is an ongoing trial and the second interim analysis (final analysis for PFS) was initially planned to be performed after approximately 468 PFS events and approximately 332 death events; however, this pre-planned second interim analysis was removed at KN-89 protocol amendment 9 as the study hypotheses for OS, PFS, and ORR were supported at the first interim analysis (06-NOV-2017 data cut-off).[3] The final analysis will evaluate OS only and will be performed after approximately 416 deaths have been observed.

The overall type I error rate was strictly controlled at one sided α=0.025 for both PFS and OS, based on the Lan-DeMets O'Brien-Fleming spending function. Between the endpoints, the type I error was controlled by the following rollover rule:

The total type I error allocated to PFS (0.0095) was subject to rollover to OS if the PFS test was positive. The type I error allocated to OS (0.0155) was subject to rollover to PFS if the OS test was positive. Furthermore, the total type I error (0.025) was subject to rollover to ORR at Interim Analysis 1 if the PFS and OS tests were both positive (Figure 6.3).

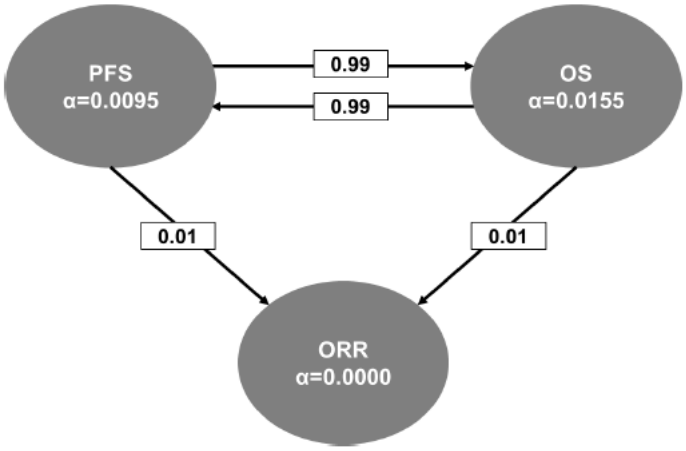
At the first interim analysis (08_NOV-2017), both BICR assessed PFS and OS were tested in a group-sequential fashion (based on the Lan-DeMets O'Brien-Fleming spending function). On the basis of the observed number of events, the multiplicity adjusted, one-sided alpha levels were 0.00559 for progression-free survival and 0.00128 for overall survival.[1]

Table 6.4: Pre-planned analyses of the KN_189 trial

Analysis	Estimated number of PFS events	Estimated number of deaths	Approximate timing	Outcomes
Interim Analysis 1	370	242	~19 months after first patient enrolled	PFS OS ORR†
Interim Analysis 2	468	332	~26 months after first patient enrolled	PFS (Final) OS
Final Analysis	NA	416	~35 months after first patient enrolled	OS

NA = not applicable; **PFS** = progression-free survival; **ORR** = overall response rate; **OS** = overall survival
† tested after superiority of pembrolizumab plus pemetrexed-platinum chemotherapy was demonstrated in PFS and OS
Source: [KN-189 Protocol/Amendment No: 189-07; Section 8.7][62]

Figure 6.3: Type I error reallocation strategy in the KN-189 trial



Source: From NEJM, Gandhi, L., et al., Pembrolizumab plus Chemotherapy in Metastatic Non-Small-Cell Lung Cancer, Volume No. 378 supplement, Page No. 2078-92 Copyright © (2018) Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society. [Figure S2][1]

Sample size and power calculation[1,62]

The trial was designed as an event driven study. The sample size was estimated at 570 to provide 90% power for detecting a hazard ratio (HR) of 0.70 for PFS at on sided α=0.0095 (based on 468 PFS events) and a HR of 0.70 for OS at a one-sided α=0.0155 (based on 416 deaths) for the comparison between the pembrolizumab and placebo-arms.

For hypothesis testing of PFS, the study was estimated to have approximately:

- 72% power for detecting a HR of 0.70 at one-sided α = 0.0095, and 84% power for detecting a HR of 0.70 at one-sided α = 0.025, with 370 PFS events at the first interim analysis
- 90% power for detecting a HR of 0.70 at one-sided α = 0.0095, and 96% power for detecting a HR of 0.70 at one-sided α = 0.025, with 468 PFS events at the final PFS analysis (second interim analysis)

For hypothesis testing of OS, the study was estimated to have approximately:

- 37% power for detecting a HR of 0.70 at one-sided α = 0.0155, and 47% power for detecting a HR of 0.70 at one-sided α = 0.025 (when the PFS test is significant), with 242 deaths at the first interim analysis
- 73% power for detecting a HR of 0.70 at one-sided α = 0.0155, and 80% power for detecting a HR of 0.70 at one-sided α = 0.025 (when the PFS test is significant), with 332 deaths at the second interim analysis
- 90% power for detecting a HR of 0.70 at one-sided α = 0.0155, and 93% power for detecting a HR of 0.70 at one-sided α = 0.025 (when the PFS test is significant), with 416 deaths at the final analysis

Based on the historical data, the durations of PFS and OS were assumed to follow an exponential distribution with median values of 6.5 months for PFS and 13 months for OS. The exponential dropout rates were assumed to be 0.35% per month for PFS and 0.1% per month for OS.

Efficacy analyses[1,62]

The efficacy analyses were based on data from the intention-to-treat (ITT) population. All randomized patients were included in the analysis, and were counted in the treatment arm to which they were randomly assigned.

The primary hypotheses for PFS and OS were evaluated by comparing pembrolizumab to saline placebo (both in combination with pemetrexed-platinum based chemotherapy) using a stratified Log-rank test. The HR was estimated using a stratified Cox regression model. Event rates over time were estimated within each treatment arm using the Kaplan-Meier method. The randomization stratification factors were applied to all stratified efficacy analyses. A summary of the statistical methods used for the efficacy analyses is provided in Table 6.5.

Safety analysis[1,62]

The analysis of safety was based on data from as-treated population, which included all patients who had undergone randomization and received at least one dose of the assigned combination therapy. Patients who received incorrect study treatment for the entire treatment period were included in the treatment arm corresponding to the treatment they received. Patients who received the incorrect study treatment for one cycle but received the correct treatment for all other cycles were analyzed according to the correct treatment arm.

The safety analysis followed a tiered approach (Table 6.6). No Tier 1 safety endpoints were specified for KN-189; all protocol specified safety endpoints were either Tier 2 or Tier 3. Tier 2 parameters were planned to be assessed using point estimates, and 95% confidence intervals were provided for between-group comparisons. Risk difference between the two treatment arms was analyzed using the Miettinen and Nurminen method. For Tier 3 safety endpoints, only point estimates were provided. In the primary safety analysis, patients in the placebo combination arm who crossed over to pembrolizumab (n=67) were censored at the time of crossover. An exploratory safety analysis was to be conducted for the crossover population including all safety events starting from the date of first dose of pembrolizumab.

Table 6.5: Summary of the analysis Strategies used for key efficacy endpoints

Endpoint/Variable (Description, Time Point)	Statistical Method†	Analysis Population	Missing Data Approach
Primary Endpoints			
PFS per RECIST 1.1 by central imaging vendor	Test: Stratified Log-rank test to assess the treatment difference Estimation: Stratified Cox model with Efron's tie handling method to assess the magnitude of treatment difference	ITT	• Primary censoring rule • Sensitivity analysis 1 • Sensitivity analysis 2
OS	Test: Stratified Log-rank test to assess the treatment difference Estimation: Stratified Cox model with Efron's tie handling method to assess the magnitude of treatment difference	ITT	Model based (censored at last known alive date)
Secondary Endpoint			
ORR per RECIST 1.1 by central imaging vendor	Stratified M&N method with sample size weights††	ITT	Subjects without assessments are considered non-responders and conservatively included in denominator

† Statistical models are described in further detail in the text. For stratified analyses, the stratification factors used for randomization (Section 5.4) will be applied to the analysis.

†† Miettinen and Nurminen method

Source: [KN-189 Protocol; Amendment # 189-07, Table 12][65]

Table 6.6: Summary of the analysis strategies used for safety endpoints

Safety Tier	Safety Endpoint	95% CI for Treatment Comparison	Descriptive Statistics
Tier 2	Any AE	X	X
	Any Serious AE	X	X
	Any Grade 3-5 AE	X	X
	Any Drug-Related AE	X	X
	Any Serious and Drug-Related AE	X	X
	Any Grade 3-5 and Drug-Related AE	X	X
	Dose Modification due to AE	X	X
	Discontinuation due to AE	X	X
	Death		
	Specific AEs, SOCs, or PDLCs (incidence ≥4 of subjects in one of the treatment groups)	X	X
Tier 3	Specific AEs, SOCs or PDLCs (incidence <4 of subjects in all of the treatment groups)		X
	Change from Baseline Results (Labs, ECGs, Vital Signs)		X

AE=Adverse event; CI=Confidence interval; ECG=Electrocardiogram; Labs=Laboratories; PDLC=Predefined limits of change; SOC=System organ class;

Source:[EMA Assessment Report (EMEA/H/C/003820/II/0043); Table 35, page 47/89][2]

Patient-reported outcomes analyses[4,62]

The PRO analyses included all patients who received at least one dose of the study treatment and completed at least one PRO instrument.

Between-group comparisons of the mean change from baseline in EORTC QLQ-C30 global health status/ quality of life score were based on a constrained longitudinal data analysis (cLDA) model, with the PRO score as the response variable, and treatment by study visit interaction and stratification factors for randomization as covariates. Analyses of time to true deterioration in composite of cough (LC13-Q1), chest pain (LC13-Q10), or dyspnea (C30-Q8) were based on the stratified log-rank test and the stratified Cox model with treatment as covariate EORTC QLQ-C30 and QLQ-LC13 scores were standardized to a scale ranging from 0 to 100 by linear transformation. Proportions of patients with improved, stable, or deteriorated EORTC QLQ-C30 global health status/quality of life scores (defined according to ≥10-point change in score) at the specified assessment time points were summarized based on multiple imputation for missing data with missing at random assumption. There was no adjustment for multiplicity.[4]

The first interim analysis of the KN-189 trial (08-NOV-2017) compared mean score changes from baseline to weeks 12 and 21 on the EORTC QLQ-C30 and QLQ-LC13 global health status/ quality of life ,functional, and symptom subscales between the pembrolizumab and placebo combination arms. The analysis also evaluated time to true deterioration in the composite endpoint of cough, chest pain or dyspnea in the pembrolizumab and placebo combination arms. Time to true deterioration was defined as the time to first onset of a ≥10-point increase from baseline, confirmed by a second adjacent ≥10-point increase from baseline. The results were presented with two-sided p-values. No adjustment was made for multiplicity.[4]

Protocol amendments

The original study protocol was issued on 28-September-2015; and there were eight protocol amendments. A summary of the major changes made to the protocol during the conduct of the

KN-189 study is provided in Table 6.7. Additionally, the protocol Amendment 09 (issued on 08-Aug-2018) removed the pre-planned second interim analysis because the study hypotheses for PFS, OS and ORR had been supported at the first interim analysis with data cut-off of 08-NOV-2017; and all of the alpha was spent.[3]

Table 6.7: Major protocol amendments in the KN-189 trial

Protocol Amendment	Most relevant changes
02 (10 Feb 2016)	Corrected the reporting periods for all AE categories following cessation of study treatment, from 14 to 90 days for SAEs or 30 days in the event of initiation of new anti-cancer therapies; removed inclusion criterion requiring TSH within normal limits; updated the list of concomitant medications allowed and prohibited; updated required assessments for PK analysis, quality of life and safety follow-up
04 (16 Mar 2017)	Revised the SAP and objectives according with FDA input to place more emphasis on OS; addition of exploratory objective n.1 to address the importance of PD-L1 expression on efficacy and objective n.8 to address the importance of outcomes post-Crossover
07 (06 Nov 2017)	Promoted OS to primary endpoint; timing of IA1 was changed to occur at approximately 370 PFS rather than 300 events PFS as previously defined, to provide a more robust analysis of the data, focusing on OS and adjust the alpha spending. In addition, subject accrual was greater than originally expected and estimated timing of interim analyses can now be calculated based on actual enrollment (N=616), rather than the planned enrollment (N=570).

Source:[EMA Assessment Report (EMEA/H/C/003820/II/0043); page 22/89][2]

b) Populations

Eligibility criteria[62]

Eligible patients were adult (≥18 years of age) patients with previously untreated NSQ NSCLC who had not received prior systemic chemotherapy treatment for their advanced or metastatic NSCLC, and in whom EGFR or ALK-directed therapy was not indicated. Other key eligibility criteria included:

- Histologically-confirmed or cytologically confirmed diagnosis of stage IV NSQ NSCLC
- Documentation of absence of tumor activating EGFR mutations AND absence of ALK gene rearrangements
- Measurable disease per RECIST version 1.1, as determined by the local site investigator/radiology assessment
- Eastern Cooperative Oncology Group performance status of 0 or 1
- Adequate organ function according to the protocol-defined values

The trial included patients who had not received prior systemic treatment for their advanced/metastatic NSCLC. However, patients who received adjuvant or neoadjuvant therapy would be eligible if the adjuvant/neoadjuvant therapy was completed at least 12 months prior to the development of metastatic disease.

KN-189 excluded patients who had:

- Active central nervous system metastases and/or carcinomatous meningitis
- Current pneumonitis or history of non-infectious pneumonitis that required steroid therapy

- Received prior systemic cytotoxic chemotherapy for metastatic disease prior to the first dose of the study treatment
- Received antineoplastic biological therapy (e.g., erlotinib, crizotinib, cetuximab)
- Undergone major surgery <3 weeks prior to first dose of the study treatment
- Received radiation therapy to the lung (> 30 Gy) within 6 months of the first dose of trial treatment

Characteristics of the study population[1,2]

A total of 616 patients from 118 sites who had met all the eligibility criteria were randomized to the pembrolizumab combination arm (n = 410) or the placebo combination arm (n = 206). The baseline demographic and disease characteristics of the KN-189 population are summarized in Table 6.8. As the table shows, the baseline characteristics were generally well balanced between the two study arms; except, in the placebo combination arm there was a higher proportion of patients who were female (47.1% versus 38.0% in the pembrolizumab combination arm; p=0.04). The proportion of younger patients who were younger than 65 years was also slightly higher in the placebo combination arm (55.8% versus 48% in the pembrolizumab combination arm; p = NS). Eighteen percent of patients in the pembrolizumab combination arm and 17% of patients in the placebo combination arm had a history of brain metastases at baseline.

Overall, the majority of patients were White (94%) and current or former smokers (88%). A PD-L1 tumor proportion score of ≥1% was reported in 63.4% of the patients in the pembrolizumab combination arm and in 62.1% of those in the placebo combination arm. Carboplatin was selected as the platinum-based chemotherapy agent in 72.4% of the patients in the pembrolizumab combination arm and 71.8% of patients in the placebo combination arm.

Table 6.8: Baseline demographic and disease characteristics of the KN-189 population

	Pembro Combo		Control	
	n	(%)	n	(%)
Subjects in population	410		206	
Gender				
Male	254	(62.0)	109	(52.9)
Female	156	(38.0)	97	(47.1)
Age (Years)				
< 65	197	(48.0)	115	(55.8)
>= 65	213	(52.0)	91	(44.2)
Mean	63.2		62.8	
SD	9.4		9.1	
Median	65.0		63.5	
Range	34 to 84		34 to 84	
Race				
Asian	10	(2.4)	8	(3.9)
Black Or African American	11	(2.7)	3	(1.5)
White	387	(94.4)	194	(94.2)
Missing	2	(0.5)	1	(0.5)
Ethnicity				
Hispanic Or Latino	5	(1.2)	7	(3.4)
Not Hispanic Or Latino	384	(93.7)	190	(92.2)
Not Reported	9	(2.2)	4	(1.9)
Unknown	12	(2.9)	5	(2.4)
Region				
US	85	(20.7)	34	(16.5)
Ex US	325	(79.3)	172	(83.5)
Region				
EU	243	(59.3)	131	(63.6)
Ex EU	167	(40.7)	75	(36.4)
Geographic Region				
East-Asian	4	(1.0)	6	(2.9)
Non-East Asian	406	(99.0)	200	(97.1)
Smoking Status				
Never Smoker	48	(11.7)	25	(12.1)
Former/Current Smoker	362	(88.3)	181	(87.9)
ECOG				
0	186	(45.4)	80	(38.8)
1	221	(53.9)	125	(60.7)
2	1	(0.2)	0	(0.0)
Missing	2	(0.5)	1	(0.5)
Histology				
Adenocarcinoma	394	(96.1)	198	(96.1)
NSCLC NOS	10	(2.4)	4	(1.9)
Other	6	(1.5)	4	(1.9)
Brain Metastasis Status at Baseline				
Yes	73	(17.8)	35	(17.0)
No	337	(82.2)	171	(83.0)
Baseline Tumor Size (mm)				
Subjects with data	402		200	
Mean	97.5		105.3	
SD	67.5		66.5	
Median	84.0		87.2	
Range	11.5 to 422.1		10.3 to 466.5	
PD-L1 Status				
< 1%	127	(31.0)	63	(30.6)
>= 1%	260	(63.4)	128	(62.1)
NOT EVALUABLE	23	(5.6)	15	(7.3)
Platinum Chemotherapy				
Cisplatin	113	(27.6)	58	(28.2)
Carboplatin	297	(72.4)	148	(71.8)
Prior Radiation				
Yes	84	(20.5)	46	(22.3)
No	326	(79.5)	160	(77.7)
Prior Thoracic Radiation				
Yes	28	(6.8)	20	(9.7)
No	382	(93.2)	186	(90.3)
Prior Adjuvant Therapy				
Yes	25	(6.1)	14	(6.8)
No	385	(93.9)	192	(93.2)
Prior Neo Adjuvant Therapy				
Yes	5	(1.2)	6	(2.9)
No	405	(98.8)	200	(97.1)
Database Cutoff Date: 08NOV2017				

Source: [P189V01MK3475: adsm-adsl]

Source:[EMA Assessment Report (EMEA/H/C/003820/II/0043); Table 7,page 23/89][2]

c) Interventions

Treatment Dosing Schedule

As shown in Figure 6.2, patients in the KN-189 trial were randomized to receive either:

- pembrolizumab 200 mg (30-minute intravenous [IV] infusion) + pemetrexed 500 mg/m^2 (10-minute IV infusion with vitamin supplementation) + the investigators' choice of cisplatin 75 mg/m^2 or carboplatin AUC 5 all on Day 1 every 3 weeks for 4 cycles followed by pembrolizumab 200 mg + pemetrexed 500 mg/m^2 every 3 weeks (pembrolizumab combination arm);

  OR

- saline placebo (30-minute IV infusion) + pemetrexed 500 mg/m^2 (10-minute IV infusion with vitamin supplementation) + the investigators' choice of cisplatin 75 mg/m^2 or carboplatin AUC 5 all on Day 1 every 3 weeks for 4 cycles, followed by saline placebo + pemetrexed 500 mg/m^2 every 3 weeks (placebo combination arm).[1]

Pembrolizumab or saline placebo was to be administered for a maximum of 35 study treatments or until disease progression. Pemetrexed was to be administered until disease progression. All study treatments were administered on an out-patient basis.[62]

After a median follow-up of 10.5 months (range 0.2 to 20.4), the mean (±SD) duration of treatment was 7.4 (±4.7) months (10.9 cycles) in the pembrolizumab combination arm and 5.4 (±4.3) months (8.1 cycles) in the placebo combination arm. The four pre-planned doses of cisplatin or carboplatin were received by 82.5% and 74.3% of patients the pembrolizumab and placebo combination arms, respectively; 76.5% of patients in the pembrolizumab combination arm and 66.8% of those in the placebo combination arm received five or more doses of pemetrexed.[1]

In the placebo-arm, patients with verified disease progression (by independent central imaging review) were permitted to crossover to pembrolizumab monotherapy. A total of 67 (32.5%) patients in the placebo combination arm crossed over during the trial to receive pembrolizumab monotherapy after disease progression.[62]

Dose modifications

Pembrolizumab dose reductions were not permitted. Pembrolizumab treatment could be interrupted or discontinued due to toxicity. In case of the occurrence of AEs that were, in the opinion of the Investigator, clearly related to one of the chemotherapy agents, the dose of one agent (and not the other agent) could be reduced. For toxicities that were related to the combination of both chemotherapy agents, both drugs should be modified according to recommended dose modifications (Table 6.9) and the related guidelines. If the toxicity was related to the combination of three agents, all three agents should be reduced (if applicable), interrupted or discontinued according to the recommended dose modifications. Patients could discontinue chemotherapy and continue on pembrolizumab or placebo alone. Similarly, they could discontinue pembrolizumab or placebo and continue on chemotherapy alone, if appropriate. Chemotherapy could be interrupted for a maximum of 6 weeks; pembrolizumab could be interrupted for a maximum of 12 weeks.[62]

Scheduled treatment interruptions were permitted in the case of medical or surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, subject vacation, and/or holidays). Patients were to be placed back on study treatment within three weeks of the scheduled interruption.[62]

Table 6.9: Dose modifications for KN-189 medications

	Dose Level 0	Dose Level -1	Dose Level -2	Dose Level -3
Cisplatin	75 mg/m^2	56 mg/ m^2	38 mg/ m^2	Discontinue
Carboplatin	AUC 5 Maximum dose 750mg	AUC 3.75 Maximum dose 562.5mg	AUC 2.5 Maximum dose 375mg	Discontinue
Pemetrexed	500mg/m2	375 mg/m2	250 mg/m2	Discontinue
Pembrolizumab/placebo	200 mg fixed dose	Dose reductions are not permitted	Dose reductions are not permitted	Dose reductions are not permitted

Source: [KN-189 (MK-3475-189-00) Final Protocol, Table 2][65]

Concomitant interventions

All patients received premedication with vitamin B12 and folic acid and corticosteroid prophylaxis as follows:[62]

- Folic Acid 350-1000 µg, orally (≥5 doses in the week preceding the first dose of pemetrexed, continued treatment during the full course of therapy and for 21 days after the last pemetrexed dose)
- Vitamin B12 1000 µg, intramuscular [IM] injection (in the week preceding the first dose of pemetrexed and once every three cycles thereafter)
- Dexamethasone prophylaxis 4 mg, orally (twice daily, taken the day before, day of, and day after pemetrexed administration)

The following treatments were prohibited during the Screening, Treatment, Crossover and Second Course Phases of the KN-189 trial: systemic anti-cancer chemotherapy, biological therapy, or immunotherapy not specified in this protocol; investigational agents other than pembrolizumab; radiation therapy (except for symptom management); live vaccines (e.g., measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine); prolonged therapy (>7 days) with systemic glucocorticoids (except for modulating symptoms from immune-related AEs or for use as a protocol-specified pre-medication); and phenytoin during treatment with cisplatin/carboplatin.[62]

Subsequent medications

In the intention-to-treat population, 125 patients (30.5%) in the pembrolizumab combination arm and 96 patients (46.6%) in the placebo combination arm received at least one subsequent therapy either while receiving the study treatments or outside the trial. Patients received up to four subsequent therapies.[1] Subsequent therapies received by patients in the KN-189 trial are summarized in Table 6.10.

Table 6.10: Subsequent anticancer therapy in the KN-189 trial, including crossover, ITT Population

Regimen	Pembrolizumab-Chemotherapy Group (N=410) Number of patients (%)	Placebo-Chemotherapy Group (N=206) Number of patients (%)
Summary:		
Any subsequent therapy	125 (30.5%)	96 (46.6%)
No subsequent therapy	285 (69.5%)	110 (53.4%)
Still on assigned therapy	137 (33.8%)	36 (17.8%)
Types of Subsequent Therapies*:		
Chemotherapy combination	51 (12.4%)	14 (6.8%)
Single-agent chemotherapy	65 (15.9%)	15 (7.3%)
Immunotherapy	31 (7.6%)	88 (42.7%)
Crossover to pembrolizumab	0	67 (32.5%)
Immunotherapy outside of study	31 (7.6%)	21 (10.2%)
	13 (3.2%)	7 (3.4%)
Targeted therapy		

*Patients received up to 4 subsequent therapies. Numbers in the table do not match numbers in the text; Table 2 reports all therapies received while the text reports the number of patients receiving one specific type of therapy at least once after primary progression. Source: Supplementary Appendix to Ghandi et al. 2018[42]

Source: [Merck Oncology KEYTRUDA® Clinical Rationale, Table 2][65]

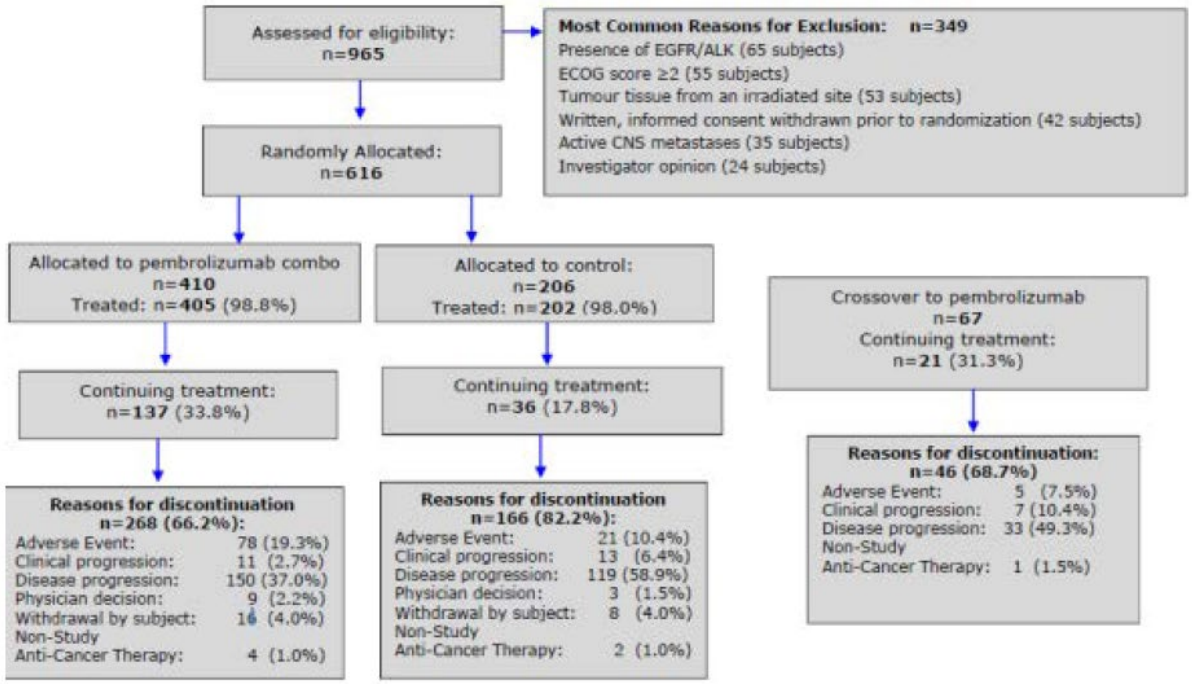
d) Patient Disposition

Figure 6.4 illustrates patient disposition in the KN-189 trial. Of 965 patients who were screened for enrollment at 126 sites (in 16 countries), 616 patients from 118 sites who met all the eligibility criteria were randomly assigned to the pembrolizumab combination arm (n = 410) or the placebo combination arm (n = 206). Patients were recruited between 26-FEB-2016 and 06-MAR-2017. A total of nine randomized patients were not treated; 405 patients (98.8%) in the pembrolizumab arm and 202 patients (98.0%) in the placebo arm received at least one dose of the assigned combination therapy.[1]

As of the 08-NOV-2017data cut-off date, after a median follow-up duration of 10.5 months, 137 of 405 patients (33.8%) in the pembrolizumab combination arm and 36 of 202 patients (17.8%) in the placebo combination group were still receiving the assigned study treatment. Overall, 66.2% of patients in the pembrolizumab combination arm had discontinued all study treatments, when compared with 82.2% of patients in the placebo combination arm. The most frequent reasons for treatment discontinuation were disease progression (37.0% with pembrolizumab combination versus 58.9% with placebo combination), and AEs (19.3% with pembrolizumab combination versus 10.4% with placebo combination).[1]

In the placebo combination arm, 67 patients (32.5%) crossed over after disease progression to receive on-study pembrolizumab monotherapy; and 18 additional patients (8.7%) received immunotherapy outside the trial (i.e., the effective cross-over rate in the placebo combination arm was 41.3% [85/206] in the ITT population and 50.0% [85/170] in patients who discontinued the placebo combination).[1]

Figure 6.4: Patient disposition in the KN-189 trial



Source:[EMA Assessment Report (EMEA/H/C/003820/II/0043);page 21/89][2]

Protocol violations/deviations

A summary of major protocol deviations are provided in Table 6.11.

Table 6.11: summary of the major protocol deviations in the KN-189 trial

Deviation Category	Number of Subjects
Inclusion criteria	
No. 2 – EGFR/ALK	3
No. 3 – no measurable disease	2
No. 8 – ECOG performance status 2	1
Exclusion criteria	
No. 9 – prior malignancy	1
No. 18 – active infection requiring therapy	1

Source:[EMA Assessment Report (EMEA/H/C/003820/II/0043); Table 6,page 22/89][2]

e) Limitations/Sources of Bias

Overall, KN-189 was a well-designed RCT, with the following steps taken to minimize potential biases:

- A double-blind study design was employed to minimize bias in the assessment and reporting of all study outcomes. Study participants, investigators, and the Sponsor's personnel or delegate(s) who were involved in the treatment administration or clinical evaluation of patients were blinded to the assignment of pembrolizumab (or placebo). An identically-packaged ready to-use blinded infusion solution was prepared on site to be administered as placebo. However, the chemotherapy agents (i.e., pemetrexed and carboplatin/cisplatin) were administered on an open-label basis in both study arms.
- To reduce selection bias, allocation concealment was performed through a centralized interactive web-based randomization system.
- A 2:1 randomization ratio was used to increase the probability that eligible patients that would be randomized to receive the pembrolizumab combination, and to increase feasibility.
- A stratified randomization procedure based on three known prognostic factors (i.e., PD-L1 expression, choice of cisplatin vs. carboplatin, and smoking history) was used to minimize potential imbalances between the study groups that might lead to biased results. The baseline characteristics were generally well balanced between the two study arms. It should be noted that in the placebo combination arm there was a higher proportion of patients who were female (47.1% versus 38.0% in the pembrolizumab combination arm; p=0.04).
- All efficacy analyses were performed in the ITT population. The co-primary (PFS) and key secondary response outcomes (ORR and DOR) were assessed by a blinded, independent central radiologic review (BICR) to reduce detection bias.
- Both PFS and OS were tested in a group-sequential fashion, and the PFS and OS analyses were adjusted for multiplicity. Furthermore, at the first interim analysis, the total type I error was adjusted for the analysis of ORR, as the PFS and OS tests were both positive. No adjustments were made for multiplicity introduced by analysing other secondary endpoints (DOR and CBR) or subgroup analyses of PFS or OS. Therefore, p-values in these analyses should be considered nominal. Multiple testing can increase the probability of type I error and, therefore, lead to false positive conclusions.

The following limitations of the KN-189 trial should be noted in interpreting the study results:

- The median OS was not reached at the time of interim analysis for the pembrolizumab combination group, and the final results on OS are not available yet. Therefore OS data should be regarded as immature and interpreted with caution.
- In the placebo combination arm, 32.5% (67/206) of patients crossed over to receive on-study pembrolizumab monotherapy, after disease progression; and 8.7% additional patients (8.7%) received immunotherapy outside the trial. Treatment crossover may confound the results of ITT analysis of OS. .
- The KN-189 trial collected PRO data as an exploratory endpoint, using validated and reliable tools. The questionnaire completion rate, defined as the proportion of patients who completed ≥1 PRO assessment was around 99% in both study arms at the time of first interim analysis. However, patient compliance rates (in completing questionnaires) were relatively lower for the assessments performed at week 21, when compared to the baseline and week 12 assessments (see Tables 6.17 – 6.20). Therefore, the PRO results should be interpreted with caution, as patients who adhered to the completion of questionnaires may be systematically different from those who did not.

KEYNOTE-021 (KN-021) – Cohort G

KN-021 is ongoing Phase I/II, multi-centre, multi-cohort randomized controlled trial to compare the efficacy and safety of combination therapy with pembrolizumab plus carboplatin-pemetrexed chemotherapy versus carboplatin-pemetrexed chemotherapy alone as first-line therapy in patients with metastatic NSQ NSCLC in whom there were no EGFR or ALK mutations. The trial was conducted at 26 academic medical centres in the USA and Taiwan, and was composed of two parts. Part 1 of the study was conducted to determine the recommended phase 2 dose for pembrolizumab in combination with different chemotherapy and/or immunotherapy regimens. Part 2 included a randomized comparison of chemotherapy with or without pembrolizumab based on the doses defined in Part 1.

As shown in Figure 6.5, the KN-021 trial included multiple cohorts. Cohort G (N=123), that is relevant to the submission under review, enrolled chemotherapy-naïve patients to receive pembrolizumab + pemetrexed and carboplatin AUC5 chemotherapy (hereafter referred to as the pembrolizumab combination arm) versus chemotherapy with pemetrexed and carboplatin AUC5 (hereafter referred to as the chemotherapy arm).[5]

a) Trial design [2,5]

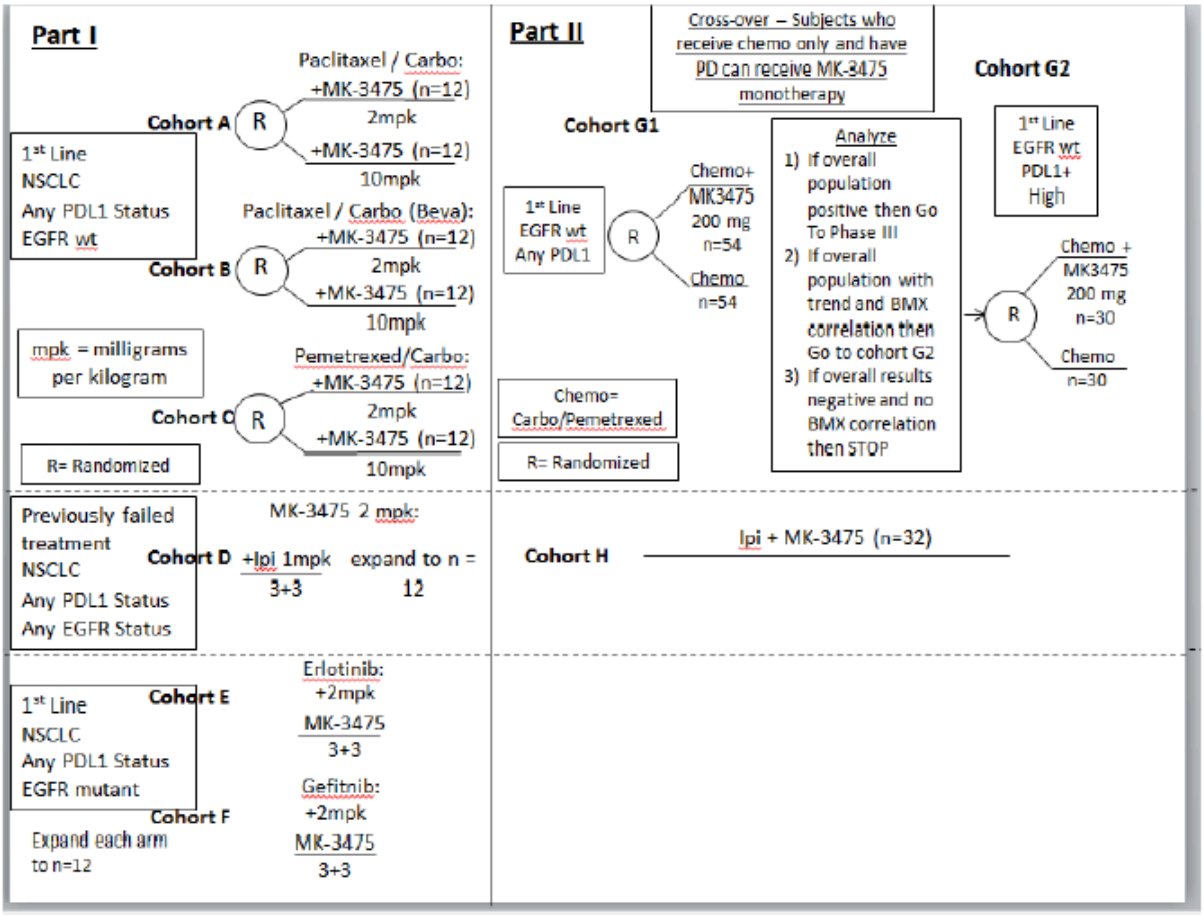
The KN-021 study design is illustrated in Figure 6.5.

During the Screening Phase (within approximately 28 days prior to randomization), potential study participants were evaluated to determine that they fulfill the entry requirements; informed consent was obtained; and tumor assessment (and clinical/laboratory examinations were performed. Patients were also screened for the presence of PD-L1 expression, ALK translocation and EGFR mutation. Patients who were EGFR wild type and did not have ALK translocation (and otherwise eligible for randomization) were enrolled in cohort G.

In the Treatment Phase, eligible patients in Cohort G were randomized (1:1 ratio) to receive pembrolizumab + pemetrexed-carboplatin chemotherapy (n=60) or pemetrexed-corboplatin chemotherapy alone (n=63). Treatment was to be continued until disease progression or protocol-defined unacceptable toxicities. Patients in the chemotherapy arm were allowed to crossover to receive pembrolizumab monotherapy, once they experienced disease progression (by RECIST 1.1). Treatment was limited up to 24 months for patients who crossed over to pembrolizumab monotherapy.

In the Follow-up Phase, response to treatment was assessed using radiographic imaging and according to the Response Evaluation Criteria in Solid Tumors (RECIST; version 1.1). Tumour imaging by CT (preferred) or MRI was performed at baseline, every 6 weeks (42 ± 7 days) for the first 18 weeks, followed by every 9 weeks in Year 1, and every 12 weeks in Year 2. Patient survival was assessed every 8 weeks, during the Follow-up Phase. AEs were monitored throughout the trial and graded in severity according to the CTCAE guidelines (version 4.0). After the end of treatment, each patient was followed for a minimum of 30 days for AEs monitoring even if the patient started new anticancer treatment.

Figure 6.5: KN-021 Study Design



Source: Reprinted from Lancet Oncology, Vol.17 / Iss.11. Langer, C.J., et al, Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study, Supplementary, Pages No. 1497-1508, Copyright (2016), with permission from Elsevier.[5]

Randomization and treatment concealment[5]

Randomization was performed centrally using an IVRS/IWRS. For Cohort G, patients were assigned randomly in a 1:1 ratio to the pembrolizumab combination and chemotherapy arms. Randomization was stratified based on negative or positive PD-L1 tumor expression. Positive PD-L1 tumor expression was defined as Tumor Proportion Score (TPS)≥1%, and PD-L1 negative as TPS <1%. PD-L1 inevaluable patients were also included in the PD-l1 negative group. Treatment was allocated in blocks of four in each stratum via a schedule generated by a computerized randomized list generator.

KN-021 was an open-label trial; therefore, patients, treating physicians, and representatives of the study funder were not masked to study treatment assignment. However, the PD-L1 biomarker results were masked in the database to the investigator. The funder was masked to aggregate data by treatment group during the study.

Study endpoints and statistical analysis[2,5]

The primary efficacy endpoint in the KN-021 trial was ORR, defined as the proportion of patients with CR or PR according to RECIST 1.1 by BICR. Patients with missing outcome on objective

response were considered non-responders. The key secondary endpoint included BICR-assessed PFS, OS and DOR. PFS was defined as the time from randomization to disease progression or death, whichever occurred earlier, based upon RECIST 1.1, by blinded independent central review. Patients without a documented PFS event were censored at the last disease assessment date. For patients who achieved an objective response (CR or PR), duration of response was defined as the time from the first documented evidence of CR or PR until disease progression or death due to any cause, whichever occurred first. OS was defined as the time from randomization to death due to any cause. Patients without documented death at the time of analysis were censored at the date last known to be alive. Exploratory endpoints included PFS2, PFS and OS following crossover to pembrolizumab.

The primary analysis of the KN-021trial (Cohort G) was planned to be performed after all patients had a minimum of 6 months follow up (i.e., ≥6 months after the last patient was enrolled). The first analysis was performed at the data cut-off date of 31-DEC-2016, two updated analyses was performed on 31- MAY-2017,[2] and 01-December-2017.[6]

The study was planned to enroll approximately 108 patients to have at least 89% power to detect a 30% difference in ORR (30% with chemotherapy alone versus 60% with the pembrolizumab combination) at a one-sided α of 0.025. Assuming 68 PFS events, the trial had around 81.5% power to detect a HR of 0.50 for PFS at a one-sided α of 0.025. The overall type I error rate was strictly controlled at a one-sided α of 0.025 by a fixed-sequence, closed testing procedure that was first applied to the primary endpoint of ORR in the total population. If pembrolizumab combination showed statistically significant benefit over chemotherapy alone at a one-sided α of 0.025, the testing procedure was then applied to the key secondary endpoint of PFS in the total population. There was no type I error adjustment for the analyses of OS or PD-L1 expression subgroups.

The efficacy analyses were based on data from the ITT population (i.e., all randomized patients were analyzed in the treatment arm to which they were randomly assigned. The ORR was compared between the treatment groups using the stratified Miettinen and Nurminen method with weighting by sample size. Patients with unknown best overall response were considered non-responders. The Kaplan-Meier method was used for the estimation of PFS, OS, and DOR. Treatment differences in PFS and OS were assessed using the stratified log-rank test. HRs and associated 95% CIs were assessed with a stratified Cox proportional hazard model with Efron's method of tie handling. The same stratification factor used for randomization was applied to all stratified statistical analyses.

The analysis of safety was based on data from as-treated population, which included all patients who had undergone randomization and received at least one dose of the assigned combination therapy. Patients who received incorrect study treatment for the entire treatment period were included in the treatment arm corresponding to the treatment they actually received. For the estimation of dose limiting toxicity (DLT) rate, data from DLT-evaluable population (i.e., patients who had completed the first cycle of therapy or discontinued from the trial due to a drug-related AE) were used. Patients who discontinued prematurely due to a non-drug-related cause were not included in the DLT evaluable population.

b) Populations

Eligibility criteria[5]

Eligible patients were adult (≥18 years of age) patients with NSQ NSCLC who had not received prior systemic chemotherapy treatment for their advanced or metastatic NSCLC. Other key eligibility criteria included:

- Histologically-confirmed or cytologically confirmed diagnosis of stage IIIB or IV NSQ NSCLC
- Documentation of absence of EGFR mutations AND absence of ALK translocations

- At least one measurable disease site per RECIST version 1.1, as determined by investigator
- Eastern Cooperative Oncology Group performance status of 0 or 1
- Life expectancy 3 months or longer
- Provision of a tumour biopsy sample for assessment of PD-L1 expression
- Adequate organ function

KN-021 excluded patients who had:

- Received radiation therapy to the lung (> 30 Gy) within 6 months of the first dose of trial treatment
- Ongoing use of systemic corticosteroids or other immunosuppressive treatment
- Active autoimmune disease requiring systemic treatment in the previous two years (excluding replacement therapy)
- Untreated brain metastases (stable, treated metastases were allowed), or active interstitial lung disease or a history of pneumonitis that required intravenous glucocorticoids

Characteristics of the study population[2,5]

A total of 123 patients from 26 sites who had met all the eligibility criteria were randomized to the pembrolizumab combination arm (n = 60) or the chemotherapy arm (n = 63). The baseline demographic and disease characteristics of stud participants in KN-021 Cohort G are summarized in Table 6.12. As the table shows, the baseline characteristics were generally well balanced between the two study arms except, in the pembrolizumab combination arm there were higher proportions of patients who were of White ethnic group (82% versus 92% in the chemotherapy arm), and had a tumour histology of adenocarcinoma (92% versus 82% in the chemotherapy arm). In addition, a higher proportion of current or former smokers were enrolled in the chemotherapy arm (86% versus 75% in the pembrolizumab combination arm).The median age was 62.5 year in the pembrolizumab combination arm and 63.2 years in the chemotherapy arm. Overall, the majority of patients were female, White, current or former smoker, with adenocarcinoma histology (proportions as described above).

Table 6.12: Baseline demographic and disease characteristics of the KN-021G population

	Pembrolizumab plus chemotherapy (N=60)	Chemotherapy (N=63)
Age, years	62·5 (54–70)	63·2 (58–70)
Sex		
Male	22 (37%)	26 (41%)
Female	38 (63%)	37 (59%)
Ethnic origin		
White	49 (82%)	58 (92%)
Asian	5 (8%)	5 (8%)
Black or African American	4 (7%)	0
Other*	2 (3%)	0
ECOG performance status†		
0	24 (40%)	29 (46%)
1	35 (58%)	34 (54%)
Tumour histology		
Adenocarcinoma	58 (97%)	55 (87%)
NSCLC not otherwise specified	2 (3%)	7 (11%)
Large cell carcinoma	0	1 (2%)
Disease stage		
IIIA	0	1 (2%)
IIIB	1 (2%)	2 (3%)
IV	59 (98%)	60 (95%)
Smoking status		
Current or former smoker	45 (75%)	54 (86%)
Never smoker	15 (25%)	9 (14%)
Stable brain metastases	9 (15%)	6 (10%)
PD-L1 TPS		
<1%	21 (35%)	23 (37%)
1–49%	19 (32%)	23 (37%)
≥50%	20 (33)	17 (27%)
Previous systemic (neo)adjuvant therapy	4 (7%)	5 (8%)

Data are median (IQR) or n (%). ECOG=Eastern Cooperative Oncology Group. NSCLC=non-small-cell lung cancer. TPS=tumour proportion score. *Other ethnic origins in the pembrolizumab plus chemotherapy group included one patient (2%) who was American Indian or Alaska Native and one patient (2%) who did not define their ethnic origin. †One patient (2%) in the pembrolizumab plus chemotherapy group had an ECOG performance status of 2; this patient did not receive study treatment.

Table 1: **Baseline demographics and disease characteristics in the intention-to-treat population**

Source: Reprinted from Lancet Oncology, Vol.17 / Iss.11. Langer, C.J., et al, Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study, Pages No. 1497-1508, Copyright (2016), with permission from Elsevier. [Table 1][5]

c) Interventions

Treatment Dosing Schedule [5]

Patients in the KN-021 trial Cohort G were randomized to receive either:

- pembrolizumab 200 mg (IV) + pemetrexed 500 mg/m^2 (IV with vitamin supplementation) + carboplatin AUC 5 all on Day 1 every 3 weeks for 4 cycles followed by pembrolizumab 200 mg + pemetrexed 500 mg/m^2 every 3 weeks (pembrolizumab combination arm);

  OR

- pemetrexed 500 mg/m^2 (IV with vitamin supplementation) + carboplatin AUC 5 all on Day 1 every 3 weeks for 4 cycles, followed by pemetrexed 500 mg/m^2 every 3 weeks (chemotherapy arm).

The study treatments were continued until disease progression or unacceptable toxicity, for a maximum of two years. In the pembrolizumab combination arm, pembrolizumab was administered at least 30 minutes before chemotherapy. Patients assigned to the chemotherapy arm who experienced radiological disease progression were allowed to crossover to receive pembrolizumab monotherapy (up to 2 years) after a 21-day washout period, if protocol-specified safety criteria were met.

Dose modifications[5]

Pembrolizumab dose reductions were not permitted. Pembrolizumab treatment could be interrupted or discontinued due to severe or life-threatening treatment-related toxicities. Modification of carboplatin and pemetrexed doses was performed according to the locally approved product information.

Concomitant interventions

All patients received premedication with vitamin B12 and folic acid and corticosteroid prophylaxis according to the local guidelines. Palliative and supportive care was permitted during the course of the trial for underlying medical conditions and management of symptoms. Surgery or radiotherapy for tumor control was not allowed during the study; however, radiotherapy or procedures for symptom management were permitted.[5]

The following treatments were prohibited during the course of the study: systemic anti-cancer chemotherapy, biological therapy , or immunotherapy not specified in this protocol; investigational agents other than pembrolizumab; radiation therapy (except for symptom management); live vaccines (e.g., measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine); prolonged therapy (>7 days) with systemic glucocorticoids (except for modulating symptoms from an event of clinical interest or for use as a pre-medication for chemotherapeutic agents specified in the protocol). Limited use of systemic corticosteroids (≤7 days) was permitted where such use was considered standard of care (e.g. as premedication for contrast allergy or for COPD exacerbation). Replacement doses of steroids (for example, prednisone 10 mg daily) were permitted while on study.

Subsequent medications

In the as-treated population, 13/59 patients (22%) in the pembrolizumab combination arm and 17/62 patients (27%) in the chemotherapy arm received at least one line of subsequent therapy, beyond the in-study cross-over. Subsequent therapies received by patients in the KN-021 trial Cohort G are summarized in Table 6.13.

Table 6.13: Subsequent anticancer therapy in the KN-021 trial, Cohort G, As-Treated Population

Therapy	Pembrolizumab + Chemotherapy (N=59)	Chemotherapy (N=62)
Any	13 (22)	17 (27)
Specific therapies*†		
Anti-Ly6E antibody drug conjugate (unspecified)	1 (2)	0 (0)
Cabozantinib	1 (2)	0 (0)
Carboplatin	3 (5)	2 (3)
Crizotinib	2 (3)	0 (0)
Docetaxel	2 (3)	5 (8)
Durvalumab	0 (0)	1 (2)
Enoblituzumab	1 (2)	0 (0)
Erlotinib hydrochloride	1 (2)	0 (0)
Gemcitabine	2 (3)	1 (2)
Ipilimumab	1 (2)	0 (0)
Mitogen-activated protein kinase inhibitor (unspecified)	1 (2)	0 (0)
Nivolumab	0 (0)	11 (18)
Paclitaxel	1 (2)	0 (0)
Palbociclib	1 (2)	0 (0)
Pembrolizumab	0 (0)	2 (3)†
Pemetrexed	3 (5)	2 (3)
Ramucirumab	0 (0)	1 (2)
Selumetinib	1 (2)	0 (0)
Seribantumab	0 (0)	1 (2)
Tremelimumab	0 (0)	1 (2)
Vinorelbine tartrate	0 (0)	1 (2)

Data are presented as n (%).
*Patients may have received more than one subsequent therapy, either as monotherapy or in combination.
†Excludes the in-study crossover.

Source: Reprinted from Lancet Oncology, Vol.17 / Iss.11. Langer, C.J., et al, Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study, Supplementary, Pages No. 1497-1508, Copyright (2016), with permission from Elsevier. [Table S1][5]

d) Patient Disposition[5]

Figure 6.6 illustrates patient disposition in the KN-021G trial. Of 219 patients who were screened for enrollment at 23 sites in the United States and three sites in Taiwan, 123 patients who met the eligibility criteria were randomly assigned to the pembrolizumab combination arm (n = 60) or the chemotherapy arm (n = 63). Patients were recruited between 25-NOV-2014 and 25-JAN-2016. One patient in the pembrolizumab combination arm did not receive study therapy due to deterioration in ECOG performance status to a score of 2 after randomization but before the initiation of treatment; and one patient in the chemotherapy group withdrew consent before receiving treatment. Overall, 59 patients in the pembrolizumab combination arm and 62 patients in the chemotherapy arm received at least one dose of the assigned study treatment. Pemetrexed maintenance therapy was received by 50 (85%) of 59 treated patients in the pembrolizumab combination arm and 43 (69%) of 62 patients in the chemotherapy arm.

As of the cut-off date of 08-AUG-2016, after a median follow-up duration of 10·6 months (IQR 8·2,13·3),. 28 (47%) of 59 patients in the as-treated pembrolizumab combination arm, and 19 (31%) of 62 patients in the as-treated chemotherapy arm, remained on assigned study treatment (Figure 6.x). The most common reason for treatment discontinuation was progressive disease (29% with the pembrolizumab combination versus 50% with chemotherapy alone). Thirty-two percent of the patients in the as-treated chemotherapy arm crossed over after disease progression to receive pembrolizumab monotherapy.

Figure 6.6: Patient disposition in the KN-021G trial

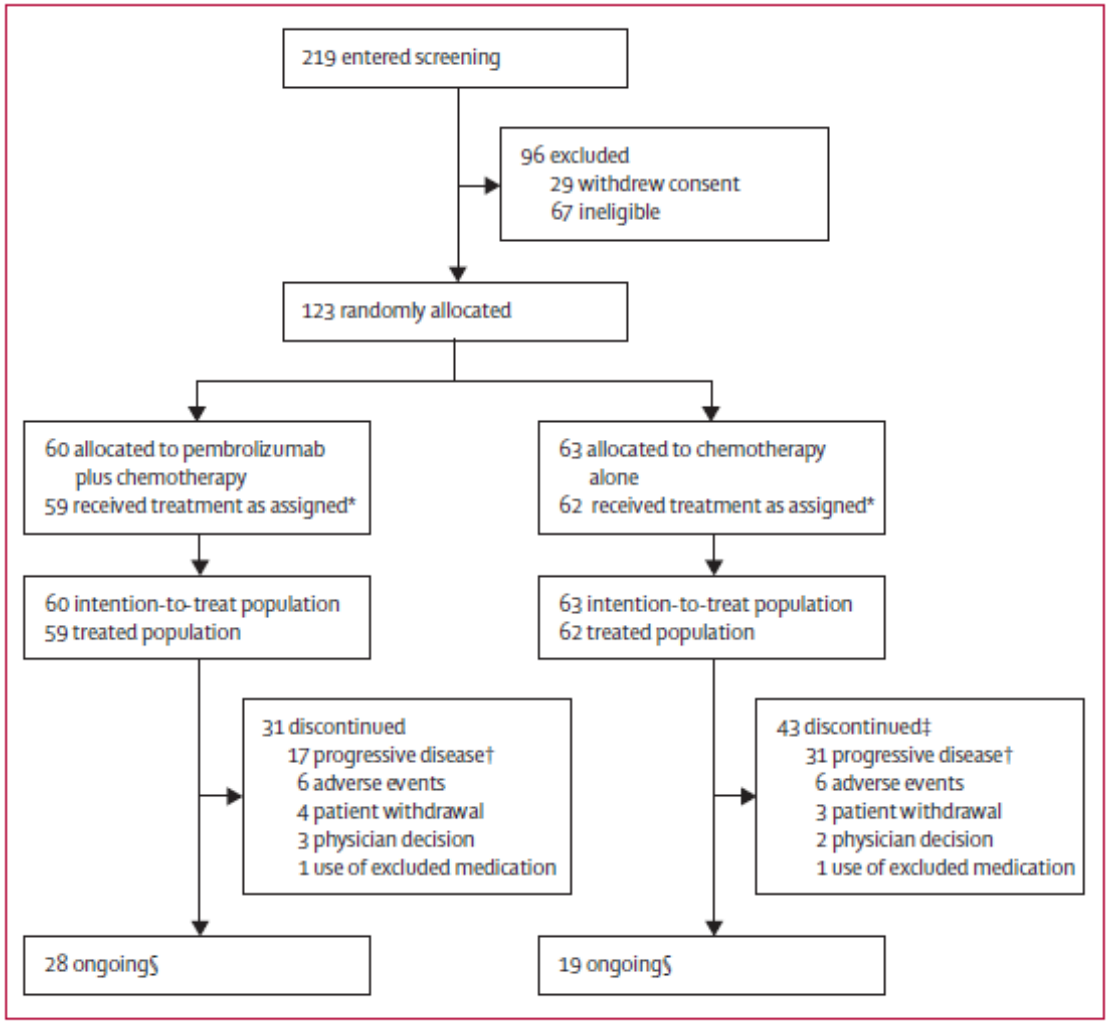


***Figure 1*: Trial profile**

*One patient allocated to pembrolizumab plus chemotherapy experienced deterioration in Eastern Cooperative Oncology Group performance status to a score of 2 after screening but before receiving the first dose of treatment. One patient allocated to chemotherapy alone withdrew consent before receiving the first dose of study treatment. †Includes clinical disease progression. ‡Includes 20 patients who crossed over to receive pembrolizumab monotherapy as part of the study. §Patients without a completed study medication discontinuation form.

Source: Reprinted from Lancet Oncology, Vol.17 / Iss.11. Langer, C.J., et al, Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study, Pages No. 1497-1508, Copyright (2016), with permission from Elsevier. [Figure 1][5]

At the 01-DEC-2017 data cut-off date, 5/59 (8.5%) patients treated with the pembrolizumab combination were continuing treatment; 11 (18.6%) patients had completed treatment; and 43 (72.9%) patients discontinued treatment (26 due to disease progression). In the chemotherapy arm, 6/ 62 (9.7%) treated patients t were continuing treatment; two (3.2%) patients had completed treatment; and 54 (87.1%) patients had discontinued the study treatment (38 due to disease progression). Of the 56 patients in the chemotherapy arm who discontinued or completed treatment, 26 (46.4%) patients crossed over to pembrolizumab during the course of the study, and an additional 15 (26.8%) patients received anti-PD-1/PD-L1 therapy outside of crossover.[6]

e) Limitations/Sources of Bias

Overall, KN-021 was a well-designed and well-conducted phase I/ randomized phase II trial:

- The randomization and allocation concealment procedures were appropriate. A stratified randomization procedure based on negative or positive PD-L1 tumor expression was used to minimize potential imbalances between the study groups that might lead to biased results, and the treatment groups were relatively well-balanced in terms of baseline and disease characteristics, with higher proportions of tumour histology of adenocarcinoma in the pembrolizumab combination arm (92% versus 82% in the chemotherapy arm), and a higher proportion of current or former smokers in the chemotherapy arm (86% versus 75% in the pembrolizumab combination arm). All efficacy analyses were based on data from the ITT population, and the overall type I error rate was controlled in a sequential manner; i.e., if pembrolizumab combination showed statistically significant benefit over chemotherapy alone, in terms of the primary endpoint of ORR, at the specified significance level, the testing procedure was then applied to the key secondary endpoint of PFS in the total population.

The following limitations should be considered when interpreting the results of the KN-021 trial.

- KN-021 was an open-label trial; i.e., patients, treating physicians, assessors, and representatives of the study funder were not blind to treatment allocation. This could potentially increase the risk of performance and detection biases, as both physician/ outcome assessors and patients are aware of the treatment status. The investigators attempted to mitigate the detection bias by using a blinded, independent central radiologic review and standardized criteria (i.e., RECIST) to assess the key efficacy outcomes (i.e., ORR and PFS). They also kept the researchers blinded to the PD-L1 biomarker results. However, the some levels of reporting and detection bias should be taken into account, especially for subjective endpoints such as AEs.
- There was no type I error adjustment for the analyses of OS or PD-L1 expression subgroups. Therefore, p-values in these analyses should be considered descriptive. Multiple testing can increase the probability of type I error and, therefore, lead to false positive conclusions.
- Data on patient-reported outcomes were not collected in the KN-021 trial.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

6.3.2.2.1 KN-189

Efficacy Outcomes

Overall Survival (OS)

OS was a co-primary endpoint in the KN-189 trial. The results of the OS analysis are summarized in Table 6.14; and Kaplan-Meier survival curves are shown in Figure 6.7A. As of the 08-NOV-2017data cut-off date, with a median follow-up duration of 10.5 months, a total of 235 deaths were reported in the KN-189 trial (127 [31.0%] in the pembrolizumab combination arm and 108 [52.4%] in the placebo combination arm). The median OS was not reached in the pembrolizumab combination arm, and was 11.3 months (95% CI 8.7, 15.1) for the placebo combination arm (HR = 0.49; 95% CI 0.38, 0.64; P<0.00001). The estimated proportion of patients who were alive at 12 months was 69.2% (95% CI 64.1, 73.8) in the pembrolizumab combination arm and 49.4% (95% CI 42.1, 56.2) in the placebo combination arm.[1,2]

The OS subgroup analyses results were consistent with those of the original OS analysis (Figure 6.7B). OS benefit with the pembrolizumab combination was sustained across all of the subgroups regardless of age, sex, and ECOG performance score, smoking status, brain metastasis at baseline, PD-L1 tumour proportion score, and the type of platinum-based chemotherapy.

Table 6.14: Results of the overall survival analysis in the KN-189 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	410	127 (31.0)	4386.5	2.9	Not Reached (., .)	85.3 (81.5, 88.4)	0.49 (0.38, 0.64)	<0.00001
Control	206	108 (52.4)	1873.0	5.8	11.3 (8.7, 15.1)	72.3 (65.7, 77.9)	---	---

† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with treatment as a covariate stratified by PD-L1 status (≥1% vs. <1%), platinum chemotherapy (cisplatin vs. carboplatin) and smoking status (never vs. former/current).
§ One-sided p-value based on stratified log-rank test.
Database Cutoff Date: 08NOV2017

Source: [P189V01MK3475: adam-adsl; adtte]

Source:[EMA Assessment Report (EMEA/H/C/003820/II/0043); Table 9,page 24/89][2]

Progression-Free Survival (PFS)

PFS was also a co-primary endpoint in the KN-189 trial. The results of the PFS analysis are summarized in Table 6.15; and Kaplan-Meier survival curves are shown in Figure 6.8A. As of the 08-NOV-2017data cut-off date, a total of 410 PFS events were reported in the KN=189 trial (244 [59.5%] in the pembrolizumab combination arm and 166 [80.6%] in the placebo combination arm). The median PFS was 8.8 months (95% CI 7.6, 9.2) in the pembrolizumab combination arm, and was 4.9 months (95% CI 4.7, 5.5) in the placebo combination arm (HR = 0.52; 95% CI 0.43, 0.64; P<0.00001). The estimated proportion of patients who were alive and progression-free at 12 months was 34.1% (95% CI 28.8, 39.5) in the pembrolizumab combination arm and 17.3% (95% CI 12.0, 23.5) in the placebo combination arm. [1,2]

The PFS subgroup analyses results were generally consistent with those of the original PFS analysis (Figure 6.8B). The point estimate of HR for PFS was less than the null hypothesis value of 1.00

across all pre-specified subgroups; however, the upper limit of the 95% CIs crossed 1.00 for patients who ≥ 65 years of age (HR = 0.75; 95% CI 0.55, 1.02) and those with a PD-L1 tumor proportion score < 1% (HR = 0.75; 95% CI 0.53, 1.05).[1]

Table 6.15: Results of the progression-free survival analysis in the KN-189 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	410	244 (59.5)	3081.8	7.9	8.8 (7.6, 9.2)	66.4 (61.5, 70.8)	0.52 (0.43, 0.64)	<0.00001
Control	206	166 (80.6)	1166.2	14.2	4.9 (4.7, 5.5)	40.1 (33.3, 46.7)	---	---

† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with treatment as a covariate stratified by PD-L1 status (≥1% vs. <1%), platinum chemotherapy (cisplatin vs. carboplatin) and smoking status (never vs. former/current).
§ One-sided p-value based on stratified log-rank test.
BICR = Blinded Independent Central Review
Database Cutoff Date: 08NOV2017

Source: [P189V01MK3475: adam-adsl; adtte]

Source:[EMA Assessment Report (EMEA/H/C/003820/II/0043); Table 10,page 26/89][2]

Objective Response Rate (ORR)

As of the 08-NOV-2017data cut-off date, the BICR-assessed response rate was 47.6% (95% CI 42.6, 52.5) in the pembrolizumab combination arm and 18.9% (95% CI 13.8, 25.0) in the placebo combination arm (estimated treatment difference = 28.5; 95% CI 21.1, 35.5; p<0.0001) (Table 6.16). The disease control rate (i.e., the proportion of patients with a confirmed CR, PR or SD) was 84.6% in the pembrolizumab combination arm and 70.4% in the placebo combination arm.[1,2]

Treatment with the pembrolizumab combination resulted in a higher response rate across all categories of PD-L1 tumor proportion score, with the greatest between-group difference in patients with a tumor proportion score of 50% or greater (61.4% versus 22.9% in the placebo combination group).[1]

Table 6.16: Results of the analysis of objective response (BICR-assessed) in the KN-189 trial (ITT population)

Treatment	N	Number of Objective Responses	Objective Response Rate (%) (95% CI)	Difference in % vs. Control	
				Estimate (95% CI)†	p-Value††
Pembro Combo	410	195	47.6 (42.6,52.5)	28.5 (21.1,35.4)	<0.0001
Control	206	39	18.9 (13.8,25.0)		

† Based on Miettinen and Nurminen method stratified by PD-L1 status (>=1% vs. <1%), platinum chemotherapy (cisplatin vs. carboplatin) and smoking status (never vs. former/current).
†† One-sided p-value for testing. H0: difference in % = 0 versus H1: difference in % > 0.
Responses are based on BICR assessment per RECIST 1.1.
BICR = Blinded independent central review.
Database Cutoff Date: 08NOV2017

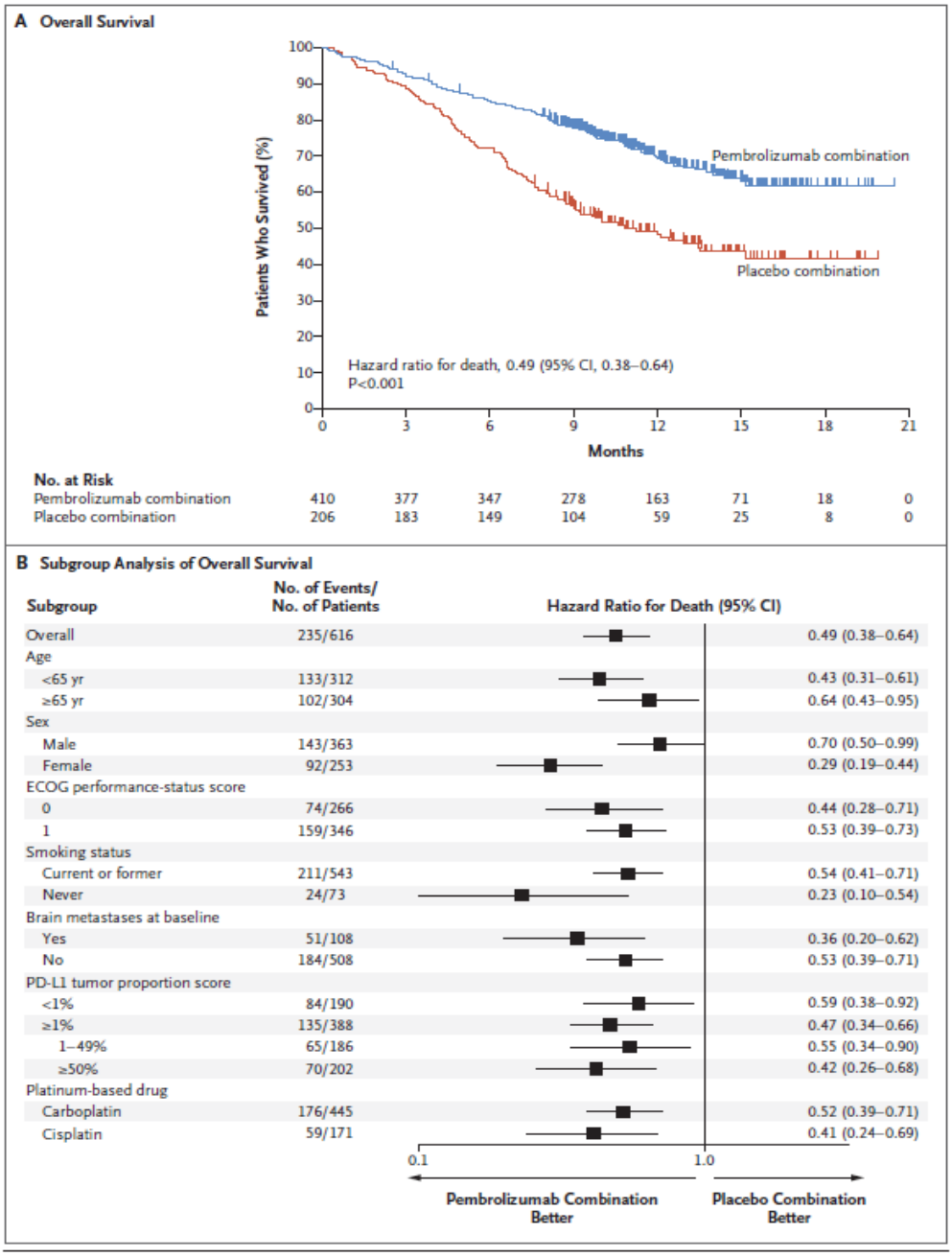
Source: [P189V01MK3475: adam-adsl; adrs]

Source:[EMA Assessment Report (EMEA/H/C/003820/II/0043); Table 11,page 28/89][2]

Duration of Response (DOR)

The median DOR was 11.2 months (range 1.1 to 18.0) in the pembrolizumab combination arm and 7.8 months (range 2.1 to 16.4) in the placebo combination arm. At the time of the data cut-off, 112 patients (57.4%) in the pembrolizumab combination arm 18 patients (46.2%) in the placebo combination arm had an ongoing response.[1]

Figure 6.7: Kaplan-Meier overall survival curves, and subgroup analyses of overall survival in the KN-189 trial



Shown are Kaplan–Meier estimates of overall survival (the first of the two primary end points) in the two trial groups (Panel A) and an analysis of overall survival in key subgroups (Panel B). Patients in the pembrolizumab- combination group received pemetrexed, a platinum-based drug, and pembrolizumab; those in the placebo-combination group received pemetrexed, a platinum-based drug, and placebo. Tick marks in Panel A indicate censoring of data at the last time the patient was known to be alive. Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with 0 indicating no symptoms and higher scores indicating increasing disability. PD-L1 denotes programmed death ligand 1.

Source: From NEJM, Gandhi, L., et al., Pembrolizumab plus Chemotherapy in Metastatic Non-Small-Cell Lung Cancer, Volume No. 378, Page No.2078-2092 Copyright © (2018) Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society. [Figure 1][1]

Figure 6.8: Progression-free survival in the KN-189 trial (ITT population and by subgroups)

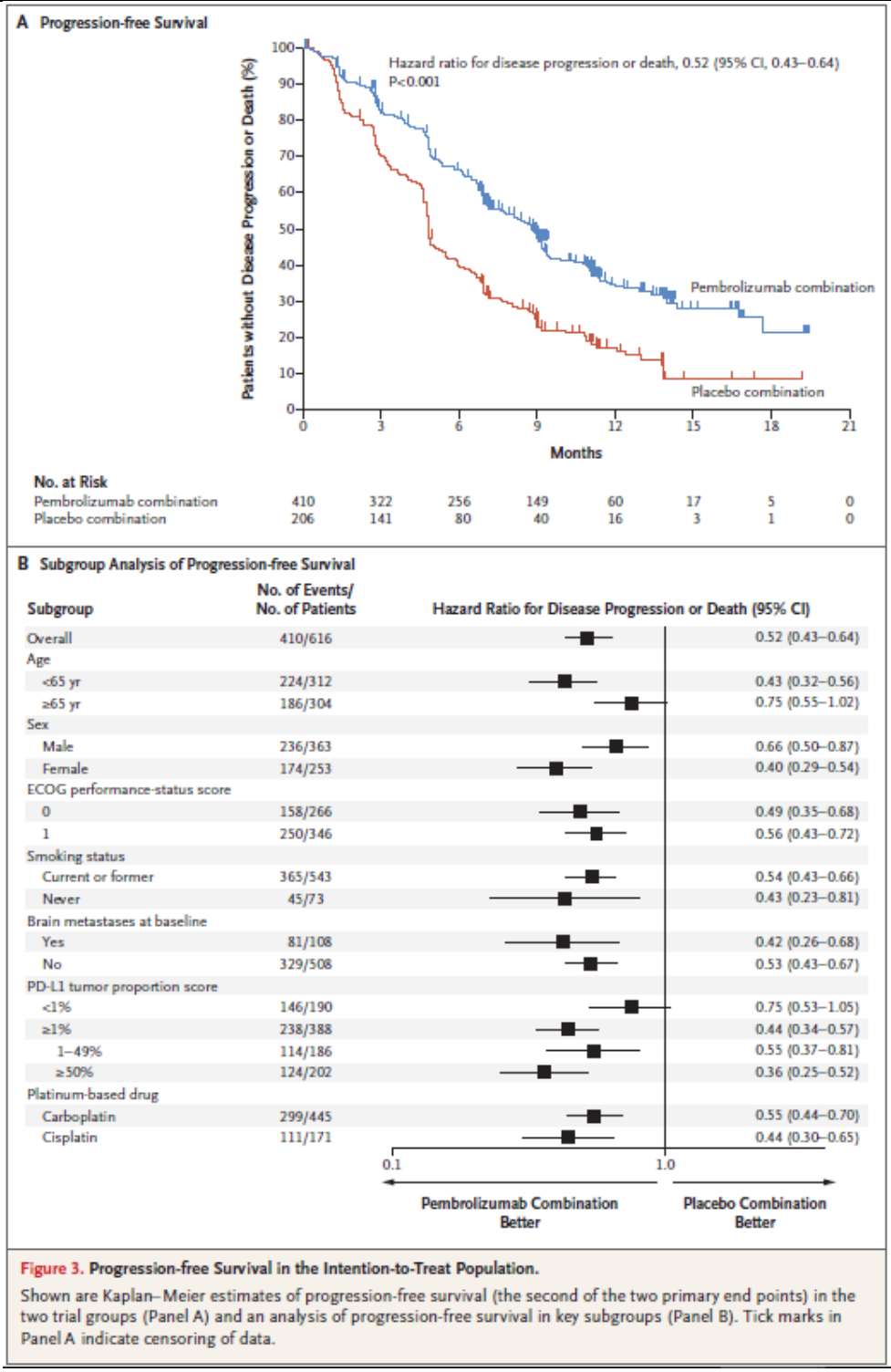


Figure 3. **Progression-free Survival in the Intention-to-Treat Population.**

Shown are Kaplan–Meier estimates of progression-free survival (the second of the two primary end points) in the two trial groups (Panel A) and an analysis of progression-free survival in key subgroups (Panel B). Tick marks in Panel A indicate censoring of data.

Source: From NEJM, Gandhi, L., et al., Pembrolizumab plus Chemotherapy in Metastatic Non-Small-Cell Lung Cancer, Volume No. 378, Page No.2078-2092 Copyright © (2018) Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society. [Figure 3][1]

Quality of Life

The PRO analysis population included 602 patients (402 in the pembrolizumab combination arm and 202 in the placebo combination arm) who had received ≥1 dose of study treatment, and completed at least one PRO assessment. As of the 08-NOV-2017 data cut-off date, 99.3% (402/405) of patients in the pembrolizumab combination arm and 99.0% (200/202) of those in the placebo combination arm completed ≥1 PRO assessment.[4]

At week 12, there was no difference in EORTC QLQ-C30 global health status/QoL change from baseline between the pembrolizumab and the placebo combination arms; the difference in least square (LS) mean change score from baseline between the two study arms was 3.58 points (95% CI -0.05, 7.22; p=0.053) (Table 6.17). At Week 21, however, a statistically significant improvement was observed with the pembrolizumab combination; the difference in LS mean change score from baseline between the two study arms was 5.27 points (95% CI 1.07, 9.74; p=0.014)(Table 6.18).[2]

At the 08-NOV-2017 data cut-off, with a median follow-up of 10.5 months, median time to true deterioration in the composite endpoint of cough, chest pain, or dyspnea was not reached in the pembrolizumab combination arm and was 7.0 months in the placebo combination arm (HR = 0.81; 95% CI 0.60, 1.09; p=0.161) (Figure 6.9).[4]

At both Week 12 and Week 21, statistically significant changes from the baseline in the EQ-5D visual analog scale (VAS) scores were observed between the two study arms, favouring the pembrolizumab combination (Table 6.19, and Table 6.20).[3]

Table 6.17: Change from baseline in EORTC QLQ-C30 global health status/QoL at week 12 (KN-189 PRO analysis set)

	Baseline		Week 12		Change from Baseline at Week 12	
Treatment	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)[†]
Pembro Combo	359	61.98 (21.270)	319	63.82 (21.495)	402	0.95 (-1.33, 3.24)
Control	180	60.56 (21.425)	150	61.06 (20.786)	200	-2.63 (-5.79, 0.53)

Pairwise Comparison	Difference in LS Means (95% CI)	p-Value
Pembro Combo vs. Control	3.58 (-0.05, 7.22)	0.053

[†] Based on cLDA model with the PRO scores as the response variable, and treatment by study visit interaction, stratification factors (PD-L1 expression (tumor proportion score ≥ 1% vs. <1%), platinum chemotherapy (cisplatin vs. carboplatin) and smoking status (never vs. former/current)) as covariates.

For baseline and Week 12, N is the number of subjects in each treatment group with non-missing assessments at the specific time point; for change from baseline, N is the number of subjects in the analysis population in each treatment group.

P-value is based on two-sided t test.

Database Cutoff Date: 08NOV2017

Source: [P189V01MK3475: adam-adplda]

Source:[EMA Assessment Report (EMEA/H/C/003820/II/0043); Table 13,page 31/89][2]

Table 6.18: Change from baseline in EORTC QLQ-C30 global health status/QoL at week 21 (KN-189 PRO analysis set)

	Baseline		Week 21		Change from Baseline at Week 21	
Treatment	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)[†]
Pembro Combo	359	61.98 (21.270)	248	66.97 (19.429)	402	1.25 (-1.15, 3.64)
Control	180	60.56 (21.425)	91	62.55 (24.068)	200	-4.02 (-7.70, -0.34)

Pairwise Comparison	Difference in LS Means (95% CI)	p-Value
Pembro Combo vs. Control	5.27 (1.07, 9.47)	0.014

[†] Based on cLDA model with the PRO scores as the response variable, and treatment by study visit interaction, stratification factors (PD-L1 expression (tumor proportion score ≥ 1% vs. <1%), platinum chemotherapy (cisplatin vs. carboplatin) and smoking status (never vs. former/current)) as covariates.

For baseline and Week 21, N is the number of subjects in each treatment group with non-missing assessments at the specific time point; for change from baseline, N is the number of subjects in the analysis population in each treatment group.

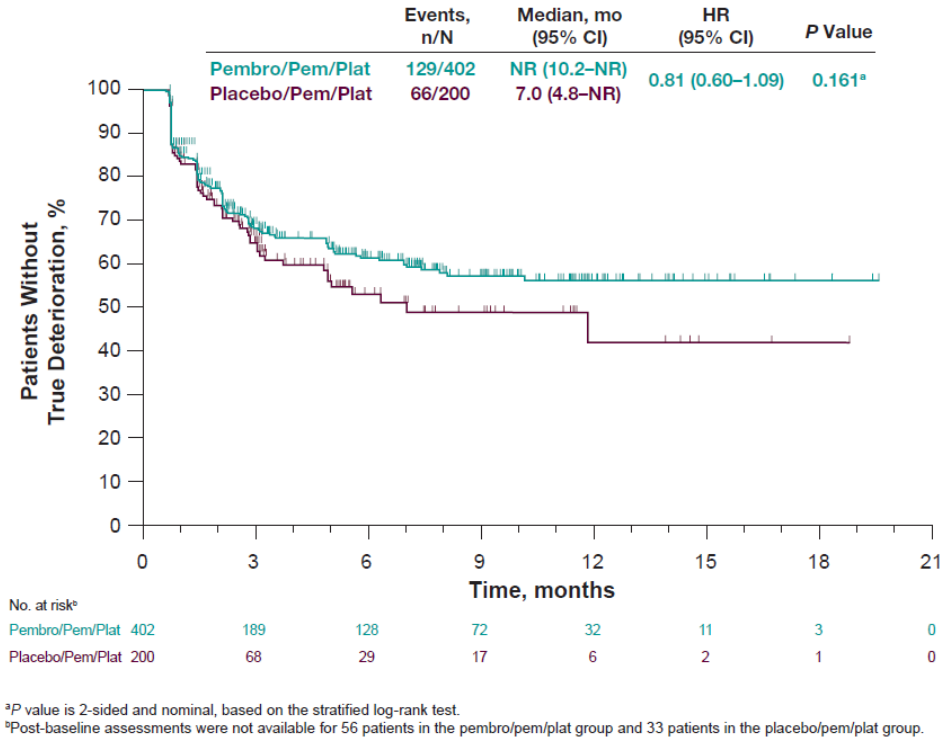
P-value is based on two-sided t test.

Database Cutoff Date: 08NOV2017

Source: [P189V01MK3475: adam-adplda]

Source:[EMA Assessment Report (EMEA/H/C/003820/II/0043); Table 14,page 32/89][2]

Figure 6.9: Time to true deterioration in composite endpoint of cough, chest pain, or dyspnea in the KN-189 trial



[a]*P* value is 2-sided and nominal, based on the stratified log-rank test.
[b]Post-baseline assessments were not available for 56 patients in the pembro/pem/plat group and 33 patients in the placebo/pem/plat group.

Source: Reprinted with permission. © (2018) American Society of Clinical Oncology. All rights reserved. Garassino, M.C., et al: Health-related quality of life (HRQoL) in the KEYNOTE-189 study of pembrolizumab (pembro) or placebo (pbo)+ pemetrexed (pem)+ platinum (plt) for metastatic NSCLC. J Clin Oncol. 36(15_suppl), 2018: 9021-9021.[4]

Table 6.19: Change from baseline in EQ-5D-VAS at week 12

	Baseline		Week 12		Change from Baseline at Week 12	
Treatment	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)†
Pembro Combo	364	69.90 (19.605)	320	73.69 (18.179)	402	3.22 (1.12, 5.31)
Control	180	67.78 (19.902)	150	70.29 (18.687)	200	-0.60 (-3.45, 2.25)

Pairwise Comparison	Difference in LS Means (95% CI)	p-Value
Pembro Combo vs. Control	3.82 (0.60, 7.04)	0.020

† Based on cLDA model with the PRO scores as the response variable, and treatment by study visit interaction, stratification factors (PD-L1 expression (tumor proportion score ≥ 1% vs. <1%), platinum chemotherapy (cisplatin vs. carboplatin) and smoking status (never vs. former/current)) as covariates.
For baseline and Week 12, N is the number of subjects in each treatment group with non-missing assessments at the specific time point; for change from baseline, N is the number of subjects in the analysis population in each treatment group.
P-value is based on two-sided t test.
Database Cutoff Date: 08NOV2017

Source: [P189V01MK3475: adam-adplda]

Source:[Merck responses to the pCODR Checkpoint meeting question (Q4)][3]

Table 6.20: Change from baseline in in EQ-5D-VAS at week 21

	Baseline		Week 21		Change from Baseline at Week 21	
Treatment	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)†
Pembro Combo	364	69.90 (19.605)	250	74.74 (16.716)	402	2.39 (0.24, 4.54)
Control	180	67.78 (19.902)	92	70.12 (19.074)	200	-2.22 (-5.42, 0.99)

Pairwise Comparison	Difference in LS Means (95% CI)	p-Value
Pembro Combo vs. Control	4.61 (1.03, 8.19)	0.012

† Based on cLDA model with the PRO scores as the response variable, and treatment by study visit interaction, stratification factors (PD-L1 expression (tumor proportion score ≥ 1% vs. <1%), platinum chemotherapy (cisplatin vs. carboplatin) and smoking status (never vs. former/current)) as covariates.
For baseline and Week 21, N is the number of subjects in each treatment group with non-missing assessments at the specific time point; for change from baseline, N is the number of subjects in the analysis population in each treatment group.
P-value is based on two-sided t test.
Database Cutoff Date: 08NOV2017

Source: [P189V01MK3475: adam-adplda]

Source:[Merck responses to the pCODR Checkpoint meeting question (Q4)][3]

Harms Outcomes

The mean duration of treatment was 7.4 ± 4.7 months in the pembrolizumab combination arm and 5.4 ± 4.3 months in the placebo combination arm.

Table 6.21 summarizes the safety outcomes reported in the KN-189 trial. AEs of any cause were reported in 99.8% of patients in the pembrolizumab combination arm and 99.0% of those in the placebo combination arm. The most common AEs reported in both groups included Nausea (55.6% with pembrolizumab versus 52.0% with placebo), anemia (46.2% with pembrolizumab versus 46.0% with placebo) and fatigue (40.7% with pembrolizumab versus 38.1% with placebo). Acute kidney injury occurred more frequently in the pembrolizumab combination arm (5.2%) than in the placebo-combination group (0.5%).[1]

The proportion of patients who had AEs of grade 3 or higher was 67.2% with the pembrolizumab combination, and 65.8% with the placebo combination. AEs of grade 3 or higher that were reported in at least 10% of the patients included anemia (16.3% with pembrolizumab versus 15.3% with placebo) and neutropenia (15.8% with pembrolizumab versus 11.9% with placebo). The AE rates were reported to be similar in patients who received carboplatin and those who received cisplatin.[1] In the KN-189 trial, 27.7% of the patients in the pembrolizumab combination arm and 14.9% of those in the placebo-combination arm discontinued all trial drugs due to an AE; with discontinuation rates of pembrolizumab and placebo being 20.2% and 10.4%, respectively There were 27 cases of fatality due to AEs in the pembrolizumab combination arm (6.7%) versus 12 cases

in the placebo combination arm (5.9%). [1] Treatment related AEs were reported in 91.9% of patients in the pembrolizumab combination arm.[2]

Immune-mediated AEs occurred in 22.7% in the pembrolizumab combination arm and in 11.9% of those in the placebo combination arm; Grade 3 or higher immune-related AES were reported in 8.9% of patients who were treated with the pembrolizumab combination and 4.5% of those who received the placebo combination. In the pembrolizumab combination arm, three patients died due to immune-mediated AEs (all pneumonitis).[1]

Table 6.21: Summary of AEs in the KN-189 trial (as-treated population)

Event	Pembrolizumab Combination (N=405)		Placebo Combination (N=202)	
	Any Grade	Grade 3, 4, or 5	Any Grade	Grade 3, 4, or 5
	number of patients (percent)			
Any event	404 (99.8)	272 (67.2)	200 (99.0)	133 (65.8)
Event leading to discontinuation of all treatment†	56 (13.8)	48 (11.9)	16 (7.9)	14 (6.9)
Event leading to discontinuation of any treatment component‡	112 (27.7)	81 (20.0)	30 (14.9)	22 (10.9)
Discontinuation of pembrolizumab or placebo	82 (20.2)	64 (15.8)	21 (10.4)	17 (8.4)
Discontinuation of pemetrexed	93 (23.0)	69 (17.0)	23 (11.4)	17 (8.4)
Discontinuation of platinum-based drug	31 (7.7)	27 (6.7)	12 (5.9)	10 (5.0)
Event leading to death§	27 (6.7)	27 (6.7)	12 (5.9)	12 (5.9)
Event occurring in ≥15% of patients in either group¶				
Nausea	225 (55.6)	14 (3.5)	105 (52.0)	7 (3.5)
Anemia	187 (46.2)	66 (16.3)	94 (46.5)	31 (15.3)
Fatigue	165 (40.7)	23 (5.7)	77 (38.1)	5 (2.5)
Constipation	141 (34.8)	4 (1.0)	64 (31.7)	1 (0.5)
Diarrhea	125 (30.9)	21 (5.2)	43 (21.3)	6 (3.0)
Decreased appetite	114 (28.1)	6 (1.5)	61 (30.2)	1 (0.5)
Neutropenia	110 (27.2)	64 (15.8)	49 (24.3)	24 (11.9)
Vomiting	98 (24.2)	15 (3.7)	47 (23.3)	6 (3.0)
Cough	87 (21.5)	0	57 (28.2)	0
Dyspnea	86 (21.2)	15 (3.7)	52 (25.7)	11 (5.4)
Asthenia	83 (20.5)	25 (6.2)	49 (24.3)	7 (3.5)
Rash	82 (20.2)	7 (1.7)	23 (11.4)	3 (1.5)
Pyrexia	79 (19.5)	1 (0.2)	30 (14.9)	0
Peripheral edema	78 (19.3)	1 (0.2)	26 (12.9)	0
Thrombocytopenia	73 (18.0)	32 (7.9)	29 (14.4)	14 (6.9)
Increased lacrimation	69 (17.0)	0	22 (10.9)	0

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

† This category includes patients who discontinued pemetrexed, a platinum-based drug, and pembrolizumab or placebo because of an adverse event at any time and patients who discontinued pemetrexed and pembrolizumab or placebo for an adverse event after completing four cycles of a platinum-based drug.

‡ 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 pneumonitis in 3 patients; intestinal ischemia in 2 patients; and acute kidney injury, acute kidney injury plus neutropenic sepsis, cardiac arrest, cardiac arrest plus respiratory failure, cardiac failure, cardiopulmonary failure, cerebral infarction, chronic obstructive pulmonary disease, encephalopathy, hemoptysis, ischemic stroke, lung infection, mesenteric-artery embolism, myocardial infarction, neutropenic sepsis, peritonitis, *Pneumocystis jirovecii* pneumonia, pneumonia, and septic shock in 1 patient each; 3 of the deaths in this group had an unspecified cause. The adverse events leading to death in the placebo-combination group were cerebral hemorrhage, disseminated intravascular coagulation, hemoptysis, intracranial hemorrhage, hypokalemia plus supraventricular tachycardia, multiple organ dysfunction syndrome, pneumonia, pneumonia plus respiratory failure, renal failure, respiratory failure, and septic shock in 1 patient each; 1 of the deaths in this group had an unspecified cause.

¶ The events are listed in descending order of frequency in the pembrolizumab-combination group.

Source: From NEJM, Gandhi, L., et al., Pembrolizumab plus Chemotherapy in Metastatic Non-Small-Cell Lung Cancer, Volume No. 378, Page No.2078-2092 Copyright © (2018) Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society. [Table 2][1]

6.3.2.2.2 KN-021G

Efficacy Outcomes

Objective Response Rate (ORR)

ORR was the primary endpoint in the KN-021G trial. Response outcomes were analyzed primarily after a minimum 6 months follow-up at the 08-AUG-2016 data cut-off date (10.6 months median duration of follow up). Two updated analyses were performed at the 31-May-2017 and 01-DEC_2017 (after 18.7 months and 23.9 months median durations of follow up, respectively).[2]

As of 08-AUG-2016 data cut-off date, the ORR was 55% (95% CI 42, 68) in the pembrolizumab combination arm and 29% (95% CI 18, 41) in the chemotherapy arm (estimated treatment difference = 26%; 95% CI 9, 42; p=0.0016). All responses were partial (PR). Median time to response was 1.5 months (IQR 1.4, 2.8) with the pembrolizumab combination and 2.7 months (IQR 1.4, 2.8) with chemotherapy alone. Median duration of response had not been reached in neither of the study arms.[5]

As of the 31-MAY-2017 data cut-off date, with an additional 8 months of follow up, the ORR was 56.7% (95% CI 43.2, 69.4) in the pembrolizumab combination arm and 31.7% (95% CI 20.6, 44.7) in the chemotherapy arm (estimated treatment difference = 24.8%; 95% CI 7.2, 40.9; p=0.0029). Median time to response was 1.6 months (IQR 1.2, 12.3) with the pembrolizumab combination and 2.8 months (IQR 1.1, 10.3) with chemotherapy alone. Median duration of response had not been reached in neither of the two study arms.[2]

Long-term ORR results (01-DEC-2017 data cut-off; 23.9 months median follow up) were consistent with those in the previous analyses. This analysis identified two additional confirmed responses: one in the pembrolizumab combination arm and one in the chemotherapy arm. The ORR was estimated to be 56.7% (95% CI not reported) in the pembrolizumab combination arm and 30.2% (95% CI not reported) in the chemotherapy arm (estimated treatment difference = 26.4%; 95% CI 8.9, 42.4; p=0.0016). Among the responders, one patient in each study arm experienced a CR that had evolved from a PR at the previous analysis. Median response duration had not been reached in neither of the study arms. At the time of data cut-off, 47% of responders in the pembrolizumab combination arm and 32% in the chemotherapy arm had ongoing responses.[6]

Progression-Free Survival (PFS)

PFS was a secondary endpoint in the KN-021G trial. As of the 08-AUG-2016 data cut-off date, a total of 56 PFS events (disease progression or death) were reported in the KN-021G trial, including 23 (38%) patients in the pembrolizumab plus chemotherapy group and 33 (52%) patients in the chemotherapy alone group (HR = 0·53; 95% CI 0.31, 0.91; p=0·010). The median PFS was 13·0 months (95% CI 8.3, not estimable) in pembrolizumab combination arm and 8·9 months (95% CI 4.4, 10.3) in the chemotherapy arm. The estimated proportion of patients who were alive and progression-free at 6 months was 77% (95% CI 64, 86) in the pembrolizumab combination arm and 63% (49, 74) in the chemotherapy arm.[5]

As of the 01-DEC-2017 data cut-off date (long-term analysis), 28 (47%) patients in the pembrolizumab combination arm and 43 (68%) patients in the chemotherapy arm had a PFS event (HR = 0.53; 95% CI, 0.33–0.86; P=0.0049). The Kaplan-Meier PFS curves are shown in Figure 6.10A.The median PFS was 24.0 months (95% CI 8.5, not estimable) with the pembrolizumab combination and 9.3 months (95% CI 6.2, 14.9) with chemotherapy alone.[6]

Overall Survival (OS)

OS was a secondary endpoint in the KN-021G trial. At the time of the primary analysis (08-AUG-2016 data cut-off), a total of 27 patients had died in Cohort G, including 13 (22%) patients in the pembrolizumab combination arm and 14 (22%) in the chemotherapy arm. The OS difference between the two treatment arms was not statistically significant (HR = 0.90; 95% CI 0.42, 1.91; p=0.39). The 6-month OS rate was estimated to be 92% in both treatment arms.[5]

As of the 01-DEC-2017 data cut-off date, after a median of approximately 24 months follow up, 22 (37%) patients in the pembrolizumab combination group and 35 (56%) patients in the chemotherapy arm had died. The OS benefit with the pembrolizumab+ chemotherapy combination was statistically higher than with chemotherapy alone (HR = 0.56; 95% CI 0.32, 0.95; P=0.0151). The Kaplan-Meier OS curves are shown in Figure 6.10B. Median OS was not reached in the pembrolizumab combination arm (95% CI 24.5 months, not estimable) and 21.1 months (95% CI 14.9, not estimable) in the chemotherapy arm.[6]

Figure 6.10: Kaplan-Meier curves of (A) progression-free survival and (B) overall survival in the KN-021G trial

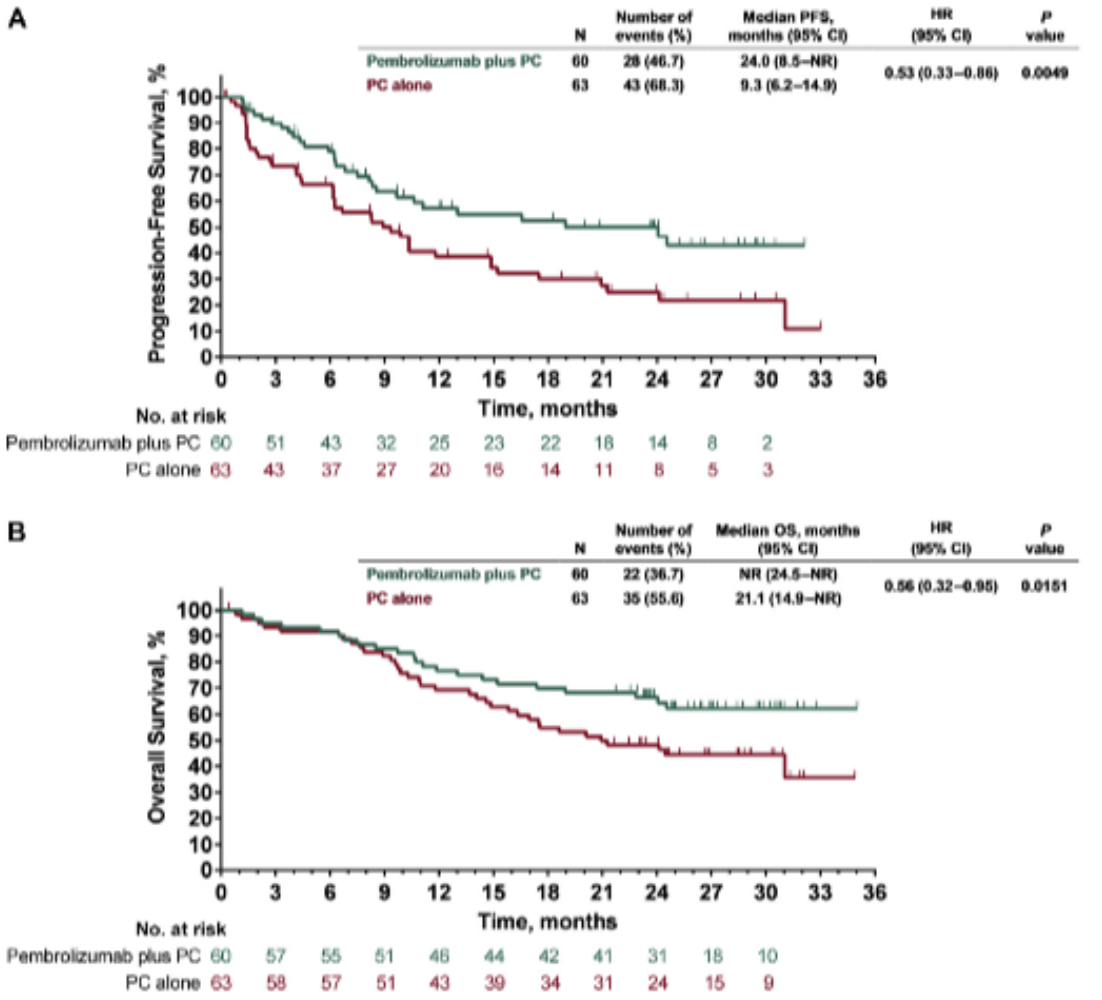


Figure 1. Kaplan-Meier analysis of progression-free survival (PFS) (per Response Evaluation Criteria in Solid Tumors, version 1, by blinded, independent central review) (*A*) and overall survival (OS) (*B*). *p* Values are descriptive (one-sided $p < 0.025$). CI, confidence interval; HR, hazard ratio; PC, pemetrexed-carboplatin; NR, not reached.

Data cut-off date: 01-DEC-2017

Source: Reprinted from Journal of Thoracic Oncology, Vol. 14 / Iss.1, 4. Borghaei, H., et al, 24-Month Overall Survival from KEYNOTE-021 Cohort G: Pemetrexed and Carboplatin with or without Pembrolizumab as First-Line Therapy for Advanced Nonsquamous Non-Small Cell Lung Cancer, Pages No. 124-129, Copyright (2019), with permission from Elsevier. [Figure 1][6]

Quality of Life

Patient- reported/ quality of life outcomes were not measured in the KN-021G trial.

Harms Outcomes[6]

As of the 01-DEC-2017 data cut-off date, after a median of 23.9 months follow up (range 0.8, 35.1), the mean duration of treatment was 10.1 (range 0 to 29.0) months in the pembrolizumab combination arm and 4.9 (range 0 to 31.0) months in the chemotherapy arm.

Table 6.22 summarizes the harm outcomes from the long-term analysis of safety data (01-DEC-2017 data cut-off) from the KN-021G trial. As shown in the table, 93.2% of patients in the pembrolizumab combination arm and 91.9% of patients in the chemotherapy arm experienced at least one AE (any grade). The most common AEs reported in both groups included fatigue (68% with pembrolizumab combination versus 44% with chemotherapy alone), nausea (59% with pembrolizumab combination versus 48% with chemotherapy alone), vomiting (31% with pembrolizumab combination versus 18% with chemotherapy alone), rash (29% with pembrolizumab combination versus 15% with chemotherapy alone), and diarrhea (24% with pembrolizumab combination versus 15% with chemotherapy alone). Anemia was reported more frequently in the chemotherapy arm (34% with pembrolizumab versus 53% with chemotherapy alone). The proportion of patients who had AEs of Grade 3 or worse was 41% with the pembrolizumab combination and 27% with chemotherapy alone. Anemia was the most common Grade 3 or 4 AE, and was reported in 12% of patients in the pembrolizumab combination arm and 13% of those in the chemotherapy arm.

Treatment-related AEs that led to discontinuation of any component of study medication were reported 16.9% of patients in the pembrolizumab combination arm and 12.9% of those in the chemotherapy arm. Treatment-related fatal AEs occurred in one (1.7%) patient in the pembrolizumab combination arm (due to sepsis) and two (3.2%) patients in chemotherapy arm (due to pancytopenia and sepsis).

Immune-mediated AEs occurred in 17 (28.8%) patients in the pembrolizumab combination arm and 7 (11.3%) patients in the chemotherapy arm. More details on the types of immune-mediated AEs are provided in Table 6.22).

Table 6.22: Summary of AEs in the KN-021G trial (as-treated population)

Treatment-related AEs, n (%)	Pembrolizumab plus PC (n = 59)		PC Alone (n = 62)	
Any grade	55 (93)		57 (92)	
Grades 3-5	24 (41)		17 (27)	
Leading to discontinuation[a]	10 (17)		8 (13)	
Leading to death	1 (2)		2 (3)	
Treatment-related AEs occurring in ≥15% of patients, n (%)	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
Fatigue	40 (68)	2 (3)	27 (44)	0 (0)
Nausea	35 (59)	1 (2)	30 (48)	0 (0)
Anemia	20 (34)	7 (12)	33 (53)	8 (13)
Vomiting	18 (31)	1 (2)	11 (18)	0 (0)
Rash	17 (29)	1 (2)	9 (15)	0 (0)
Diarrhea	14 (24)	0 (0)	9 (15)	1 (2)
Decreased appetite	13 (22)	0 (0)	12 (19)	0 (0)
Aspartate aminotransferase level increased	11 (19)	1 (2)	8 (13)	1 (2)
Constipation	11 (19)	0 (0)	6 (10)	0 (0)
Dysgeusia	11 (19)	0 (0)	7 (11)	0 (0)
Alanine aminotransferase level increased	10 (17)	1 (2)	8 (13)	1 (2)
Blood creatinine level increased	10 (17)	0 (0)	4 (7)	0 (0)
Neutrophil count decreased	10 (17)	4 (7)	8 (13)	2 (3)
Lacrimation increased	9 (15)	0 (0)	8 (13)	0 (0)
Pruritus	9 (15)	0 (0)	3 (5)	0 (0)
Immune-mediated AEs and infusion reactions,[b] n (%)	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
Hypothyroidism	9 (15)	0 (0)	2 (3)	0 (0)
Hyperthyroidism	6 (10)	0 (0)	1 (2)	0 (0)
Pneumonitis	4 (7)	1 (2)	0 (0)	0 (0)
Infusion reactions	1 (2)	1 (2)	3 (5)	0 (0)
Severe skin toxicity	1 (2)	1 (2)	1 (2)	1 (2)
Colitis	1 (2)	0 (0)	0 (0)	0 (0)

[a]Any component of study medication.
[b]Adverse events with a possible immune etiology regardless of attribution to study treatment or immune-relatedness by the investigator.
AE, adverse event; PC, pemetrexed-carboplatin.

Source: Reprinted from Journal of Thoracic Oncology, Vol. 14 / Iss.1, 4. Borghaei, H., et al, 24-Month Overall Survival from KEYNOTE-021 Cohort G: Pemetrexed and Carboplatin with or without Pembrolizumab as First-Line Therapy for Advanced Nonsquamous Non-Small Cell Lung Cancer, Pages No. 124-129, Copyright (2018), with permission from Elsevier.[Table 1][6]

6.4 Ongoing Trials

No additional ongoing trials were identified as being relevant to this review.

7 SUPPLEMENTAL QUESTIONS

The following supplemental issues were identified during development of the review protocol as relevant to the pCODR review of pembrolizumab plus platinum-doublet chemotherapy, for the treatment of metastatic non-squamous (NSQ) non-small cell lung cancer (NSCLC) in adults with no EGFR or ALK genomic tumour aberrations and no prior systemic treatment for metastatic NSQ NSCLC:

- Issue 1: Summary and critical appraisal of the manufacturer-submitted indirect treatment comparison of pembrolizumab in combination with chemotherapy versus pembrolizumab monotherapy
- Issue 2: Summary and critical appraisal of the manufacturer-submitted network meta-analysis of pembrolizumab + platinum + pemetrexed for the 1st line treatment of metastatic NSQ NSCLC patients whose tumors are sensitizing EGFR mutation and ALK translocation negative

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

7.2 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 of pembrolizumab in combination with chemotherapy vs. pembrolizumab as monotherapy when used for the 1st line treatment of metastatic NSQ NSCLC patients with no EGFR or ALK genomic tumour aberrations.

7.1.2 Methods

Data from the KN-189 and KN-024 trials were used in this ITC:

- KN- 189 was a phase III randomized, double-blind trial of pembrolizumab combined with pemetrexed-platinum chemotherapy versus placebo combined with pemetrexed-platinum chemotherapy in patients with advanced or metastatic NSQ NSCLC with no prior systemic therapies for advanced disease and no EGFR or ALK genomic tumor aberrations. Chemotherapy consisted of carboplatin or cisplatin doublet, as per Investigator's choice (see Section 6 for more information). Pembrolizumab was administered at the dose of 200 mg every three weeks.
- KN- 024 was a phase III, randomized, open-label trial of pembrolizumab monotherapy versus platinum-based chemotherapy (standard of care) in patients with stage IV, PD-L1 strong TPS ≥ 50%), NSCLC who were not previously treated for advanced disease. Standard of care consisted of one of the following treatment combinations, as per investigator's choice: pemetrexed + carboplatin; paclitaxel + carboplatin; gemcitabine +carboplatin; pemetrexed + cisplatin; and gemcitabine + cisplatin. Pembrolizumab was administered at the dose of 200 mg every three weeks.

Data from following patients were selected for the ITC analyses of OS and PFS:

- [redacted]
- [redacted]

- [redacted]

(*Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until December 4, 2019 or until notification by manufacturer that it can be publicly disclosed, whichever is earlier.*)

The inverse probability of treatment weighting (IPTW) methodology using propensity scores was used to balance out the following four arms:

1. [redacted]
2. [redacted]
3. [redacted]
4. [redacted]

(*Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until December 4, 2019 or until notification by manufacturer that it can be publicly disclosed, whichever is earlier.*)

The following covariates were used in the analysis: [redacted]. (*Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until December 4, 2019 or until notification by manufacturer that it can be publicly disclosed, whichever is earlier.*)

A statistical indirect comparison of pembrolizumab-chemotherapy combination and pembrolizumab monotherapy was performed using Bucher method after the IPTW adjustment of the trial populations and treatment arms. Outcomes of interest included progression-free survival and overall survival.

7.1.3 Findings

Patient population:

- From the KN-189 trial: [redacted].
- From the KN-024 trial: [redacted].

(*Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until December 4, 2019 or until notification by manufacturer that it can be publicly disclosed, whichever is earlier.*)

IPTW weighting:

The IPTW weights calculated for each patient ranged from [redacted] with a median of [redacted]. (*Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until December 4, 2019 or until notification by manufacturer that it can be publicly disclosed, whichever is earlier.*) Patients in the KN-189 chemotherapy arm received the [redacted] weight, with a median of [redacted] (range [redacted] to [redacted]). (*Non-disclosable information was*

used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until December 4, 2019 or until notification by manufacturer that it can be publicly disclosed, whichever is earlier.) The most imbalanced factors before weighting included: [redacted]. These co-variates were [redacted] (Table 7.1). (*Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until December 4, 2019 or until notification by manufacturer that it can be publicly disclosed, whichever is earlier.*) The geographic region of the enrolling site (East Asia vs non-East Asia) was a stratification factor in study KN-024, but it was not included in the IPTW model because of the very low number of patients enrolled in East Asia for the KN-189 trial.

Summary of the ITC results:

After IPTW adjustments, indirect comparisons of pembrolizumab + chemotherapy vs. pembrolizumab monotherapy yielded the following key results:

- Overall survival: HR = 0.65 (95% CI 0.33, 1.28)[45]
- Progression-free survival: HR = 0.69 (95% CI 040, 1.19)[45]

In both KN-189 and KN-024 trials, patients randomized to the chemotherapy arm could have received pembrolizumab 200 mg, every three weeks, after documented disease progression. Several sensitivity analyses were performed to account for this switch-over. Overall survival adjusted for switch-over without re-censoring resulted in HRs [redacted] between the pembrolizumab + chemotherapy and pembrolizumab monotherapy arms. (*Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until December 4, 2019 or until notification by manufacturer that it can be publicly disclosed, whichever is earlier.*)

Table 7.1: IPTW adjustment by patient characteristics
(*Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until December 4, 2019 or until notification by manufacturer that it can be publicly disclosed, whichever is earlier*.)
Source: [ITC provided by the Submitter (04.01.03_Keytruda_PE References_ITC-KN024), Tables 4&5][66]

7.1.4 Summary and conclusions

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.[67] Details of the critical appraisal are presented in Table 7.2.

Table 7.2: Adapted ISPOR Questionnaire to Assess the Credibility of the indirect treatment comparison of pembrolizumab in combination with chemotherapy versus pembrolizumab monotherapy †

ISPOR Questions	Details and Comments
1. Is the population relevant?	**Yes**. The study populations of the studies included in indirect comparisons aligned with the indication under review. The Submitters' ITC included two trials of adult patients with advanced/metastatic NSCLC who did not receive prior therapies in the advanced setting. From the included trials, the ITC selected patients with NSQ histology and strong PD-L1 (TPS≥50%).
2. Are any critical interventions missing?	**No.** The submitted ITC compared pembrolizumab + chemotherapy vs. pembrolizumab monotherapy as a comparator. During the protocol development phase, the review team also identified standard of care with chemotherapy as a potential

Table 7.2: Adapted ISPOR Questionnaire to Assess the Credibility of the indirect treatment comparison of pembrolizumab in combination with chemotherapy versus pembrolizumab monotherapy †

ISPOR Questions		Details and Comments
		comparator. An NMA of pembrolizumab + chemotherapy vs. other 1st line treatment options for NSQ NSCLC was also provided by the Submitter, which is be summarized in section 7.2
3.	Are any relevant outcomes missing?	**Yes, in part.** The following outcomes were assessed: OS and PFS. Other relevant outcomes such as ORR, quality of life, and safety results were excluded from the submitted
4.	Is the context (e.g., settings and circumstances) applicable to your population?	**Yes**. The settings of the included trials were relevant to that in this pCODR review.
5.	Did the researchers attempt to identify and include all relevant randomized controlled trials?	**Yes**. For the purpose of this pCODR submission, the Submitter conducted a systematic literature review of randomized controlled trials of pembrolizumab + platinum- pemetrexed chemotherapy and competing interventions for the 1st line treatment of metastatic NSQ NSCLC in patients with no EGFR and ALK mutations. Details of the systematic review methodology (e.g., databases, search strategy, study selection criteria and process) were provided in the Submitted NMA report.
6.	Do the trials for the interventions of interest form one connected network of randomized controlled trials?	**Not applicable**. Data from to RCTs were used for the purpose of this ITC. The statistical indirect comparison of was performed using Bucher method after IPTW adjustments for the trial populations and treatment arms.
7.	Is it apparent that poor quality studies were included thereby leading to bias?	**No.** Based on the Submitter's systematic review report, the Cochrane Collaboration's Risk of Bias tool was used to assess risk of bias in included clinical trials. The results of the quality assessment of individual trials were provided as an appendix in the submitted NMA report.
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 most imbalanced factors before weighting included: [redacted]. (*Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until December 4, 2019 or until notification by manufacturer that it can be publicly disclosed, whichever is earlier.*)
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?	**Unclear**. The Submitter used IPTW methodology (using propensity scores) to balance out the study populations with regard to the following covariates: [redacted] across the four arms after weighting; however, the provided data shows [redacted] between the four study arms. (*Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until December 4, 2019 or until notification by*

Table 7.2: Adapted ISPOR Questionnaire to Assess the Credibility of the indirect treatment comparison of pembrolizumab in combination with chemotherapy versus pembrolizumab monotherapy †

ISPOR Questions		Details and Comments
		manufacturer that it can be publicly disclosed, whichever is earlier.) [redacted]. (*Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until December 4, 2019 or until notification by manufacturer that it can be publicly disclosed, whichever is earlier.*) Therefore, it is unclear if the remaining imbalances between the study arms.
11.	Were statistical methods used that preserve within-study randomization? (No naïve comparisons)	**Yes**. An IPTW methodology (using propensity scores) was used
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**
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 of trials, did the researchers attempt to minimize this bias with the analysis?	**Yes**. The submitter attempted to minimize imbalances between the treatment arms, in terms of known effect modifiers, using propensity scores.
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?	**Not applicable**
19.	Are the individual study results reported?	**Yes**. The effect estimates (OS and PFS) for both KN189 and KN 024 were provided in the submitted ITC.
20.	Are results of direct comparisons reported separately from results of the indirect comparisons or network meta-analysis?	**Not applicable**
21.	Are all pairwise contrasts between interventions as obtained with the network meta-analysis reported along	**Not applicable**

Table 7.2: Adapted ISPOR Questionnaire to Assess the Credibility of the indirect treatment comparison of pembrolizumab in combination with chemotherapy versus pembrolizumab monotherapy †

ISPOR Questions		Details and Comments
	with measures of uncertainty?	
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?	**Yes, in part** No subgroup analyses were conducted based on specific patient characteristics Several sensitivity analyses were performed to adjust for the effect of switching to pembrolizumab in the chemotherapy (standard of care) arms.
24.	Are the conclusions fair and balanced?	**Yes.** The submitted ITC concluded that the there was a numerical benefit in OS and PFS for pembrolizumab + chemotherapy over pembrolizumab monotherapy in metastatic, NSQ NSCLC with strong PD-L1. The Submitter also discussed that the confidence intervals around the estimated hazard ratios were wide (and included the null hypotheses value) possibly due to the limited sample sizes in KN189 and KN024 trials due to the matching for covariates.
25.	Were there any potential conflicts of interest?	**Not reported.**
26.	If yes, were steps taken to address these?	**Not applicable.**

ALK = anaplastic large-cell lymphoma kinase; **ECOG PS**= Eastern Cooperative Oncology Group performance score; **EGFR =** epidermal growth factor receptor; **ISPOR** = International Society For Pharmacoeconomics and Outcomes Research; ITC = indirect treatment comparison; **NMA**= network meta-analysis; **NSCLC**= non-small cell lung cancer; **NSQ** = non squamous**; OS** = overall survival; **PD-L1** = programmed death-ligand1**PFS** = progression-free survival;
† Adapted from Jansen, Value Health. 2014;17(2):157-73[67]

Conclusion

Using data from the KN-189 and KN-024 trials, the Submitter provided an ITC to estimate the treatment difference of pembrolizumab in combination with chemotherapy vs. pembrolizumab as monotherapy for the 1st line treatment of metastatic NSQ NSCLC patients with no EGFR or ALK genomic tumour aberrations. The indirect comparisons were performed using Bucher method after the IPTW (propensity score) adjustment of the treatment arms and concluded that there was a numerical benefit in OS and PFS for pembrolizumab + chemotherapy over pembrolizumab monotherapy in metastatic, NSQ NSCLC with strong PD-L1. In other words, although the point estimates of effect resulting from the ITC (HR < 1) suggested that pembrolizumab + chemotherapy could be superior to pembrolizumab monotherapy in terms of progression-free survival and overall survival, these results should be interpreted with caution as the corresponding confidence intervals cross the null hypothesis value (i.e., statistical non-significance). Therefore, the relative efficacy of pembrolizumab + chemotherapy over pembrolizumab monotherapy remains uncertain in the patient population of interest.

7.2 Summary and critical appraisal of the manufacturer-submitted network meta-analysis of pembrolizumab + platinum + pemetrexed for the 1st line treatment of metastatic NSQ NSCLC patients whose tumors are sensitizing EGFR mutation and ALK translocation negative

7.2.1 Objectives

The objectives of the submitted NMA report was to conduct a systematic literature review of randomized controlled trials (RCTs) describing the efficacy and safety of pembrolizumab + platinum-pemetrexed chemotherapy and competing interventions (relevant to the global perspective) for the 1st line treatment of metastatic NSCLC in patients with non-squamous histology who are EGFR mutation and ALK translocation negative.

7.2.2 Methods

Systematic Review: The submitter conducted a systematic literature review of literature in May 2016 with updates in March 2017 and November 2017; that involved data base search (MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials) and gray literature searches to identify RCTs assessing the efficacy of pembrolizumab or competing interventions for 1st line treatment of advanced NSCLC. Efficacy outcomes of interest for NMA were OS and PFS. Data on ORR, treatment-related AEs, Grade 3 or 4 AEs, and discontinuations due to AEs were also extracted.

Network meta-analysis: Where results of the RCTs identified in the systematic review formed part of one evidence network and were deemed to be sufficiently similar for each population and outcome of interest, they were synthesized by means of Bayesian NMAs. For OS and PFS, models relying on the proportional hazards assumption were used, as well as models anticipating time-varying HRs. Normal non-informative prior distributions were used for all parameters (mean 0; variance of 10,000). Relative treatment effects were expressed as HRs with 95% credible intervals (CrI). Analyses were carried out in the non-squamous population irrespective of PD-L1 expression level for the base case. Scenario analyses were performed using data from specified PD-L1 expression level subsets for PD1/PD-L1 directed therapies, with sensitivity analyses that removed trials conducted exclusively in an East Asian population for each scenario.

For the purpose of NMA, the Submitter used random-effect models, unless it was noted that only fixed-effects results could be calculated due to data restrictions. However, all sensitivity analyses utilized fixed-effects models because removing trials conducted in exclusively East Asian patients did not leave enough trials in the network to estimate a stable heterogeneity parameter.

7.2.3 Results

A total of 20 relevant trials were identified and included in the NMAs. Networks of evidence were developed separately for each scenario subject to data availability and corresponding to various PD-L1 expression subgroups in trials assessing PD-L1-directed therapies. In total there were 7 scenarios including the base case scenario which comprised patients with all PD-L1 expression levels (Figure 7.1).

Overall Survival

The OS results from the individual studies included in the NMA are presented in Table 7.3 and the pair wise NMA results are shown in Table 7.4. As shown, under the random-effects proportional hazards model, pembrolizumab + platinum-pemetrexed chemotherapy showed statistically

meaningful benefit for OS over most competing interventions except for atezolizumab regimen and other pembrolizumab regimens.

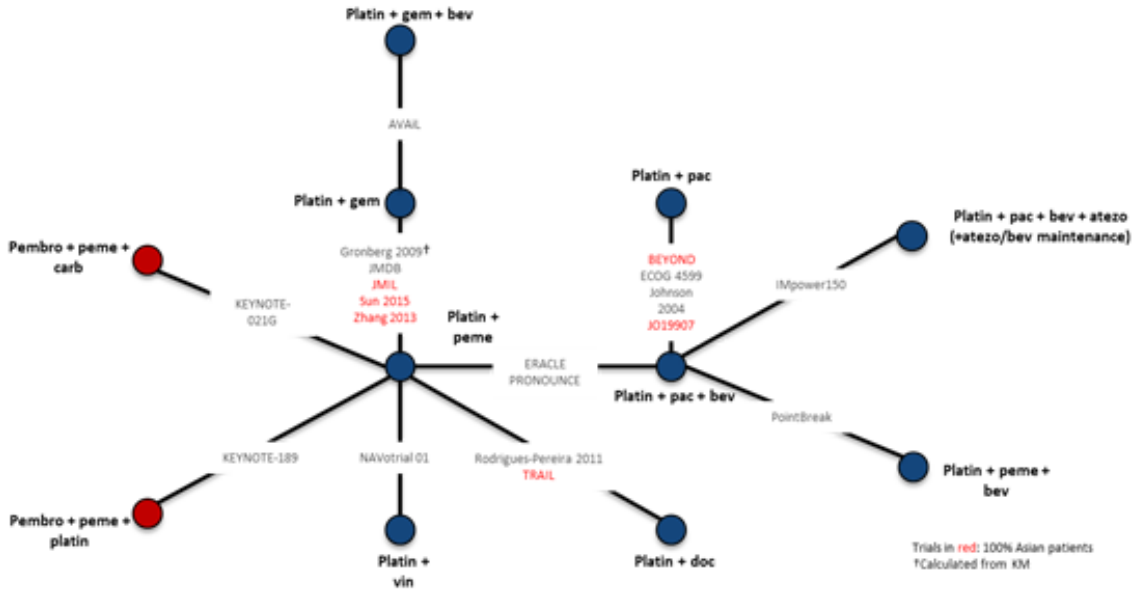
Progression-Free Survival

The PFS results from the individual studies included in the NMA are presented in Table 7.5 and the pair wise NMA results are shown in Table 7.6. As shown, under the random-effects proportional hazards model, pembrolizumab + platinum-pemetrexed chemotherapy showed statistically meaningful benefit for PFS over most competing interventions except for atezolizumab regimen and other pembrolizumab regimens.

Scenario and sensitivity analyses:

Proportional hazards models revealed that pembrolizumab + platinum-pemetrexed chemotherapy HRs for both OS and PFS were numerically less efficacious in the (PD-L1 TPS 1-49%) 4 (PD-L1 TPS < 1%) scenarios compared to the (PD-L1 TPS>50%) scenario. Fixed-effects sensitivity analyses (excluding trials conducted in an exclusively East Asian population) in all scenarios and for both OS and PFS revealed pembrolizumab + platinum-pemetrexed chemotherapy was statistically superior compared to almost all competing interventions. Under the time-varying NMA model, the first shape parameter did not differ significantly from zero for any pembrolizumab intervention except for pembrolizumab monotherapy for PFS (PD-L1 TPS>50% scenario). In this scenario, the HR for Pembrolizumab monotherapy vs platinum-pemetrexed chemotherapy decreased over time, with this result becoming statistically meaningful after approximately 6 months. Because most HRs did not vary significantly over time for pembrolizumab, the proportional HR models provided the best combination of fit and parsimony.

Figure 7.1: Network of evidence for overall survival and progression-free survival(base case)



Source: [NMA report Figure 57, Page 128][68]

Table 7.3: Constant hazard ratios for overall survival in the submitted network meta-analysis (base case)

Study	Reference	Intervention	HR	logHR(SE)
AVAiL	Platin + gem	Platin + gem + bev	1.03	0.03 (0.09)
BEYOND	Platin + pac	Platin + pac +bev	0.68	-0.39 (0.16)
ECOG 4599	Platin + pac	Platin + pac +bev	0.79	-0.24 (0.08)
ERACLE	Platin + peme	Platin + pac +bev	1.08	0.08 (0.22)
Gronberg, 2009	Platin + peme	Platin + gem	1.04	0.04 (0.13)
IMPower150	Platin + pac + bev	Platin + pac + bev + atezo	0.78	-0.25 (0.11)
JMDB	Platin + peme	Platin + gem	1.23	0.21 (0.08)
JMIL	Platin + peme	Platin + gem	1.00	0.00 (0.15)
JO19907	Platin + pac	Platin + pac +bev	0.99	-0.01 (0.21)
Johnson, 2004	Platin + pac	Platin + pac +bev	0.85	-0.16 (0.27)
KEYNOTE021G	Platin + peme	Pembro + peme + carb	0.59	-0.53 (0.29)
KEYNOTE-189	Platin + peme	Pembro + peme + platin	0.49	-0.71 (0.13)
NAVotrial01	Platin + peme	Platin + vin	1.00	0.00 (0.22)
PointBreak	Platin + pac + bev	Platin + pem + bev	1.00	0.00 (0.08)
PRONOUNCE	Platin + peme	Platin + pac + bev	0.93	-0.07 (0.13)
Rodrigues-Pereira, 2011	Platin + peme	Platin + doc	1.01	0.01 (0.17)
Sun, 2015	Platin + peme	Platin + gem	1.14	0.13 (0.17)
TRAIL	Platin + peme	Platin + doc	0.68	-0.39 (0.18)
Zhang, 2013	Platin + peme	Platin + gem	1.05	0.05 (0.17)

Source: [NMA report Table 76. Page 128][68]

Table 7.4: Pairwise comparison results from random-effects NMA (overall survival; base case)

Platin + peme	1.20 (0.90, 1.60)	0.89 (0.78, 1.05)	0.86 (0.64, 1.21)	0.82 (0.59, 1.12)	1.03 (0.78, 1.33)	1.03 (0.71, 1.47)	1.00 (0.62, 1.62)	1.32 (0.88, 1.98)	1.71 (0.93, 3.10)	**2.04 (1.44, 2.85)**
0.83 (0.63, 1.11)	**Platin + doc**	0.74 (0.54, 1.03)	0.72 (0.48, 1.12)	0.68 (0.44, 1.04)	0.86 (0.57, 1.26)	0.86 (0.53, 1.37)	0.83 (0.47, 1.46)	1.10 (0.67, 1.81)	1.42 (0.73, 2.76)	**1.69 (1.09, 2.64)**
1.12 (0.95, 1.28)	1.35 (0.97, 1.84)	**Platin + gem**	0.97 (0.74, 1.29)	0.92 (0.63, 1.29)	1.15 (0.83, 1.55)	1.16 (0.75, 1.69)	1.12 (0.68, 1.85)	1.48 (0.95, 2.26)	**1.91 (1.02, 3.51)**	**2.29 (1.56, 3.27)**
1.16 (0.83, 1.56)	1.39 (0.89, 2.10)	1.03 (0.78, 1.36)	**Platin + gem + bev**	0.95 (0.59, 1.46)	1.19 (0.77, 1.77)	1.19 (0.72, 1.89)	1.15 (0.65, 2.04)	1.53 (0.90, 2.51)	**1.98 (1.00, 3.79)**	**2.36 (1.46, 3.65)**
1.22 (0.89, 1.71)	1.48 (0.97, 2.28)	1.09 (0.78, 1.58)	1.06 (0.69, 1.69)	**Platin + pac**	**1.26 (1.04, 1.50)**	1.26 (0.91, 1.73)	1.22 (0.69, 2.23)	**1.62 (1.12, 2.31)**	**2.08 (1.05, 4.13)**	**2.50 (1.56, 4.02)**
0.97 (0.75, 1.28)	1.17 (0.79, 1.75)	0.87 (0.65, 1.20)	0.84 (0.57, 1.30)	**0.79 (0.66, 0.96)**	**Platin + pac + bev**	1.00 (0.77, 1.29)	0.97 (0.57, 1.73)	1.29 (0.94, 1.76)	1.65 (0.85, 3.19)	**1.98 (1.29, 3.07)**
0.97 (0.68, 1.42)	1.16 (0.73, 1.89)	0.86 (0.59, 1.32)	0.84 (0.53, 1.40)	0.79 (0.58, 1.10)	1.00 (0.77, 1.30)	**Platin + peme + bev**	0.96 (0.54, 1.80)	1.29 (0.86, 1.91)	1.65 (0.81, 3.38)	**1.98 (1.20, 3.28)**
1.00 (0.62, 1.61)	1.20 (0.69, 2.11)	0.89 (0.54, 1.47)	0.87 (0.49, 1.55)	0.82 (0.45, 1.45)	1.03 (0.58, 1.76)	1.04 (0.55, 1.85)	**Platin + vin**	1.33 (0.69, 2.49)	1.70 (0.79, 3.68)	**2.03 (1.12, 3.66)**
0.76 (0.51, 1.14)	0.91 (0.55, 1.50)	0.67 (0.44, 1.05)	0.65 (0.40, 1.12)	**0.62 (0.43, 0.89)**	0.78 (0.57, 1.06)	0.78 (0.52, 1.16)	0.75 (0.40, 1.45)	**Platin + pac + bev + atezo**	1.29 (0.62, 2.65)	1.54 (0.91, 2.62)
0.59 (0.32, 1.08)	0.70 (0.36, 1.38)	**0.52 (0.28, 0.98)**	**0.51 (0.26, 1.00)**	**0.48 (0.24, 0.96)**	0.61 (0.31, 1.17)	0.60 (0.30, 1.24)	0.59 (0.27, 1.27)	0.78 (0.38, 1.62)	**Pembro + peme + carb**	1.19 (0.60, 2.43)
0.49 (0.35, 0.69)	**0.59 (0.38, 0.92)**	**0.44 (0.31, 0.64)**	**0.42 (0.27, 0.69)**	**0.40 (0.25, 0.64)**	**0.50 (0.33, 0.78)**	**0.50 (0.30, 0.83)**	**0.49 (0.27, 0.89)**	0.65 (0.38, 1.10)	0.84 (0.41, 1.67)	**Pembro + peme + platin**

Note: Each cell represents the comparison (hazard ratio and 95% CrI) of the row treatment versus the column treatment.
All bolded values are statistically meaningful at the 0.05 significance level.
DIC: 28.53; Deviance: 16.29; SD: 0.08

Source: [NMA report Table 77. Page 129][68]
Results presented as constant hazard ratios between all competing interventions along with 95% credible intervals

Table 7.5: Constant hazard ratios for progression-free survival in the submitted network meta-analysis (base case)

Study	Reference	Intervention	HR	logHR(SE)
AVAiL	Platin + gem + bev	Platin + gem	0.82	-0.20 (0.09)
BEYOND	Platin + pac	Platin + pac + bev	0.40	-0.92 (0.16)
ECOG 4599	Platin + pac	Platin + pac + bev	0.66	-0.42 (0.08)
ERACLE	Platin + peme	Platin + pac + bev	1.27	0.24 (0.20)
IMpower150	Platin + pac + bev	Platin + pac + bev + atezo	0.62	-0.48 (0.09)
JMDB	Platin + peme	Platin + gem	1.11	0.11 (0.07)
JMIL	Platin + peme	Platin + gem	0.95	-0.05 (0.13)
JO19907	Platin + pac	Platin + pac + bev	0.61	-0.49 (0.19)
KEYNOTE021G	Platin + peme	Pembro + peme + carb	0.54	-0.62 (0.25)
KEYNOTE-189	Platin + peme	Pembro + peme + platin	0.52	-0.65 (0.10)
NAVotrial01	Platin + peme	Platin + vin	1.16	0.15 (0.19)
PointBreak	Platin + pac + bev	Platin + peme + bev	0.83	-0.19 (0.08)
PRONOUNCE	Platin + peme	Platin + pac + bev	0.94	-0.06 (0.12)
Rodrigues-Pereira, 2011	Platin + doc	Platin + peme	1.04	0.04 (0.15)
Sun, 2015	Platin + peme	Platin + gem	1.33	0.29 (0.12)
TRAIL	Platin + peme	Platin + doc	0.97	-0.03 (0.16)

Source: [NMA report Table 4. Page 63][68]

Table 7.6: Pairwise comparison results from random-effects NMA (progression-free survival; base case)

Platin + peme	0.99 (0.68, 1.47)	0.89 (0.67, 1.20)	1.09 (0.61, 1.96)	**0.54 (0.31, 0.85)**	0.95 (0.63, 1.38)	1.15 (0.61, 2.09)	0.86 (0.47, 1.55)	1.55 (0.79, 2.88)	1.85 (0.97, 3.64)	**1.92 (1.17, 3.13)**
1.01 (0.68, 1.48)	Platin + doc	0.90 (0.56, 1.45)	1.09 (0.54, 2.18)	**0.54 (0.28, 0.96)**	0.96 (0.55, 1.62)	1.16 (0.55, 2.34)	0.86 (0.43, 1.75)	1.56 (0.71, 3.23)	1.86 (0.87, 4.07)	**1.93 (1.04, 3.62)**
1.12 (0.83, 1.50)	1.12 (0.69, 1.79)	Platin + gem	1.22 (0.74, 2.00)	0.61 (0.32, 1.03)	1.07 (0.64, 1.71)	1.29 (0.64, 2.51)	0.96 (0.49, 1.85)	1.74 (0.83, 3.44)	**2.08 (1.01, 4.24)**	**2.16 (1.23, 3.86)**
0.92 (0.51, 1.64)	0.91 (0.46, 1.84)	0.82 (0.50, 1.36)	Platin + gem + bev	0.50 (0.22, 1.03)	0.88 (0.43, 1.74)	1.06 (0.45, 2.43)	0.79 (0.34, 1.80)	1.42 (0.60, 3.34)	1.70 (0.71, 4.16)	1.77 (0.82, 3.82)
1.85 (1.18, 3.21)	**1.84 (1.04, 3.60)**	1.65 (0.97, 3.13)	2.01 (0.97, 4.55)	Platin + pac	**1.76 (1.33, 2.47)**	**2.13 (1.22, 3.87)**	1.60 (0.76, 3.66)	**2.86 (1.63, 5.31)**	**3.44 (1.58, 8.12)**	**3.55 (1.87, 7.59)**
1.05 (0.72, 1.58)	1.04 (0.62, 1.83)	0.93 (0.58, 1.56)	1.14 (0.58, 2.34)	**0.57 (0.41, 0.75)**	Platin + pac + bev	1.21 (0.74, 1.97)	0.90 (0.45, 1.88)	1.62 (0.98, 2.68)	1.94 (0.93, 4.24)	**2.01 (1.10, 3.86)**
0.87 (0.48, 1.64)	0.86 (0.43, 1.83)	0.78 (0.40, 1.57)	0.95 (0.41, 2.24)	**0.47 (0.26, 0.82)**	0.83 (0.51, 1.34)	Platin + peme + bev	0.75 (0.32, 1.74)	1.34 (0.68, 2.71)	1.61 (0.67, 3.98)	1.67 (0.78, 3.73)
1.17 (0.65, 2.12)	1.16 (0.57, 2.34)	1.04 (0.54, 2.03)	1.26 (0.56, 2.92)	0.63 (0.27, 1.32)	1.11 (0.53, 2.23)	1.34 (0.57, 3.09)	Platin + vin	1.80 (0.74, 4.31)	2.15 (0.91, 5.29)	**2.24 (1.03, 4.94)**
0.65 (0.35, 1.26)	0.64 (0.31, 1.40)	0.57 (0.29, 1.20)	0.70 (0.30, 1.67)	**0.35 (0.19, 0.61)**	0.62 (0.37, 1.02)	0.74 (0.37, 1.48)	0.56 (0.23, 1.34)	Platin + pac + bev + atezo	1.20 (0.49, 3.06)	1.24 (0.57, 2.90)
0.54 (0.27, 1.04)	0.54 (0.25, 1.15)	**0.48 (0.24, 0.99)**	0.59 (0.24, 1.40)	**0.29 (0.12, 0.63)**	0.52 (0.24, 1.07)	0.62 (0.25, 1.48)	0.47 (0.19, 1.10)	0.84 (0.33, 2.03)	Pembro + peme + carb	1.04 (0.45, 2.30)
0.52 (0.32, 0.85)	**0.52 (0.28, 0.96)**	**0.46 (0.26, 0.82)**	0.56 (0.26, 1.22)	**0.28 (0.13, 0.53)**	**0.50 (0.26, 0.91)**	0.60 (0.27, 1.28)	**0.45 (0.20, 0.97)**	0.81 (0.35, 1.75)	0.96 (0.43, 2.23)	Pembro + peme + platin

Note: Each cell represents the comparison (hazard ratio and 95% CrI) of the row treatment versus the column treatment.
All bolded values are statistically meaningful at the 0.05 significance level.
DIC: 30.15; Deviance: 16.01; SD: 0.2

Source: [NMA report Table 5. Page 64][68]
Results presented as constant hazard ratios between all competing interventions along with 95% credible intervals

7.2.4 Summary

The quality of the NMA provided by the Submitter[68] was assessed according to the recommendations made by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force on Indirect Treatment Comparisons. Details of the critical appraisal are presented in Table 7.7.

Table 7.7: Adapted ISPOR Questionnaire to Assess the Credibility of the network meta-analysis pembrolizumab + platinum + pemetrexed for the 1st line treatment of EGFR and ALK negative metastatic NSQ NSCLC patients†

ISPOR Questions		Details and Comments
1.	Is the population relevant?	**Yes**. The study populations of the studies included in the submitted NMA aligned with the indication under review.
2.	Are any critical interventions missing?	**No.** The Manufacturer included all relative interventions for this patient population in the systematic review and NMAs.
3.	Are any relevant outcomes missing?	**Yes, in part.** The Manufacturer included PFS and OS as the key efficacy outcomes in the NMAs. They also indicated that data on ORR and Safety outcomes (e.g., treatment-related AEs, WDAEs) were extracted from the identified studies. However, these outcomes were not considered in the submitted NMA.
4.	Is the context (e.g., settings and circumstances) applicable to your population?	**Yes**. The settings of the included trials were relevant to that in this pCODR review.
5.	Did the researchers attempt to identify and include all relevant randomized controlled trials?	**Yes**. The Submitter provided a summary of the systematic literature review process used in the NMA. In the summary, the Manufacturer took adequate steps to ensure an unbiased selection of studies for inclusion in their analysis.
6.	Do the trials for the interventions of interest form one connected network of randomized controlled trials?	**Yes**. The Manufacturer constructed a network of all evidence by linking treatments irrespectively of the outcome of interest.
7.	Is it apparent that poor quality studies were included thereby leading to bias?	**No.** The Submitter used the Cochrane Collaboration's Risk of Bias tool to assess methodological quality of the included clinical trials. The results of the quality assessment of individual trials were provided as an appendix in the submitted NMA report. Overall, the trials were considered to have low risk of bias based on the Cochrane Collaboration's tool.
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**. In order to show between-study similarities, the -submitted NMA report described the distribution of key baseline characteristics of the study populations along with a description of study design characteristics. The between group differences in effect modifiers between trials were highlighted in the NMA report.
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 Manufacture-submitted NMA report, the study design and the patient characteristics of each RCT were investigated to detect potential effect-modifiers. The NMA feasibility analyses were conducted for each outcome, which included an assessment of the availability and the comparability of the data across the studies.
11.	Were statistical methods used that	**Yes**. The Submitter used a Bayesian NMA (hazard-based

Table 7.7: Adapted ISPOR Questionnaire to Assess the Credibility of the network meta-analysis pembrolizumab + platinum + pemetrexed for the 1st line treatment of EGFR and ALK negative metastatic NSQ NSCLC patients†		
	ISPOR Questions	**Details and Comments**
	preserve within-study randomization? (No naïve comparisons)	approach) to analyze data on outcomes of interest from the included RCTs, along with additional models anticipating time-varying HRs.
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 of trials, did the researchers attempt to minimize this bias with the analysis?	**Yes, partly.** . The manufacturer presented the distributions of potential effect-modifiers among the included studies. In their NMA report, the Submitter stated: "given the network structure assumed for the analysis, there may be systematic differences in effect modifiers between trials; however, the limited evidence base prevented the use of meta-regression to explain heterogeneity and minimize inconsistency".
15.	Was a valid rationale provided for the use of random effects or fixed effect models?	**Yes.** The submitter explained that the results of random-effect models would be more plausible for all constant hazards NMAs. Therefore, they presented random-effects results, unless it is only fixed-effects results could be calculated due to data restriction (e.g., for sensitivity analyses).
16.	If a random effects model was used, were assumptions about heterogeneity explored or discussed?	**Yes.** When the evidence was considered to be insufficient to estimate between-study heterogeneity, fixed-effects models were used.
17.	If there are indications of heterogeneity, were subgroup analyses or meta-regression analysis with pre-specified covariates performed?	**Yes, in part.** Scenario analyses were performed by PD-L1 status. Meta-regression analysis (to assess the impact of multiple covariates) was not performed due to the limited evidence.
18.	Is a graphical or tabular representation of the evidence network provided with information on the number of RCTs per direct comparison?	**Yes**. The NMA networks for each outcome were presented in the Submitter's NMA report.
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?	**Yes.** However, 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 Manufacturer's NMA report provided the pairwise NMA results for pembrolizumab + chemotherapy versus each of the competing interventions. Measures of uncertainty (95% CrI) were reported for estimates of effect.
22.	Is a ranking of interventions provided given the reported treatment effects and its uncertainty by outcome?	**Yes, in part**. In the submitted NMA report, hazard ratios of competing interventions were plotted over time (under the best fitting models). However, probabilities of being best for each treatment were not presented.

Table 7.7: Adapted ISPOR Questionnaire to Assess the Credibility of the network meta-analysis pembrolizumab + platinum + pemetrexed for the 1st line treatment of EGFR and ALK negative metastatic NSQ NSCLC patients†		
ISPOR Questions		**Details and Comments**
23.	Is the impact of important patient characteristics on treatment effects reported?	**Yes, in part.** Scenario analyses were performed by PD-L1 status, as well as sensitivity analysis which excluded trials that were conducted exclusively in East Asian patients.
24.	Are the conclusions fair and balanced?	**Yes.** The submitted NMA s concluded that in the patient population of interest, pembrolizumab + chemotherapy could be superior to most competing interventions in terms of OS and PFS except for atezolizumab regimen and other pembrolizumab regimens.
25.	Were there any potential conflicts of interest?	**Not reported.**
26.	If yes, were steps taken to address these?	**Not applicable.**
CrI = credible interval**; HRQoL** = health-related quality of life; **ISPOR** = International Society For Pharmacoeconomics and Outcomes Research; **NMA**= network meta-analysis; **OS** = overall survival **PFS** = progression-free survival; **SUCRA** = surface under the cumulative ranking curve † Adapted from Jansen, Value Health. 2014;17(2):157-73[67]		

7.2.5 Conclusion

The submitter conducted a systematic review of literature and NMA to provide indirect comparisons between pembrolizumab + platinum-pemetrexed chemotherapy and competing interventions for the 1st line treatment of metastatic NSCLC in patients with non-squamous histology who are EGFR mutation and ALK translocation negative.

The submitted NMAs concluded that in the patient population of interest, pembrolizumab + chemotherapy could be superior to most competing interventions in terms of OS and PFS except for atezolizumab regimen and other pembrolizumab regimens. Some levels of heterogeneity in effect modifiers between trials. However, these results should be interpreted with caution due to limitations that may arise from between-study differences in some covariates; and lack of sufficient evidence to minimize heterogeneity and inconsistency (e.g., by performing meta-regression analysis).

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 (Keytruda) non-squamous 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 Economic Guidance Report was handled in accordance with the *pCODR Disclosure of Information Guidelines*. The manufacturer, as the primary data owner, did not agree to the disclosure of some clinical information which was provided to pERC for their deliberations, and this information has been redacted in this publicly posted Guidance Report.

This Initial Economic Guidance Report is publicly posted at the same time that a pERC Initial Recommendation is issued. A Final Economic Guidance Report will be publicly posted when a pERC Final Recommendation is issued. The Final Economic Guidance Report will supersede this Initial Economic 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 August 2018, Embase 1974 to 2018 September 26, Ovid MEDLINE(R) ALL 1946 to September 26, 2018
Search Strategy:

#	Searches	Results
1	(Keytruda* or Pembrolizumab* or Lambrolizumab* or HSDB 8257 or HSDB8257 or Merck 3475 or Merck3475 or MK 3475 or MK3475 or Sch 900475 or Sch900475 or DPT0O3T46P).ti,ab,ot,kf,kw,hw,rn,nm.	9734
2	Carcinoma, Non-Small-Cell Lung/	52993
3	Carcinoma, Large Cell/ and exp lung/	430
4	(NSCLC? or LCLC?).ti,ab,kf,kw.	106811
5	((non small cell or nonsmall cell or large cell or undifferentiated) adj5 (lung or bronchial or pulmonary) adj5 (cancer* or tumor* or tumour* or carcinoma* or neoplasm*)).ti,ab,kf,kw.	150881
6	((bronchial or pulmonary or lung) adj3 (adenocarcinoma* or adeno-carcinoma*)).ti,ab,kf,kw.	43893
7	((bronchioloalveolar or bronchiolo alveolar) adj3 (carcinoma* or cancer* or neoplasm* or tumor* or tumour*)).ti,ab,kf,kw.	3639
8	or/2-7	208468
9	1 and 8	2128
10	9 use medall	437
11	9 use cctr	155
12	*pembrolizumab/ or (Keytruda* or Pembrolizumab* or Lambrolizumab* or HSDB 8257 or HSDB8257 or Merck 3475 or Merck3475 or MK 3475 or MK3475 or Sch 900475 or Sch900475).ti,ab,kw,dq.	6339
13	non small cell lung cancer/ or large cell lung carcinoma/ or lung adenocarcinoma/	115255
14	(NSCLC? or LCLC?).ti,ab,kw,dq.	106631
15	((non small cell or nonsmall cell or large cell or undifferentiated) adj5 (lung or bronchial or pulmonary) adj5 (cancer* or tumor* or tumour* or carcinoma* or neoplasm*)).ti,ab,kw,dq.	150443
16	((bronchial or pulmonary or lung) adj3 (adenocarcinoma* or adeno-carcinoma*)).ti,ab,kw,dq.	44009
17	((bronchioloalveolar or bronchiolo alveolar) adj3 (carcinoma* or cancer* or neoplasm* or tumor* or tumour*)).ti,ab,kw,dq.	3633
18	or/13-17	220993
19	12 and 18	1772
20	19 use oemezd	1207
21	20 and conference abstract.pt.	595
22	limit 21 to yr=2013-current	594
23	20 not conference abstract.pt.	612
24	(Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or Equivalence Trial or Clinical Trial, Phase III).pt.	1102197
25	Randomized Controlled Trial/	982511
26	exp Randomized Controlled Trials as Topic/	277267
27	"Randomized Controlled Trial (topic)"/	148937

28	Controlled Clinical Trial/	550661
29	exp Controlled Clinical Trials as Topic/	288423
30	"Controlled Clinical Trial (topic)"/	9557
31	Randomization/	175392
32	Random Allocation/	192220
33	Double-Blind Method/	393762
34	Double Blind Procedure/	152947
35	Double-Blind Studies/	258107
36	Single-Blind Method/	74482
37	Single Blind Procedure/	32401
38	Single-Blind Studies/	76429
39	Placebos/	324106
40	Placebo/	323146
41	Control Groups/	111323
42	Control Group/	111231
43	(random* or sham or placebo*).ti,ab,hw,kf,kw.	3940770
44	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.	771578
45	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.	2908
46	(control* adj3 (study or studies or trial* or group*)).ti,ab,kf,kw.	2568326
47	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf,kw.	93310
48	allocated.ti,ab,hw.	173965
49	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf,kw.	112268
50	((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.	24207
51	(pragmatic study or pragmatic studies).ti,ab,hw,kf,kw.	920
52	((pragmatic or practical) adj3 trial*).ti,ab,hw,kf,kw.	10746
53	((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.	16907
54	(phase adj3 (III or "3") adj3 (study or studies or trial*)).ti,hw,kf,kw.	124946
55	or/24-54	5641715
56	22 and 55	236
57	10 or 23	1049
58	55 and 57	299
59	11 or 58	454
60	remove duplicates from 59	368
61	56 or 60	604
62	limit 61 to english	562

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

Search	Query	Items found
#18	Search **(#17 AND publisher[sb])** Filters: **English**	33
#17	Search **(#8 AND #15)** Filters: **English**	416
#16	Search **(#8 AND #15)**	437
#15	Search **(#9 OR #10 OR #11 OR #12 OR #13 OR #14)**	91642
#14	Search **((bronchioloalveolar[tiab] OR bronchiolo alveolar[tiab]) AND (carcinoma*[tiab] OR cancer*[tiab] OR neoplasm*[tiab] OR tumor*[tiab] OR tumour*[tiab]))**	1790
#13	Search **((bronchial[tiab] OR pulmonary[tiab] OR lung[tiab]) AND (adenocarcinoma*[tiab] OR adeno-carcinoma*[tiab]))**	32469
#12	Search **((nonsmall cell[tiab] OR non small cell[tiab] OR large cell[tiab] OR undifferentiated[tiab]) AND (lung[tiab] OR bronchial[tiab] OR pulmonary[tiab]) AND (cancer*[tiab] OR tumor*[tiab] OR tumour*[tiab] OR carcinoma*[tiab] OR neoplasm*[tiab]))**	59324
#11	Search **NSCLC[tiab] OR NSCLCs[tiab] OR LCLC[tiab] OR LCLCs[tiab]**	35334
#10	Search **("Carcinoma, Large Cell"[Mesh]) AND "Lung"[Mesh]**	160
#9	Search **"Carcinoma, Non-Small-Cell Lung"[Mesh]**	45533
#8	Search **(#6 OR #7)**	1858
#7	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]**	1858
#6	Search **"pembrolizumab" [Supplementary Concept]**	686

3. Cochrane Central Register of Controlled Trials (Central)
Searched via Ovid

4. Grey Literature search via:

Clinical Trial Registries:

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

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

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

Select international agencies including:

Food and Drug Administration (FDA):

http://www.fda.gov/

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

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

Conference abstracts:

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

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

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

Detailed Methodology

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

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-) with in-process records & daily updates via Ovid; Embase (1974-) via Ovid; The Cochrane Central Register of Controlled Trials (September 2018) via Ovid, and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were pembolizumab, Keytruda, and 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 March 7, 2019.

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

Study Selection

One member of the pCODR Methods Team selected studies for inclusion in the review according to the predetermined protocol. All articles considered potentially relevant were acquired from library sources.

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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submission: Keytruda (pembrolizumab), powder for reconstitution for infusion - 50 mg , solution for infusion 100 mg/4mL vial. Kirkland (QC): Merck Canada Inc.; 2018.

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