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CADTH PCODR INITIAL CLINICAL GUIDANCE REPORT

Clinical Report

Nivolumab (Opdivo) in combination with Ipilimumab (Yervoy)

(Bristol-Myers Squibb)

Indication: for the first-line treatment of patients with metastatic or recurrent NSCLC with no EGFR or ALK genomic tumour aberrations.

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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Abbreviations

3-IGI	three-Item Global Index
ABSI	Average Burden Symptom Index
AE	adverse event
ALK	anaplastic lymphoma kinase
AUC	area under the curve
BICR	Blinded Independent Central Review
BOR	best overall response
CGP	Clinical Guidance Panel
CI	confidence interval
CNS	central nervous system
CR	complete response
CTCAE	Common Terminology Criteria for Adverse Events
DBL	database lock
DOR	duration of response
ECOG PS	Eastern Cooperative Oncology Group performance status
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency
EQ-5D-3L	EuroQol 5 dimensional 3 level
FDA	Food and Drug Administration
HR	hazard ratio
HRQoL	health-related quality of life
IO	immunotherapy
irAE	immune-related adverse event
ITC	indirect treatment comparison
IV	intravenous
IWRS	interactive web response system
KM	Kaplan-Meier
LCSS	Lung Cancer Symptom Scale
MedDRA	Medical Dictionary for Regulatory Activities

MID	minimal clinically important difference
NA	not applicable
Nab	nanoparticle albumin bound
NI	nivolumab plus ipilimumab
NI plus PDC	nivolumab plus ipilimumab plus 2 cycles of platinum-doublet chemotherapy
NOC	Notice of Compliance
NR	not reported
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PAG	Provincial Advisory Group
PDC	platinum-doublet chemotherapy
PD-L1	programmed death ligand 1
pERC	pCODR Expert Review Committee
PFS	progression-free survival
PFS2	progression-free survival after next line of treatment
PH	proportional hazards
PR	partial response
PRO	patient-reported outcome
RCT	randomized controlled trial
SAE	serious adverse event
TKI	tyrosine kinase inhibitor
TMB	tumor mutational burden
TTD	time-to-deterioration
TTR	time to response
UI	utility index
ULN	upper limit of normal
VAS	visual analogue scale

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 nivolumab in combination with ipilimumab and two cycles of platinum-based chemotherapy as first-line treatment in patients with metastatic or recurrent non-small cell lung cancer (NSCLC). The Clinical Guidance Report is one source of information that is considered in the *pERC Deliberative Framework*. The *pERC Deliberative Framework* is available on the CADTH website (www.cadth.ca/pcodr).

This Clinical Guidance is based on: a systematic review of the literature conducted by the Clinical Guidance Panel (CGP) and the CADTH Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group (PAG); 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. Background clinical information provided by the CGP, a summary of submitted Patient Advocacy Group Input, a summary of submitted PAG Input, and a summary of submitted Registered Clinician Input, and are provided in Sections 2, 3, 4, and 5, respectively.

1.1 Introduction

The objective of this review is to evaluate the efficacy and safety of nivolumab in combination with ipilimumab (NI) and two cycles of platinum-based chemotherapy for the first-line treatment of adult patients with metastatic or recurrent NSCLC with no known epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic tumour aberrations.

On August 6, 2020, Health Canada issued a Notice of Compliance (NOC), without conditions, for NI and two cycles of platinum-doublet chemotherapy (PDC) [NI plus PDC] for the treatment of adult patients with metastatic NSCLC with no EGFR or ALK genomic tumour aberrations, and no prior systemic therapy for metastatic NSCLC.[1] The requested reimbursement criteria aligns with the Health Canada indication; the sponsor, Bristol-Myers Squibb Canada, is requesting reimbursement of NI and two cycles of platinum-based chemotherapy for the first-line treatment of patients with metastatic or recurrent NSCLC with no EGFR or ALK genomic tumour aberrations.

Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody that binds to the program death (PD)-1 receptor and blocks its interaction with PD ligands 1 and 2 (PD-L1 and PD-L2), releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumour immune response.[1] When nivolumab (anti-PD-1) is combined with ipilimumab, a monoclonal antibody that targets cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) mediated inhibition results in enhanced T-cell function that is greater than the effects of either antibody alone and has shown improved anti-tumour responses in clinical studies in metastatic melanoma.[1]

The recommended dose of nivolumab is 360 mg administered as a 30-minute IV infusion every three weeks in combination with ipilimumab,1mg/kg administered as a 30-minute IV infusion every six weeks, and histology-based PDC administered every three weeks for two cycles.[1] After completion of two cycles of PDC, treatment with NI is continued at the same dose and schedule until disease progression, unacceptable toxicity, or up to two years in patients without disease progression. Treatment with NI may be continued in clinically stable patients with initial evidence of disease progression until disease progression is confirmed. According to the Health Canada product monograph, atypical responses (i.e., an initial transient increase in tumour size or small new lesions within the first few months of treatment followed by tumour shrinkage) have been observed with NI.[1]

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

The CADTH systematic review included one randomized controlled trial (RCT), CheckMate 9LA. A summary of the trial, its results, and key limitations are provided below.

Checkmate 9LA CheckMate 9LA is an ongoing international, open-label, randomized, active-controlled, phase III trial evaluating the efficacy and safety of NI plus PDC compared to PDC alone for patients with metastatic or recurrent NSCLC.[2] Eligible patients included adults (≥18 years) with stage IV or recurrent NSCLC without the presence of EGFR mutations or known ALK alterations, with an Eastern Cooperative Oncology Group (ECOG) PS of 0 or 1, no prior history of systemic therapy for advanced or metastatic disease, and with a life expectancy of at least three months. Patients were eligible regardless of their histology (squamous or non-squamous) or PD-L1 status. Testing of tumour tissues for PD-L1 status was conducted during the screening period and performed by a central laboratory. Patients who had previously received systemic anti-cancer therapy for advanced or metastatic disease were not eligible for enrolment.[3] However, prior adjuvant or neoadjuvant chemotherapy was permitted for early stage cancer provided it was completed at least six months prior to initiating study treatment.[3] Prior definitive chemoradiation for locally advanced disease was also permitted as long as the last dose of radiation or chemotherapy occurred at least six months to enrolment.

Patients were randomized 1:1 to receive either NI plus PDC or PDC alone. Patients in the NI plus PDC group were administered nivolumab at 360 mg every three weeks and ipilimumab at 1 mg/kg every six weeks; treatment was permitted until progression or unacceptable toxicity for up to 24 months. Two cycles of histology-based PDC were administered every three weeks as follows:[3]

- Squamous histology: carboplatin area under the concentration time curve (AUC) 6 plus paclitaxel at 200 mg/m^2, or 175 mg/m^2 as per local institutional practice
- Non-squamous histology: carboplatin AUC 5 or 6 plus pemetrexed at 500 mg/m^2, or cisplatin at 75 mg/m^2 plus pemetrexed at 500 mg/m^2

Patients randomized to the PDC group received four cycles of platinum chemotherapy based on their histology in the same manner as was prescribed to patients in the NI plus PDC group. Non-squamous patients were provided with the option of receiving pemetrexed maintenance after completion of the four cycles of chemotherapy. Treatment crossover was not permitted.[3] Patients in the NI plus PDC treatment group who experienced disease progression (based on investigator assessment) were permitted to continue receiving NI (up to month 24) provided they had no rapid disease progression, had stable performance status, and were considered by the investigator to be clinical benefiting from and tolerating the treatment.[3] The median duration of treatment was 6.1 months (range, 0-23.5) for patients in the NI plus PDC group and 2.4 months (range, 0-24.0) in the PDC group.[4] [redacted].[5] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

Randomization occurred via interactive web response system (IWRS). Patients were stratified based on histology (squamous, non-squamous), sex (male, female), and PD-L1 status (<1%, ≥1%). Patients for whom PD-L1 status was recorded as "not quantifiable" were eligible to enrol in the trial and were stratified into the PD-L1 <1% category; an enrollment cap was placed so that no greater than 10% of patients with PD-L1 status of "not quantifiable" accounted for the total randomized population. Due to the open-label design, both patients and investigators were aware of treatments received. Although, an independent data monitoring committee (IDMC) was charged with general oversight and safety considerations during the trial.[3]

The primary endpoint of the trial was overall survival (OS). An interim analysis was prespecified to test for superiority of OS (P<0.033) based on a Lan-DeMets alpha spending function with O'Brien-Fleming stopping boundaries. Secondary endpoints of the trial included progression-free survival (PFS) and objective response rate (ORR). A statistical testing hierarchy was used such that testing of PFS and ORR were only to occur at the interim or final analyses if OS was statistically significant. Efficacy endpoints of OS, PFS and ORR by PD-L1 expression were also secondary endpoints. Exploratory outcomes included safety, health-related quality of life (HRQoL) and PFS2.[3]

A total of 719 patients were randomized in the CheckMate 9LA trial with 361 randomized to the NI plus PDC group and 358 to the PDC group. Demographic and disease characteristics were balanced between the treatment groups with the exception of the presence of liver metastases, which was lower in the NI plus PDC group (18.8%) compared to the PDC group (24.0%). The median age of patients in both groups was 65 years. Most patients were white (88.7%), male (70.1%), from Europe (59.1%), had an ECOG PS of 1 (68.4%), were classified as current or former smokers (86.2%), had non-squamous NSCLC (68.8%), and stage IV disease (92.9%; NI plus PDC group: 91.4%; PDC group: 94.4%).[3,5] In terms of PD-L1 expression, the percentage of patients with PD-L1

expression <1%, 1 to 49% and ≥ 50% were 36.7%, 32.4%, and 24.1%, respectively.[3] [redacted].

(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).

A summary of the key outcomes of the CheckMate 9LA trial is provided in Table 1.

Efficacy

Efficacy results were reported based on a prespecified interim analysis (database lock [DBL]: October 3, 2019) that was performed at a minimum follow-up of 8.1 months. An updated analysis (DBL: March 9, 2020) was also performed based on a minimum follow-up of 12.7 months; this analysis was not prespecified in the study protocol.

At the interim analysis (DBL: October 3, 2019), the trial met its primary endpoint based on the prespecified threshold for superiority. Therefore, the interim analysis is considered the primary analysis of the trial. At the primary analysis, the median OS was 14.1 months (95% CI, 13.24 to 16.16) in the NI plus PDC group compared to 10.7 months (95% CI, 9.46 to 12.45) in the PDC group, demonstrating a statistically significant prolongation in OS with NI plus PDC over PDC alone (HR=0.69; 95% CI, 0.55 to 0.87; P=0.0006).

The updated analysis, which provided an additional 4.6 months of follow-up, showed consistent results and a sustained OS benefit for NI plus PDC over PDC (HR=0.66; 95% CI, 0.55-0.80).[3] The OS benefit with NI plus PDC was observed regardless of histology or PD-L1 status. The majority of other prespecified subgroup analyses of OS also showed an OS benefit of NI plus PDC over PDC alone at both the primary and updated data analyses, except for patients aged 75 years or older, of other race, who never smoked, or had non-quantifiable PD-L1 status. However, the interpretation of subgroup analyses should be interpreted with caution due to the exploratory nature of the analyses and the small sample sizes in some groups.

All secondary efficacy endpoints assessed (Table 1), including PFS and ORR by BICR assessment, demonstrated superior treatment efficacy of NI plus PDC compared to PDC alone:

- PFS by BICR assessment:
  - At the primary analysis, median PFS was 6.83 months (95% CI, 5.55 to 7.66) in the NI plus PDC group and 4.96 months (95% CI, 4.27 to 5.55) in the PDC group (HR=0.70; 95% CI, 0.57 to 0.86; P=0.0001).
  - At the updated analysis, the clinical benefit with NI plus PDC was maintained; median PFS was longer in the NI plus PDC group at 6.47 months (95% CI, 5.55 to 7.75) and 4.96 months (95% CI, 4.27 to 5.55) in the PDC group (HR=0.68; 95% CI, 0.57 to 0.82).
- ORR by BICR assessment:
  - At the primary analysis, the ORR was 37.7% (95% CI, 32.7 to 42.9) in the NI plus PDC group and 25.1% (95% CI, 20.7 to 30.0) in the PDC group (stratified CMH test P=0.0003).
  - At the updated analysis, the ORR remained higher in the NI plus PDC group at 38.2% (95% CI, 33.2 to 43.5) compared to 24.9% in the PDC group (95% CI, 20.5 to 29.7).[3]

Patient Reported Outcomes – LCSS-ABSI and 3-IGI, EQ-5D-3L UI and VAS

HRQoL was assessed using the Lung Cancer Symptom Scale (LCSS) Average Burden Symptom Index (ASBI) and three-Item Global Index (3-IGI) scale, and the EuroQoL, 5-dimension, 3-level (EQ-5D-3L) Utility Index (UI) and visual analogue scale (VAS). Completion rates for the LCSS questionnaire were greater than 90% at baseline and declined over time but remained at a rate of ≥80% at most on-treatment assessments with sufficient data (≥10% patients). Compliance was lower during the follow-up period,

with compliance rates ranging from 60% to 72% in both treatment groups. Similar compliance rates were observed for the EQ-5D-3L (VAS and UI).[4]

At the updated analysis, patients in the NI plus PDC group had slightly lower mean LCSS ABSI scores (i.e., less symptom burden) at baseline (21.28; 95% CI, 19.67 to 22.89) compared to patients in the PDC group (24.39; 95% CI, 22.75 to 26.03). At on-treatment assessment timepoints with sufficient data (≥10%, as defined in the trial, through to week 90 for the NI plus PDC group and through to week 78 for the PDC group), LCSS ABSI scores decreased in both treatment groups, indicative of improved lung cancer symptoms and HRQoL; however, the MID of 10 points was not reached in either treatment group at any time point where there were sufficient data (N ≥10%).[6] The 3-IGI showed trends of improvement in both treatment groups, as the mean change from baseline increased over time; however, the MID of 30 was not reached in either treatment group.[6]

At baseline, mean EQ-5D VAS score was slightly higher (i.e., better overall self-rated health) among patients in the NI plus PDC group (73.47; 95% CI, 71.63 to 75.31) compared to patients in the PDC group (69.50; 95% CI, 67.34 to 71.67). While on treatment, patients' mean VAS scores increased in both treatment groups, indicating patients' self-rated health improved. However, during follow-up visits there was a decrease in scores in both treatment groups, indicating worsening of patient's health status. [redacted]. *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until June 30, 2021 or until notification by the sponsor that it can be publicly disclosed).* Overall, both treatment groups experienced improved HRQoL over the course of the trial; however, there were no clinically meaningful differences in scores between the two treatment groups based on the MIDs for EQ-5D-3L [redacted] or VAS (defined as seven points). [4] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until June 30,2021 or until notification by the sponsor that it can be publicly disclosed).*

A time to deterioration (TTD) analysis was conducted for the ABSI and 3-IGI subscales of the LCSS, and the EQ-5D-3L UI and VAS. All subscales of the LCSS and EQ-5D demonstrated a longer time to deterioration in the NI plus PDC group compared to the PDC group, and a greater probability of worsening for patients in the PDC group.[6]

Harms

Safety data were reported for all treated patients (N=707), including 358 patients in the NI plus PDC group and 349 patients in the PDC group. Results of safety at the updated analysis were consistent with the primary analysis of safety and no new safety signals were identified for NI plus PDC, and therefore results of the updated analysis have been presented. Based on the updated analysis (DBL: March 9, 2020), the incidence of grade 3 or 4 AEs ([redacted]), any grade SAEs ([redacted]), any grade drug-related SAEs ([redacted]), any grade drug-related AEs ([redacted]), and grade 3 or 4 drug-related AEs ([redacted]) was higher in the NI plus PDC group compared to the PDC group.[4] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this safety information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

AEs of any grade were common in both treatment groups ([redacted]), with most AEs being of low grade (i.e., grade 1-2). [redacted].[4] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this safety information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).* Nausea and anemia were the most common drug-related AEs in each treatment group but they occurred in lower frequency in the NI plus PDC group compared to the PDC group ([redacted]% versus [redacted]%, and [redacted]% versus [redacted]%, respectively). [7] Neutropenia and anemia were the most common drug-related grade 3 or 4 AEs in each treatment group; however, the incidence of neutropenia ([redacted]% versus [redacted]%) and anemia ([redacted]% versus [redacted]%) was lower in the NI plus PDC group

compared to the PDC group.[7] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this safety information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

[redacted].[4] [redacted].[4] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this safety information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed)*

The trial assessed select AEs, which were defined in the trial as AEs with potential immunologic aetiology. Most select AEs were low grade (grade 1-2) and were deemed drug-related by the investigator. Select AEs as well as drug-related select AEs were more common in the NI plus PDC group compared to the PDC group. In the NI plus PDC group, the most common grade 3-4 select AEs were reported as gastrointestinal ([redacted]%) and skin and hepatic ([redacted]% each).[7] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this safety information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).* [redacted].[4] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed)*

[redacted].[4]*(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed)*

[redacted]. *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed)* [redacted]. *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed)* [redacted].[4] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed)*

Limitations and Potential Sources of Bias

A complete list of limitations and sources of bias are available in section 6 of this report. A summary of the major limitations and sources of bias are summarized below:

- The open-label study design of the CheckMate 9LA trial allowed for both investigators and patients to be aware of the assigned treatment of patients. The choice of an open-label design is considered appropriate given the differences in treatment administration (i.e., schedule, optional maintenance therapy), mechanisms of action resulting in distinct AE profiles (i.e., chemotherapy versus immunotherapy), and planned duration of therapy in the two treatment groups. OS was the primary endpoint and is an objective measure that is unlikely to be biased by the open-label study design. For the assessment of secondary efficacy endpoints (i.e., PFS, ORR), BICR was implemented to mitigate the potential for bias introduced by this trial design. However, the risk of bias due to lack of blinding is of greater concern for subjective outcomes including HRQoL and safety, as patient or investigator knowledge of treatment assignment could have influenced the assessment and reporting of these outcomes.
- The CheckMate 9LA trial compared NI plus PDC to PDC alone. Pembrolizumab, with or without PDC is currently considered the standard of care in Canada for the treatment of patients with metastatic or recurrent NSCLC with no EGFR or ALK genomic tumour aberrations, therefore PDC is not the most relevant treatment comparator. Accordingly, the sponsor provided an ITC comparing NI plus PDC to other relevant first-line treatments, which is summarized and critically appraised in Section 7 of this report.
- The testing of some secondary efficacy endpoints (i.e., PFS and ORR) was adjusted to control for multiplicity and the risk of type 1 error, while the results of other efficacy endpoints (i.e., TTR, DOR, efficacy by PD-LI expression) were not included in the statistical testing hierarchy. There were also many prespecified subgroup analyses performed for multiple endpoints. These analyses should be considered exploratory in nature as the trial was not powered to test specific hypotheses in these outcomes and subgroups. Overall, the results of all efficacy outcomes and most subgroup analyses showed a consistent treatment benefit in favour of NI plus PDC when compared to PDC alone. For some subgroups, however, including patients older than 75, never smokers, and those with unquantifiable PD-L1 expression, treatment effect estimates favoured PDC. The results obtained for these subgroups are particularly uncertain given the smaller sample size in these groups.
- Given the short duration of follow-up in the trial, the updated analysis was conducted to further characterize the clinical benefit of NI plus PDC compared to PDC, providing an additional 4.6 months of follow-up.[3] This unplanned analysis was not prespecified; therefore, no statistical considerations were employed to account for multiplicity.
- Censoring in the analysis of OS, the primary endpoint, did not take into consideration the use of subsequent therapies that patients received after completion of assigned study treatment. [redacted]. *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed)* As expected, the types of subsequent therapies differed between the groups with the most common subsequent systemic therapy being [redacted].[7] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed)* It is expected that patients in the PDC group who received subsequent immunotherapy would experience additional clinical benefit, which confounds the analysis of OS and likely underestimates the treatment effect associated with NI plus PDC compared to PDC alone.
- PRO questionnaires required a compliance rate of ≥10% of patients to be deemed sufficient for analyses. While compliance was stated to be over 90% at baseline and over 80% at subsequent assessments, compliance rates dropped to a low of 60% over the course of the trial. While this is above the required 10% threshold of patient compliance, the number of patients included in the analyses of PROs at later assessment timepoints was reduced and the patients left in the trial who completed PRO assessments are likely not representative (i.e., have better HRQoL) of all patients randomized in each treatment group. In this scenario, data are not missing at random since patients who have left the trial are likely sicker or have died, and therefore, the HRQoL results at later timepoints are likely biased. TTD analysis of HRQoL outcomes mitigates some of the bias associated with analyses based on mean changes in scores from baseline because all available patient data are used in the analysis. In the CheckMate 9LA trial, the TTD analysis of all subscales of the LCSS and EQ-5D-3L demonstrated a longer TTD in the NI plus PDC group compared to the PDC group, and a greater probability of worsening for patients in the PDC group.
- The MID used for the LCSS ABSI instrument has not been validated among NSCLC patients. The sponsor provided supporting literature that demonstrates the measurement properties of the instrument based on its use in multicentre trials. However, currently, there is no established MID to guide the analysis and interpretation of PRO data using the LCSS ABSI in patients with metastatic NSCLC. Consequently, it is unclear if the threshold used in the trial (i.e., MID of 10 points) is appropriate and reflective of a clinically meaningful change in outcome in patients with NSCLC.

Table 1: Highlights of Key Outcomes

Key Outcomes	Primary Analysis (DBL: October 3, 2019)[a]		Updated Analysis (DBL: March 9, 2020)[b]	
	NI plus PDC N=361	PDC N=358	NI plus PDC N=361	PDC N=358
Primary				
OS, median in months (95% CI)	14.13 (13.24-16.16)	10.74 (9.46-12.45)	15.64 (13.93-19.98)	10.91 (9.46-12.55)
HR (95% CI)	0.69 (0.55-0.87)		0.66 (0.55-0.80)	
P value	0.0006		NR	
Secondary				
PFS, median in months (95% CI)	6.83 (5.55-7.66)	4.96 (4.27-5.55)	6.74 (5.55-7.75)	4.96 (4.27-5.55)
HR (95% CI)	HR=0.70 (0.57-0.86)		HR=0.68 (0.57-0.82)	
P value	0.0001		NR	
ORR, n responders	136	90	138	89
% (95% CI)	37.7 (32.7-42.9)	25.1 (20.7-30.0)	38.2 (33.2-43.5)	24.9 (20.5-29.7)[a]
P value	0.0003		NR	
Confirmed BOR, n (%)				
CR	7 (1.9)	3 (0.8)	8 (2.2)	4 (1.1)
PR	129 (35.7)	87 (24.3)	130 (36.0)	85 (23.7)
SD	166 (46.0)	184 (51.4)	164 (45.4)	185 (51.7)
PD	32 (8.9)	45 (12.6)	32 (8.9)	45 (12.6)
UTD	24 (6.6)	30 (8.4)	27 (7.5)	36 (10.1)
NR	3 (0.8)	9 (2.5)	0	3 (0.8)
Exploratory				
Harms Outcomes, n (%)	**n=358**	**n=349**	**n=358**	**n=349**
AE (any grade)	355 (99.2)	341 (97.7)	[redacted]	[redacted]
AE Grade ≥3	228 (63.7)	184 (52.7)	[redacted]	[redacted]
TRAE	322 (89.9)	304 (87.1)	[redacted]	[redacted]
TRAE Grade ≥3	159 (44.4)	129 (37.0)	[redacted]	[redacted]
SAE	203 (56.7)	144 (41.3)	[redacted]	[redacted]
SAE Grade ≥3	157 (43.9)	111 (31.8)	[redacted]	[redacted]
Drug-related SAE	104 (29.1)	61 (17.5)	[redacted]	[redacted]
AEs leading to discontinuation	100 (27.9)	59 (16.9)	[redacted]	[redacted]
TRAE leading to discontinuation	68 (19.0)	26 (7.4)	[redacted]	[redacted]

AE = adverse event; BOR = best overall response; CI = confidence interval; CR = confirmed complete response; HR = hazard ratio; HRQoL = health-related quality of life; NI plus PDC = nivolumab plus ipilimumab and 2 cycles of chemotherapy; NR = not reported; ORR = objective response rate; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PR = confirmed partial response; SAE = serious adverse event; SD = stable disease; TRAE = treatment-related adverse event; WDAE = withdrawal due to adverse event.

[a] At the updated analysis, two patients in the PDC group had their responses changed from SD due to re-adjudication by BICR and one patient had their response changed from SD to PR.

*HR < 1 favours NI plus PDC group

Source: CADTH Submission,[7] Clinical Study Report,[4,8] EMA Assessment Report[3]

(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this safety information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed)

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

Two patient groups, Lung Cancer Canada (LCC) and the Lung Health Foundation (LHF) provided input to inform on CADTH's appraisal of NI plus PDC for the treatment of adults with metastatic or recurrent NSCLC with no known EGFR or ALK genomic tumour aberrations. LCC submitted information from two previous pCODR reviews of chemotherapy and immunotherapy that was obtained via environmental scans of traditional and social media, surveys, and physician outreach, as well as two female patients located in Canada who were diagnosed with stage IV NSCLC. LHF provided input based on one phone interview with a female patient from Ontario. Both patient groups were unable to contact patients with treatment experience with the combination under review (NI plus PDC); however, LCC reported on the experience of two patients treated with combination NI (without PDC). Patients highlighted several important symptoms of the disease that affect QoL including fatigue, weight loss, severe cough, difficulty breathing, and pleural effusion. Chemotherapy, immunotherapy, or a combination of both, are often the standard of care in advanced NSCLC without EGFR mutations or ALK translocations. According to patients, chemotherapy treats the cancer but has well known side effects such as nausea, vomiting, and fatigue, which vary in severity depending on the dose. Durability of treatment is a concern among patients as many patients respond to chemotherapy but subsequently progress and require additional treatment. Further, the hematologic toxicity associated with chemotherapy was also mentioned to lower patients' immunity and limit their social activities. Consequently, patients indicated a desire to not undergo chemotherapy longer than necessary; and LCC specified durability of treatment as an unmet need for NSCLC patients who are not treated with targeted therapies. Immunotherapy was reported by patients to be associated with fewer side effects compared to chemotherapy. Most patients providing input reported immunotherapy-related side effects to be mild, tolerable, and easily managed with little interference on daily life; and chemotherapy and immunotherapy combination treatment with a pembrolizumab-based regimen was noted to improve disease symptoms (e.g., pleural effusion) and control the disease with manageable side effects. Overall, patients expressed a desire for new treatments that reduce or eliminate symptoms (e.g., pain, fatigue, nausea, and shortness of breath); stop, slow, or delay disease progression; and improve appetite and QoL to a state that enables patients to function independently. Among the two patients who had experience with NI (not in combination with PDC), one patient received NI for one year but discontinued due to health issues related to their pancreas but has remained stable and has not received treatment for their lung cancer since NI was discontinued; and the other patient completed a two-year trial of NI and has since only received radiation therapy for metastasis to the brain but is considered stable since discontinuing the combination. Both patients developed occasional fatigue while receiving NI that did not affect their daily activities, and both indicated they were able to be independent, functional, and physically active.

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 CADTH website. PAG identifies factors that could affect the feasibility of implementing a funding recommendation.

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:

- Place in therapy and sequencing with currently available treatments
- Use after adjuvant/consolidation therapy

Economic factors:

- Discontinuation rules for one or both drugs
- Sizeable budget impact

Registered Clinician Input

Two registered clinician inputs were provided input to inform on CADTH's appraisal of NI plus PDC for the treatment of adults with metastatic or recurrent NSCLC with no known EGFR or ALK genomic tumour aberrations: two clinicians provided input on behalf of Cancer Care Ontario (CCO) Lung Drug Advisory Committee (DAC) and 15 clinicians provided input on behalf of LCC. Registered clinicians reported that the standard of care in the first-line treatment setting for NSCLC with no EGFR or ALK genomic tumour aberrations varies based on PD-L1 level and histology.1 For tumours with unknown or any PD-L1 expression level, four to six cycles of PDC plus pembrolizumab is typically administered. For squamous histologies, the platinum doublet administered is carboplatin and paclitaxel followed by pembrolizumab maintenance. For non-squamous histologies, the platinum doublet administered is cisplatin or carboplatin plus pemetrexed followed by pembrolizumab and pemetrexed maintenance. For tumours with a PD-L1 expression level of ≥50%, pembrolizumab monotherapy is another funded treatment option. Both clinician groups indicated that NI plus PDC (two cycles) serves as an alternative first-line treatment option for patients with newly diagnosed metastatic NSCLC without a driver mutation or patients with contraindications to immunotherapy. In terms of sequencing, the LCC clinician group indicated NI plus PDC would be followed by treatment with PDC with or with pemetrexed maintenance therapy (for patients with non-squamous histology in the second-line setting, followed by docetaxel in the third-line setting. The LCC clinicians indicated they would be most interested in offering this NI plus PDC to the PD-L1 negative patient population; while the CCO clinicians indicated a preference for use in patients pre-treated with durvalumab. Both clinician groups highlighted the favourability of NI plus PDC for patients seeking to minimize the duration and associated toxicity of chemotherapy due to the reduced number of chemotherapy cycles. Regarding the preferential use of NI plus PDC among currently available treatment options, the CCO clinicians specified that patient choice and desire to avoid an additional two cycles of chemotherapy would be justifying factors for preferential administration. The LCC clinicians stated that most clinicians would administer pembrolizumab monotherapy to patients with tumours that have high PD-L1 expression ≥ 50%. However, an exception to this practice may include patients with a heavy disease burden where achieving an objective response early in the treatment course is highly desirable (where both pembrolizumab and pembrolizumab plus chemotherapy are available in the PD-L1 highly expressing patient population). Patients with tumours that have PD-L1 expression < 50%, would be administered chemotherapy plus immunotherapy for benefits of the latter.

Summary of Supplemental Questions

In the absence of direct trial evidence, the sponsor submitted ITCs that compared the efficacy of NI plus PDC to standard of care immunotherapy (IO)-based treatments currently funded in Canada.[9] The ITCs that were performed were based on the pivotal CheckMate 9LA trial of NI plus PDC and four comparators trials contributing to three comparisons: 1) pembrolizumab plus PDC in patients with non-squamous NSCLC (KEYNOTE 189), 2) pembrolizumab plus PDC in squamous NSCLC patients (KEYNOTE 407), and 3) pembrolizumab monotherapy in high PD-L1 expression (≥50%) and mixed histology NSCLC patients (KEYNOTE 024 and KEYNOTE 042). The data from the full intent-to-treat population from CheckMate 9LA trial were used in the ITCs despite patient population differences compared with the comparator trials with respect to PD-L1 expression level and histology; this was based on the assumption that histology and PD-L1 expression levels do not modify treatment effect. The primary ITC results showed comparable, statistically non-significant differences in OS, PFS and ORR when NI plus PDC was compared to IO-based treatment for each comparison. In sensitivity analyses, the results did not change significantly when data from the CheckMate 9LA based on PD-L1 expression (≥1%, >1%) and histology were used (non-squamous and squamous). The ITCs represent quantitative estimates of treatment effect over the first year of treatment with NI plus PDC relative to other IO-based regimens. Given the identified limitations of the ITC, which include heterogeneity of study populations, differential treatment effects in the common comparator of chemotherapies, varied trial designs, and lengths of follow-up, the findings of the ITC should be interpreted with caution.

See section 7.1 for more information.

Comparison with Other Literature

Data from the CheckMate 227 trial were included to support the sponsor's submission to CADTH for the reimbursement of NI plus PDC for the first-line treatment of patients with metastatic or recurrent NSCLC without EGFR or ALK tumour aberrations. Since efficacy data from the pivotal trial, CheckMate 9LA, were considered immature based on 12.7 months of follow-up, data from the CheckMate 227 trial were used to inform the submitted pharmacoeconomic model on the long-term efficacy of NI compared to PDC, which provided data for NI based on a median of 37.7 months of follow-up.[10] The trial also provides additional safety data on the NI combination including data on patient deaths, which also informed the model. The final analysis of OS in patients with PD-L1 expression >1% demonstrated superior OS with NI compared to PDC, however, there was evidence of non-proportional hazards.

Patients treated with NI experienced a slight detriment in OS during the initial months of treatment with NI but thereafter, the curves showed a sustained long-term benefit in OS over PDC. Similar findings were shown for PFS. Under the assumption of non-proportional hazards, the treatment effect estimates from the trial were interpreted as overall estimates of the average treatment effect. In a positive trial, such estimates may be biased towards overestimating the magnitude of clinical benefit. The most recent data from the trial, based on 43.1 months of follow-up, show sustained benefit from treatment with NI over PDC in patients with PD-L1 ≥1 and PD-L1 <1%.[11] The CheckMate 9LA and 227 trials used similar eligibility criteria and therefore the distributions of most baseline characteristics were also similar. Aside from the addition of two cycles of PDC to the combination of NI, there were other notable differences in the treatment regimens evaluated that included the timing and dosing of nivolumab (a flat dose of 360 mg every three weeks in CheckMate 9LA versus a weight-based dose of 3 mg/kg every two weeks in CheckMate 227) and the type of PDC administered to patients with squamous NSCLC (patients with squamous histology received carboplatin plus paclitaxel in CheckMate 9LA versus either gemcitabine plus cisplatin or gemcitabine plus carboplatin in CheckMate 227). The better survival of the PDC control group in the CheckMate 227 trial, based on one-year survival estimates, suggests differential treatment effects of the PDC regimens used in each trial. Overall, visual comparison of the KM curves of OS and PFS from each trial show that the additional short course of PDC added to NI in the CheckMate 9LA trial addresses the early OS detriment observed in CheckMate 227. However, in the absence of a direct trial comparison of NI to NI plus PDC, equivalent long-term efficacy of the NI-based regimens cannot be assumed due to noted differences between the trials and the limitations associated with CheckMate 227. In terms of safety, the data on drug-related events in the PDC control groups of each trial showed a similar safety profile. When compared to the toxicity profile of NI, NI plus PDC appeared to be associated with higher rates of drug-related AEs that included nausea, anemia, asthenia, pruritus, and neutropenia, as well as more drug-related SAEs and drug-related AEs leading to treatment discontinuation. These data suggest that greater monitoring may be required for patients receiving NI plus PDC, and generalizability of safety data from the CheckMate 227 trial to the CheckMate 9LA trial for patients in the intervention group may be limited.

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

1.2.3 Factors Related to Generalizability of the Evidence

Table 2 addresses the generalizability of the evidence from the CheckMate 9LA trial; an assessment of the limitations and potential sources of bias associated with the trial can be found in Sections 6.3.2.1a and 6.3.2.1b (regarding internal validity).

Table 2: Assessment of Generalizability of Evidence for NI plus PDC as First-Line Treatment for Metastatic or Recurrent NSCLC

Domain	Factor	Evidence from CheckMate 9LA[2]	Generalizability Question	CGP Assessment of Generalizability
Population	ALK and EGFR mutations	The CheckMate 9LA trial eligibility criteria required that patients have no EGFR and ALK mutations	Do the trial results apply to patients who have EGFR mutations or ALK translocations?	Patients with EGFR mutations and ALK translocations have been excluded from most trials of immune checkpoint inhibitors, other than atezolizumab trials. As such, the CheckMate 9LA trial results would not be generalizable to patients with EGFR- and ALK-positive NSCLC.

Domain	Factor	Evidence from CheckMate 9LA[2]	Generalizability Question	CGP Assessment of Generalizability
Intervention	Line of therapy	The CheckMate 9LA trial excluded patients who had received prior systemic therapy for advanced or metastatic NSCLC. However, patients who had received adjuvant or neoadjuvant therapy were eligible if their treatment was completed at least six months prior to initiating study treatment.	Do the trial results apply to patients who have been previously treated with systemic therapy in the advanced/metastatic setting?	The Checkmate 9LA trial results are generalizable to patients who received prior adjuvant chemotherapy that was completed more than six months prior to developing advanced disease. The results would also be generalizable to patients who received concurrent chemoradiation and consolidation durvalumab, so long as the
				durvalumab was completed at least six months prior to developing recurrent disease. This is appropriate as it is consistent with the inclusion criteria for the Checkmate 9LA trial, the standard of care applied by lung cancer clinicians, and prior funding decisions for pembrolizumab in the same setting.
	Treatment administration	The infusion times for nivolumab and ipilimumab monotherapies are 60 minutes and 90 minutes, respectively. In the CheckMate 9LA trial infusion times were shortened to 30 minutes for both drugs.	Can shortened infusion times for nivolumab and ipilimumab affect the efficacy of treatment?	There is no reason to believe that shortened infusion times will impact treatment efficacy and infusion times as per the Checkmate 9LA trial were reasonable.
Outcomes	Appropriateness of primary and secondary outcomes	Primary outcome: OS Secondary outcomes: PFS, ORR, efficacy by PD-L1 expression (OS, PFS, ORR)	Were the primary and secondary outcomes appropriate for the trial design?	Yes, the outcome assessed were appropriate.
Setting	Countries participating in the trial	The CheckMate 9LA trial was conducted in 103 sites across 19 countries, including Europe, Asia, and North America, including four sites in Quebec, Canada which included six patients.	Are there any potential differences in the practice patterns between the other countries that the trial was conducted in and Canada?	The trial was conducted in multiple settings that are reflective of practice in Canada and are therefore generalizable to Canadian patients.

Domain	Factor	Evidence from CheckMate 9LA[2]	Generalizability Question	CGP Assessment of Generalizability
	Practices of participating in the trial	Dose reductions for chemotherapy regimens were conducted per local standards.	Are there any known potential differences in practice patterns between institutions regarding dose modifications?	Approaches to dose reduction are generally consistent and this is not felt to be an issue by the CGP.

ALK = anaplastic lymphoma kinase; CGP = Clinical Guidance Panel; EFGR = epidermal growth factor receptor; ORR = objective response rate; OS = overall survival; PD-L1 = programmed death ligand 1; PFS = progression-free survival

1.2.4 Interpretation

Burden of illness and need

Lung cancer remains the largest cause of death from cancer in Canada, with the majority of cases being NSCLC. Nationally, there are approximately 29, 800 new cases and 21, 200 deaths annually.[12] Significant advancements have been made in the last decade in both the diagnosis and management of NSCLC. A proportion of patients have underlying targetable molecular abnormalities, for which oral TKIs remain the most effective initial therapies. However, the majority of patients receiving treatment for advanced and metastatic NSCLC have tumours without targetable molecular abnormalities, representing over 5500 patients annually across Canada. Treatment algorithms for these patients are dependent on tumour histology and PD-L1 expression.

Multiple randomized trials have established immune checkpoint inhibitor therapy, either alone or in combination with chemotherapy, as the standard of care for the initial management of advanced or metastatic NSCLC; namely, pembrolizumab trial data have demonstrated the extension of median survival from around one year, up to 18 or 24 months.[13,14] With longer follow up of pembrolizumab, approximately one in three patients remain alive at three years, with the promise of some longer term sustained improvements in survival. Nevertheless, advanced or metastatic NSCLC is still considered to be an incurable illness and better therapies are needed. In the setting where treatment duration may continue for up to two years, more effective and/or less toxic treatment options are desirable.

The current standard of care for patients with metastatic NSCLC and no targetable mutations is pembrolizumab monotherapy or pembrolizumab in combination with four to six cycles of PDC. The KEYNOTE-024 trial of pembrolizumab monotherapy compared with platinum-based chemotherapy in patients with metastatic NSCLC and tumours exhibiting high expression of PD-L1 (TPS ≥50%), demonstrated significantly longer OS for patients randomized to pembrolizumab compared with platinum-based chemotherapy (HR=0.60; 95% CI, 0.41 to 0.89).[15] Longer term follow up of this trial confirmed the OS benefit for patients randomized to pembrolizumab (median OS 30.0 months versus 14.2 months; HR=0.63; 95% CI, 0.47 to 0.86),[16] with an additional 20% of patients alive at three years (43.7% versus 24.9%). Recent data support the use of pembrolizumab in combination with PDC as initial therapy for advanced squamous and non-squamous NSCLC, irrespective of PD-L1 expression.[13,14,17] KEYNOTE-407 and KEYNOTE-189 both demonstrated significant improvements in OS for the addition of pembrolizumab to four to six cycles of platinum-based chemotherapy in patients with squamous NSCLC (HR=0.71; 95% CI, 0.58 to 0.88)[18] and non-squamous NSCLC (HR=0.56; 95% CI, 0.45 to 0.70).[19]

CheckMate 227 evaluated a chemotherapy free regimen of NI. Patients were stratified based on PD-L1 expression (<1% versus ≥ 1%) and PD-L1 positive patients were randomized to NI, PDC, or nivolumab monotherapy; whereas, PD-L1 negative patients were randomized to NI, PDC, or nivolumab plus PDC.[20,21] The primary analysis, in patients with PD-L1 positive NSCLC (PD-L1 expression of ≥1%), demonstrated superior OS for the combination of NI compared to PDC (median OS 17.1 months versus 14.9 months; HR=0.79; 97.72% CI, 0.65 to 0.96). With longer follow up, the observed three-year OS was 33% versus 22%, respectively.[11] However, during the initial six months both PFS and OS favoured PDC. In an exploratory analysis of patients with PD-L1 negative tumours, OS was improved as well (median OS 17.2 months versus 12.2 months; HR=0.64; 95% CI, 0.51 to 0.81) with three-year OS of 34% versus 15%.[11]

Effectiveness

It was postulated that a short course of chemotherapy added on to NI might improve early survival and preserve the long-term benefit from NI. Therefore, the CheckMate 9LA trial randomized patients with metastatic NSCLC to NI plus PDC (two cycles) for two years, versus four cycles of PDC plus maintenance pemetrexed if appropriate. [2] Patients with non-squamous NSCLC received cisplatin or carboplatin plus pemetrexed with the option of maintenance pemetrexed. Patients with squamous histology received carboplatin plus paclitaxel. CheckMate 9LA included good performance status patients (ECOG 0 to 1) with previously untreated metastatic or recurrent NSCLC. Patients were stratified by PD-L1 expression (<1% versus ≥1%), sex (male versus female), and histology (non-squamous versus squamous). Patients who received prior chemoradiation for locally advanced disease or prior adjuvant chemotherapy for resected NSCLC were eligible so long as there was a minimum of six months from completion of chemotherapy to study enrollment. Patients with known EGFR mutations or ALK translocations were excluded from the trial as were patients who had contraindications to or previously received an immune checkpoint inhibitor. Patients with treated CNS metastases were eligible so long as their neurological status returned to baseline.

The primary outcome of CheckMate 9LA was OS. Secondary outcomes included PFS, ORR (both by BICR), and efficacy outcomes reported by PD-L1 expression. The trial was stopped early for superiority (at the first planned interim analysis), at the recommendation of the IDMC. Reported analyses included data from the interim analysis, which was based on a minimum follow up time of 8.1 months, as well as data from an unplanned updated analysis that provided an additional 4.6 months of follow up (minimum follow up time of 12.7 months).[3]

CheckMate 9LA randomized 719 patients to NI plus PDC (two cycles) (n=361) versus four cycles of PDC (n=358). Treatment with NI continued for a maximum of two years. Baseline characteristics between the treatment groups were similar. At the updated analysis, there were slightly more patients in the NI plus PDC group (NI plus PDC: 35.2% versus PDC: 29.6%) with PD-L1 expression of 1-49% and slightly more patients in the PDC group (NI plus PDC: 21.1% versus PDC: 27.1%) with PD-L1 ≥ 50%.[3] Given that PD-L1 expression was not predictive of outcome, these differences are unlikely to be clinically important. Crossover to NI was not allowed in CheckMate 9LA. [redacted].[22] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed)* Despite these differences, survival outcomes favoured NI plus PDC.

OS was significantly improved in both the primary analysis (median OS 14.1 months versus 10.7 months; HR=0.69; 95% CI, 0.55 to 0.87) and the updated analysis (median OS 15.6 months versus 10.9 months; HR=0.66; 95% CI, 0.55 to 0.80)[3]. Subgroup analyses for OS favoured NI plus PDC in most subgroups. At the primary analysis, the magnitude of benefit was observed regardless of histology (non-squamous HR=0.72; 95% CI, 0.55 to 0.93; squamous HR=0.65; 95% CI, 0.46 to 0.93), sex (female HR=0.73; 95% CI, 0.47 to 1.13; male HR=0.69; 95% CI, 0.54 to 0.88), or PD-L1 expression (PD-L1 <1% HR=0.65; 95% CI, 0.46 to 0.92; PD-L1 1-49% HR=0.69; 95% CI, 0.48 to 0.98; PD-L1 ≥50% HR=0.64; 95% CI, 0.41 to 1.02).[3] In updated analyses of other endpoints, PFS significantly favoured NI plus PDC (median PFS 6.7 months versus 5.0 months, HR=0.68; 95% CI, 0.57 to 0.82). ORR was also significantly higher (38.2% versus 24.9%) and DOR significantly longer (median DOR 11.3 months versus 5.6 months). [3]

HRQoL was assessed with the LCSS and EQ-5D-3L. HRQoL scores improved in both groups on treatment but these improvements were less than the predefined MID for both instruments.

Safety

Consistent with other trials of chemotherapy plus an immune checkpoint inhibitor, more AEs were observed among patients receiving NI plus PDC compared with PDC alone.[4,22] At the updated analysis, there was a higher reported incidence of grade 3 or 4 AEs ([redacted]), any grade SAEs ([redacted]), drug-related SAEs of any grade ([redacted]), and grade 3 or 4 drug related SAEs ([redacted]).[4] [redacted].[4] [redacted]

[redacted].[4] [redacted].[4] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this safety information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed)* However, the CGP noted that oncologists are very familiar with managing the side effect profile associated with immunotherapy and chemotherapy including irAEs; therefore, there should be minimal issues for patient care.

Other considerations

Randomized trials of immune checkpoint inhibitors in NSCLC have established multiple treatment options with immunotherapy monotherapy, immunotherapy plus platinum-based chemotherapy (+/- bevacizumab), or dual immunotherapy as initial therapy for metastatic and recurrent disease. Not all of these treatment options are Health Canada approved and currently pembrolizumab is the only immune checkpoint inhibitor funded in the first-line therapy of NSCLC (although decisions are pending in two provinces). NI plus PDC is superior to PDC alone; therefore, representing an additional treatment option for first-line therapy of advanced or metastatic NSCLC. Longer term data are unavailable for CheckMate 9LA; therefore, data from the CheckMate 227 trial of NI (median follow up of 36 months) were used to support the current CADTH submission, to provide an estimate of two- and three-year OS. Additionally, the design of CheckMate 9LA, with a control group of PDC, does not allow clinicians to evaluate the impact of adding two cycles of PDC to NI, in comparison to NI alone.

Two clinician submissions, one from OH-CCO and the other from LCC were received for this CADTH submission. Both groups recognize the lack of any direct comparison between NI plus PDC versus existing standards of care with pembrolizumab monotherapy, or in combination with PDC. Both identified that limiting treatment to two cycles of chemotherapy represents an advantage for patients; particularly, for those wanting to avoid chemotherapy. The submission from LCC is more detailed and identified a potential benefit of NI plus PDC in patients with PD-L1 negative tumours. However, this represents cross trial comparison and an extrapolation of longer term follow up data from CheckMate 227. A patient submission from LCC identifies an unmet need for improved therapies in lung cancer. It notes that patients' adverse effects from chemotherapy increase with increasing duration of treatment. A regimen with less chemotherapy is felt to be more appealing to patients and would increase patient choice in decision making for advanced or metastatic NSCLC.

As stated earlier, there are no direct comparisons of first-line treatment regimens incorporating an immune checkpoint inhibitor. The sponsor submitted an ITC to address this gap. The CADTH Methods Team identified a number of limitations with this analysis but the results showed similar OS for NI plus PDC when compared with pembrolizumab monotherapy, or pembrolizumab in combination with PDC; and the PFS of platinum pemetrexed and pembrolizumab was shown to be superior to NI plus PDC

1.3 Conclusions

The CGP concludes there is a net clinical benefit of NI plus two cycles of PDC, given as first-line therapy for patients with metastatic or recurrent NSCLC without EGFR mutations or ALK translocations. The following factors were considered in reaching this conclusion:

- The CheckMate 9LA trial demonstrated a statistically significant improvement in OS for NI and PDC compared with four cycles of PDC alone (median OS 15.6 months versus 10.9 months; HR=0.66; 95% CI, 0.55 to 0.80). The CGP considers this to be a clinically meaningful improvement in OS with an absolute improvement in median OS of 4.7 months.
- All secondary outcomes assessed (PFS, ORR, DoR) favoured NI plus PDC. In addition, preplanned subgroup analyses for these outcomes favoured NI plus PDC over PDC regardless of sex, histology, or PD-L1 expression.
- Overall, more AEs were experienced by patients receiving NI plus PDC; although, patients receiving four cycles of PDC experienced more chemotherapy associated AEs. Additionally, more patients discontinued treatment because of AEs in the NI plus PDC group. However, these safety findings are consistent across other trials of chemotherapy plus an immune checkpoint inhibitor. Clinicians already have experience in managing these AEs; thus, implementation of NI plus PDC should not create additional challenges for clinicians.
- There was no detriment in HRQoL for patients receiving NI plus PDC compared with PDC.

Data from the CheckMate 9LA trial need to be considered in the context of other recent data. Pembrolizumab monotherapy in patients with PD-L1 positive tumors (TPS ≥ 50%);[15,16] pembrolizumab plus platinum and pemetrexed in non-squamous NSCLC and any PD-L1 expression;[13,19] pembrolizumab plus carboplatin and (nab)/paclitaxel in squamous NSCLC and any PD-L1 expression;[14,18] atezolizumab plus carboplatin, paclitaxel and bevacizumab;[23] atezolizumab monotherapy in patients with high PD-L1 expression (TC/IC 3+);[24] and NI in patients with any PD-L1 expression,[21,25] have all been shown to have superior efficacy to PDC alone. NI plus two cycles of PDC represents another regimen that is superior to PDC. There are no direct comparisons of any of these regimens to confirm whether one of them offers superior efficacy in this setting. Therefore, NI plus PDC should be considered one of the accepted standards of care for the initial treatment of advanced and metastatic NSCLC without EGFR mutations or ALK translocations. The CGP avoided making comparisons of treatment outcomes across trials, for specific patient subgroups, because this was felt to be methodologically unsound. However, input from clinicians and patients suggest that the option of a short duration chemotherapy represents reduced chemotherapy related AEs, which is of value to patients.

NI plus PDC would provide another option to the existing treatment algorithm as initial therapy for metastatic and recurrent NSCLC without EGFR mutations or ALK translocations (Figure 1). Eligible patients would have an ECOG PS of 0 to 2, received no prior systemic therapy for advanced or metastatic disease, squamous or non-squamous histology, and any PD-L1 expression including patients with unknown PD-L1 expression. Patients who received prior chemoradiation for locally advanced disease or prior adjuvant chemotherapy for resected NSCLC would be eligible so long as there was a minimum of six months from completion of chemotherapy to study enrollment. Patients with known EGFR mutations or ALK translocations would not be eligible for NI and PDC, nor would patients who had contraindications to an immune checkpoint inhibitor. Patients with treated CNS metastases or untreated asymptomatic CNS metastases would be eligible. Patients on NI who remain free of disease progression at two years will discontinue treatment. There was no retreatment allowed in CheckMate 9LA. However, similar regimens using pembrolizumab allow retreatment for patients who complete two years of treatment and subsequently progress. The CGP believes consideration should be given to allowing retreatment with NI in this subgroup of patients.

Several questions were raised by the PAG, if NI plus PDC were to be recommended for reimbursement, specifically with respect to the eligible patient population, implementation factors, and sequencing of available treatments. The CGP's responses to these questions are summarized in Table 3. For the CGP's assessment of generalizability (external validity of the CheckMate 9LA trial evidence related to specific factors), refer to Table 2 in Section 1 of this report.

Table 3: CADTH CGP Response to PAG Implementation Questions

PAG Implementation Questions	CGP Response
Eligible Patient Population	
• PAG is seeking clarity on whether the following patients would be eligible for treatment with NI plus PDC: ○ Patients with PS ≥ 2 ○ Patients with no PD-L1 results ○ Patients with untreated CNS metastases ○ Patients with stage IIIB NSCLC ○ Patients with non-metastatic or non-recurrent disease that is not amenable to resection ○ Patients who have experienced disease progression on anti-PD-L1 therapy (e.g. durvalumab) for stage III NSCLC, or who have experienced disease progression on chemotherapy for stage III NSCLC within six months of completion, or for stage III NSCLC have experienced disease progression after six months of completion ○ Patients who progressed on maintenance pemetrexed in the non-squamous setting ○ Patients with rare subtypes of lung cancer (e.g., typical or atypical carcinoid)	• Clinicians routinely extrapolate trial evidence to patients with an ECOG PS of 2. The CGP noted previous lung cancer CADTH submissions have generalized to ECOG PS of 2, however, the CGP would not. offer NI plus IDC to patients with an ECOG PS of 3 or 4. • The improved OS in CheckMate 9LA was seen in patients with all levels of PD-L1 expression. Therefore, patients with no PD-L1 result would be eligible. • The trial did not allow patients with untreated brain metastases. However, patients with asymptomatic brain metastases have been included in other trials of immunotherapy and the CGP felt they should be eligible for NI plus PDC. • Patients with stage IIIB NSCLC who are not candidates for radical treatment would be eligible for NI plus PDC as per the inclusion criteria of the CheckMate 9LA trial. • Patients with non-metastatic or non-recurrent disease that is not amenable to resection or radical radiation would be eligible. • Patients with stage III NSCLC progressing on consolidation durvalumab, or within six months of completion of durvalumab would not be eligible for NI plus PDC. Patients progressing beyond

PAG Implementation Questions	CGP Response
• PAG seeks guidance on whether specific subgroups of patients defined by PD-L1 expression (≥ 50%, any, unknown or other) or histology (squamous versus non-squamous) should be treated differently. • PAG would like confirmation that other driver mutations (e.g., ROS-1, NTRK) should also be excluded when results are available.	six months from the completion of durvalumab should be eligible to be consistent with other funded regimens (i.e., pembrolizumab). • Patients who progressed on maintenance pemetrexed would not be eligible as they would already have received initial PDC for advanced/metastatic disease. • Patients with carcinoid tumours should not be eligible as these subtypes of lung cancer are treated differently to NSCLC. Patients with large cell neuroendocrine tumours, or other uncommon subtypes of NSCLC should be eligible if they are being treated with a NSCLC treatment regimen. • Patients with PD-L1 expression ≥50% are most commonly treated with pembrolizumab monotherapy. However, they are eligible for pembrolizumab in combination with platinum-based chemotherapy. Therefore, the CGP felt they should also be eligible for NI plus PDC. • As patients with EGFR mutations and ALK translocations were excluded from CheckMate 9LA, the CGP felt these patients should not be eligible for NI plus PDC. However, patients with other rare molecular abnormalities (e.g., ROS-1, NTRK) should be eligible for NI plus PDC as they were eligible for the trial.
Implementation Factors	
• After two cycles of induction treatment, NI treatment (nivolumab 360 mg every three weeks and ipilimumab 1 mg/kg every six weeks) will continue until progression, unacceptable toxicity, or other reasons. PAG would like clarification of “disease progression” and “other reasons” for discontinuation.	• There are standard definitions for disease progression according to RECIST and iRECIST. These should be followed in general.
• PAG noted that patients in the CheckMate 9LA trial were treated with NI for a maximum of two years. PAG is looking for confirmation that the patient must be a suitable candidate for two cycles of PDC before being considered for NI therapy.	• At the outset of NI therapy, a patient should be a candidate for two cycles of PDC to be eligible for this regimen. If a patient experiences a major toxicity from the initial cycle of PDC, particularly if that results in hospitalization, then there should be a process to proceed with therapy without the need to administer a second cycle of PDC.
• PAG seeks guidance on the adequacy of alternate weight-based dosing for nivolumab (4.5 mg/kg) with or without a cap of 360 mg. PAG noted that Q3W dosing and the 360 mg fixed dose both differ from approved nivolumab monotherapy regimens (flat 240/480 mg every 2/4 weeks) and may cause confusion.	• The trial evaluated nivolumab in fixed dose of 360 mg every three weeks. This is not one of the approved dosing schedules but represents the same average dose intensity. These doses from Checkmate 9LA demonstrated improved OS and the CGP does not believe the dose schedule used is a concern. The CGP also believes therapy should be implemented according to the evidence that supports the treatment. Using weight-based dosing with a cap deviates from the evidence that generated the data.
• PAG is seeking information on the use of NI in combination with other chemotherapy regimens (e.g. non-platinum-based regimens).	• There is no evidence for NI in combination with other non-platinum regimens. The CGP does not support the use of NI in combination with non-platinum doublets or single agent chemotherapy as there is no evidence for supporting the use of platinum and gemcitabine combined with NI. However, as noted in the LCC clinician input received for this CADTH submission, platinum and gemcitabine have been combined with durvalumab plus tremelimumab in the CCTG IND 2261[26] and BR342 trials.[27] Given there were no safety concerns identified in those trials, PAG may wish to consider allowing the use of platinum and gemcitabine.
• Greater monitoring would be required as significant toxicities are likely in the presence of both immunotherapy drugs. PAG is seeking guidance on dose adjustment and/or discontinuation of one of the drugs in the event of such toxicity.	• Clinicians are familiar with the AEs from immune checkpoint inhibitors. These may occur with increased frequency with dual immunotherapy but the types of AEs are the same. In addition, many clinicians treat other disease sites where dual immunotherapy is already used and with no dose reduction of these agents. If there

PAG Implementation Questions	CGP Response
• PAG is seeking guidance on whether there are any special considerations for older patients with comorbidities. • PAG seeks to clarify whether pseudoprogression is recognized or likely with this treatment. If so, PAG noted that prompt access to more frequent imaging may be required to re-assess. • For patients having initiated platinum chemotherapy, PAG would like confirmation that they should discontinue chemotherapy after two additional cycles in combination with NI.	is a significant AE then ipilimumab should be omitted and consideration given to continuing nivolumab monotherapy. • Older patients or those with comorbidities are at an increased risk of treatment-related AEs. Beyond this there are no additional or unique concerns. • Pseudoprogression may occur and therefore is always a concern, however, the frequency is less in lung cancer compared to other malignancies. Therefore, clinicians should be given the judgement to continue treatment if pseudoprogression is suspected. If pseudoprogression is suspected, then imaging should be repeated within two months to confirm disease status. • Given that most current patients are likely to have access to pembrolizumab plus platinum-based chemotherapy, the CGP wonders why a patient who is eligible for immunotherapy would be receiving just a platinum-doublet. However, if an immunotherapy eligible patient is only receiving PDC it is reasonable for them to add NI and two additional cycles of PDC.
Sequencing and Priority of Treatments	
• PAG is seeking to confirm the place in therapy and sequencing with NI plus PDC, including the scenarios below: ○ Factors justifying the preferential use of NI plus PDC, pembrolizumab monotherapy, or pembrolizumab plus PDC. ○ Confirmation that subsequent anti-PD1/PD-L1 cannot be given upon progression while on NI plus PDC. ○ Suitability of re-treatment with NI plus PDC or treatment with pembrolizumab (and timing thereof) upon relapse after the two-year treatment. ○ Addition of NI to any ongoing first-line chemotherapy regimen and termination of the latter after two additional cycles (i.e. induction). ○ Optimal choice of next line chemotherapy upon disease progression. ○ In the next line setting, appropriateness of full platinum chemotherapy despite the two cycles of PDC given in the NI plus PDC induction phase. ○ Appropriateness of re-treatment with agents used in PDC during the NI plus PDC induction phase (e.g., pemetrexed, paclitaxel, cisplatin, carboplatin)	• The majority of patients with PD-L1 positive NSCLC (TPS ≥50%) will be treated with pembrolizumab monotherapy. There may be some patients with high tumour burden where pembrolizumab plus PDC or NI plus PDC might be preferred. For patients with PD-L1 expression <50%, there are no clinical factors that predict improved efficacy for NI plus PDC or pembrolizumab plus PDC. There may be patient or physician choice factors (i.e., desire to limit chemotherapy), that influence the decision between NI plus PDC or pembrolizumab plus PDC. • Patients progressing on NI would not be eligible for subsequent immunotherapy. • CheckMate 9LA did not allow retreatment after two years. However, in Canada, patients receiving pembrolizumab who complete two years of therapy and then progress are eligible for retreatment. The CGP believes that there should be consistency across treatment options and that retreatment with NI for one year be an option for patients progressing after completion of two years of NI. • As noted above, there is no evidence for platinum and gemcitabine combined with NI. However, as pointed out in the LCC clinician received for this CADTH submission, platinum and gemcitabine have been combined with durvalumab plus tremelimumab in the CCTG IND 226[26] and BR34 trials.[27] Given there were no safety concerns identified in those trials, PAG may wish to consider allowing the use platinum and gemcitabine with NI. • Patient progressing on NI plus two cycles of PDC would be most appropriately treated with chemotherapy as the next option. For patients progressing more than six months from completion of PDC, retreatment with a histology appropriate platinum-doublet would be recommended. Patients progressing within six months would likely be treated with docetaxel. The CGP recognizes that retreatment with pemetrexed may pose funding issues in some jurisdictions and this gap should be addressed during implementation. Patients with non-squamous NSCLC who have only received two cycles of pemetrexed, should have access to the most effective PDC (i.e., platinum plus pemetrexed).
Companion Diagnostic Testing	

PAG Implementation Questions	CGP Response
• PAG would like confirmation that PD-L1 testing is not required.	• The benefit of NI plus PDC over PDC was seen irrespective of PD-L1 expression. Therefore, PD-L1 expression will not be used to determine which patients are eligible for NI plus PDC. However, as stated above, patients with PD-L1 ≥50% are likely to be treated with pembrolizumab monotherapy and so PD-L1 testing will still be required in the standard pathology work up of a patient with NSCLC.

PAG = Provincial Advisory Group; CGP = Clinical Guidance Panel.

2 Background Clinical Information

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 2020, there were approximately 29,800 new cases of lung cancer and 21,200 deaths from lung cancer.[12] About 85% of these cases would be classified as NSCLC and in approximately 70% of these cases, the histologic subtype would be adenocarcinoma. Approximately 50% of NSCLC patients have stage IV disease at the time of presentation, with another 20-25% presenting with locally advanced stage III disease.[2] 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 of disease, it is not surprising that the expected five-year survival is only 19%.[12]

Recent advances in molecular profiling of NSCLC have demonstrated the presence of underlying molecular (oncogenic) drivers, in particular in lung adenocarcinomas.[28] The most frequently observed molecular abnormalities include mutations of the EGFR gene and translocations of the ALK gene. These two molecular abnormalities are distinct subgroups of lung adenocarcinomas, with a combined frequency of approximately 20%. Oral tyrosine kinase inhibitors (TKIs) targeting the underlying molecular abnormality represent the most effective initial treatment for these subgroups of NSCLC. However, the majority of patients with advanced and metastatic NSCLC have tumours without targetable molecular abnormalities. Treatment algorithms for these patients are dependent on tumour histology and expression of PD-L1 (refer to Figure 1). These patients represent the focus of the background information below.

2.2 Accepted Clinical Practice

Treatment algorithms for advanced and metastatic NSCLC without targetable molecular abnormalities have evolved rapidly over the last five years (Figure 1). Immune checkpoint inhibitors targeting the PD-1 receptor, or its ligand PD-L1, have demonstrated activity in the majority of patients with advanced NSCLC. Early clinical trials demonstrated tumour response in heavily pretreated patients, with 16% of these patients remaining alive beyond five years.[29] Multiple trials of nivolumab,[30,31] pembrolizumab [32] and atezolizumab,[33,34] compared with docetaxel, in patients previously treated with platinum-based chemotherapy, demonstrated superior OS for patients treated with an immune checkpoint inhibitor. Data from these trials of single agent immune checkpoint inhibitor suggested that tumour expression of PD-L1 was predictive of greater benefit.

Subsequent clinical trials of immune checkpoint inhibitors in advanced NSCLC have focused on previously untreated patients (Table 4). The KEYNOTE-024 trial of pembrolizumab compared with platinum-based chemotherapy in patients with metastatic NSCLC and tumours demonstrating high expression of PD-L1 (tumour proportion score [TPS] ≥50%), demonstrated greater OS for patients randomized to pembrolizumab compared with platinum-based chemotherapy (HR=0.60; 95% CI, 0.41 to 0.89).[15] Longer term follow up of this trial confirmed significantly greater OS for patients randomized to pembrolizumab (median OS, 26.3 months versus 14.2 months; HR=0.63; 95% CI, 0.47 to 0.86).[35] At three years, 20% more patients in the pembrolizumab group were alive (43.7% versus 24.9%). The primary outcome, PFS, was significantly improved for patients randomized to pembrolizumab (median PFS, 10.3 months versus 6.0 months; HR=0.50; 95% CI, 0.37 to 0.68), as were response rates (ORR, 44.8% versus 27.8%). There were fewer treatment related AEs in the pembrolizumab group, with the most common AEs from pembrolizumab being diarrhea, fatigue, and pyrexia. Common irAEs included thyroid abnormities, pneumonitis, skin reactions, colitis, and hypophysitis. Similar findings were observed in the KEYNOTE-042 trial that compared pembrolizumab with platinum-based chemotherapy in NSCLC patients with tumours having any PD-L1 expression (TPS ≥1%).[36] OS favoured the pembrolizumab group in the ITT population (median OS, 20.0 months versus 12.2 months; HR=0.69; 95% CI, 0.56 to 0.85). However, the survival curves crossed early on and the benefit appeared to be driven by patients with high PD-L1 expressing tumours (HR=0.69, 95% CI 0.56 to 0.85).[36] An exploratory subgroup analysis performed in patients with low PD-L1 expression (1-49%) showed no improvement in OS (HR=0.92; 95% CI, 0.77 to 1.11). The findings from KEYNOTE-042 only support the adoption of pembrolizumab monotherapy as the initial therapy for patients with advanced/metastatic NSCLC and tumours with high PD-L1 expression (TPS ≥ 50%).[36]

Additional trials have evaluated immune checkpoint inhibitors in combination with platinum-based chemotherapy. KEYNOTE-189 randomized patients with non-squamous NSCLC to pembrolizumab in combination with platinum and pemetrexed versus platinum

and pemetrexed chemotherapy.[13] Patients randomized to pembrolizumab, platinum plus pemetrexed had longer OS (median OS, 22.0 months versus 10.7 months; HR=0.56; 95 %CI, 0.45 to 0.70), longer PFS (median PFS, 9.0 months versus 4.9 months; HR = 0.48; 95% CI, 0.40 to 0.58) and higher ORR (48% versus 19.4%).[19] The improved OS was observed regardless of PD-L1 expression (PD-L1 ≥ 50%, HR=0.59; 95% CI, 0.39 to 0.88; PD-L1 1-49%, HR=0.62; 95% CI, 0.42 to 0.92; PD-L1 < 1%, HR=0.52; 95% CI, 0.36 to 0.74). The incidence of chemotherapy associated AEs was similar between the two groups. There were more irAEs in patients randomized to pembrolizumab plus chemotherapy (26.4% versus 12.9%) and more patients in the pembrolizumab group discontinued therapy as a result of AEs (33.6% versus 16.3%). Similar findings were observed in the KEYNOTE-407 trial which randomized patients with squamous NSCLC to pembrolizumab plus carboplatin and (nab)paclitaxel versus carboplatin and (nab)paclitaxel.[14,18] OS (median 17.1 months versus 11.6 months; HR=0.71; 95% CI, 0.58 to 0.88) and PFS (median 8.0 months versus 5.1 months; HR=0.57; 95% CI, 0.47 to 0.69) were both significantly longer for patients randomized to pembrolizumab plus platinum-based chemotherapy.[18] The magnitude of effect for OS did have some variability based on PD-L1 expression (PD-L1 ≥ 50%, HR=0.79; 95% CI, 0.52 to 1.21; PD-L1 1-49%, HR= 0.59; 95% CI 0.42 to 0.84; PD-L1 < 1%, HR=0.79; 95% CI, 0.56 to 1.11). These two trials established pembrolizumab plus platinum-based chemotherapy as standards of care for first-line therapy of advanced NSCLC, in patients with adequate PS and no contraindication to an immune checkpoint inhibitor. While there are no direct comparisons of pembrolizumab monotherapy to pembrolizumab plus platinum-based chemotherapy, pembrolizumab monotherapy is commonly used for patients with tumours with high PD-L1 expression. Patients with EGFR mutations and ALK translocations were excluded from all of these trials evaluating pembrolizumab.

Multiple trials have evaluated atezolizumab, either alone, or in combination with platinum-based chemotherapy as first-line therapy for advanced/metastatic NSCLC (Table 4). While these trials did allow entry of patients with EGFR mutations and ALK translocations, the primary analyses of these trials reported data only on patients with wild type (WT) NSCLC. IMpower110 randomized patients with PD-L1 positive (tumor cells [TC] or immune cells [IC] >1%) squamous or non-squamous NSCLC to atezolizumab versus platinum-based chemotherapy.[24] The primary outcome, analyzed in patients with high PD-L1 expression (TC3 or IC3), showed significant improvements in OS (median OS 20.2 months versus 13.1 months; HR=0.59; 95% CI, 0.40to 0.89). Similar benefits were observed for PFS (median PFS 8.1 months versus 5.0 months, HR=0.63; 95% CI, 0.45 to 0.88). IMpower130, 131, and 132 trials evaluated atezolizumab in combination with platinum-based chemotherapy.[37-39] The addition of atezolizumab to carboplatin and (nab)paclitaxel, in either squamous[37] or non-squamous NSCLC significantly improved PFS. However, OS was only improved in the IMpower130 trial in patients with non-squamous NSCLC (18.6 months versus 13.9 months; HR=0.79; 95% CI, 0.64 to 0.98).[39] IMpower132 evaluated the addition of atezolizumab to platinum and pemetrexed.[38] While OS was numerically greater, this difference was not statistically significant. Atezolizumab has also been evaluated in combination with carboplatin, paclitaxel, and bevacizumab (IMpower150).[23] The addition of atezolizumab to carboplatin, paclitaxel and bevacizumab improved both PFS (median PFS 8.3 months versus 6.8 months; HR=0.62; 95% CI, 0.52 to 0.74) and OS (median OS 19.2 months versus 14.7 months; HR=0.78; 95% CI, 0.64 to 0.96).[23] Analysis of the subgroup of patients with sensitizing EGFR mutations demonstrated improved OS as well (median not reached versus 17.5 months; HR=0.31, 95% CI, 0.11 to 0.83). Uptake of bevacizumab in NSCLC in Canada is low, in part because of the lack of funding. The combination of atezolizumab plus carboplatin, paclitaxel and bevacizumab is approved by Health Canada. However, atezolizumab has not been incorporated into current first-line NSCLC treatment algorithms in Canada.

Dual immune checkpoint inhibitor therapy, targeting both the CTLA-4 and the PD-1/PD-L1 axis have also been evaluated as initial therapy for advanced or metastatic NSCLC. The CheckMate 227 trial was a complicated design in which PD-L1 positive patients were randomized to NI, PDC, or nivolumab monotherapy, whereas PD-L1 negative patients were randomized to NI, PDC, or PDC plus nivolumab.[20,21] Co-primary outcomes evaluated PFS for the combination of NI versus PDC in patients with high tumour mutation burden (TMB),[20] as well as OS in patients with PD-L1 positive tumours.[21,25] In PD-L1 positive patients, the combination of NI resulted in superior OS to PDC (median OS 17.1 months versus 14.9 months; HR=0.79; 95% CI, 0.67 to 0.93) and three-year OS was 33% versus 22%. In an exploratory analysis of patients with PD-L1 negative tumours, OS was significantly improved (median OS, 17.2 months versus 12.2 months; HR=0.64; 95% CI, 0.51 to 0.81) with three-year OS of 34% versus 15%.[21,25]

In the CheckMate 227 trial, patients in the NI group had worse OS during the initial six months of therapy. It was postulated that a short course of chemotherapy might improve early survival and preserve the long-term improvements from NI. Therefore, the CheckMate 9LA trial, the pivotal trial that is the focus of this submission, randomized patients with metastatic NSCLC to NI plus PDC for two years, versus four cycles of platinum-based chemotherapy plus maintenance pemetrexed if appropriate.[25] The trial included patients with good PS (ECOG 0-1), squamous and non-squamous histology, and tumors positive and negative for PD-L1 expression.

The trial was stopped early upon recommendation of the DSMB and OS was significantly improved (median 15.6 months vs 10.9 months; HR=0.66, 95% CI, 0.55 to 0.80). The improvement in OS was observed in patients with squamous (HR=0.62) and non-squamous (HR=0.69) histology and for all levels of PD-L1 expression (PD-L1 < 1%, HR=0.62; PD-L1 1-49%, HR=0.61; and PD-L1 ≥ 50%, HR=0.66). No early detriment in OS was observed for patients receiving NI plus PDC. PFS was also significantly improved for patients receiving NI plus PDC (median PFS, 6.7 months versus 5.0 months; HR=0.68; 95% CI, 0.57 to 0.82). The incidence of treatment related AEs in both arms were similar but there were more serious treatment related AEs (30% versus 18%) and more treatment related AEs resulting in treatment discontinuation (19% versus 7%) in the NI plus PDC group. For a more comprehensive review and critical appraisal of the CheckMate 9LA trial refer to section 6 of this report.

Figure 1: Treatment Algorithm with Additions Proposed by the CGP

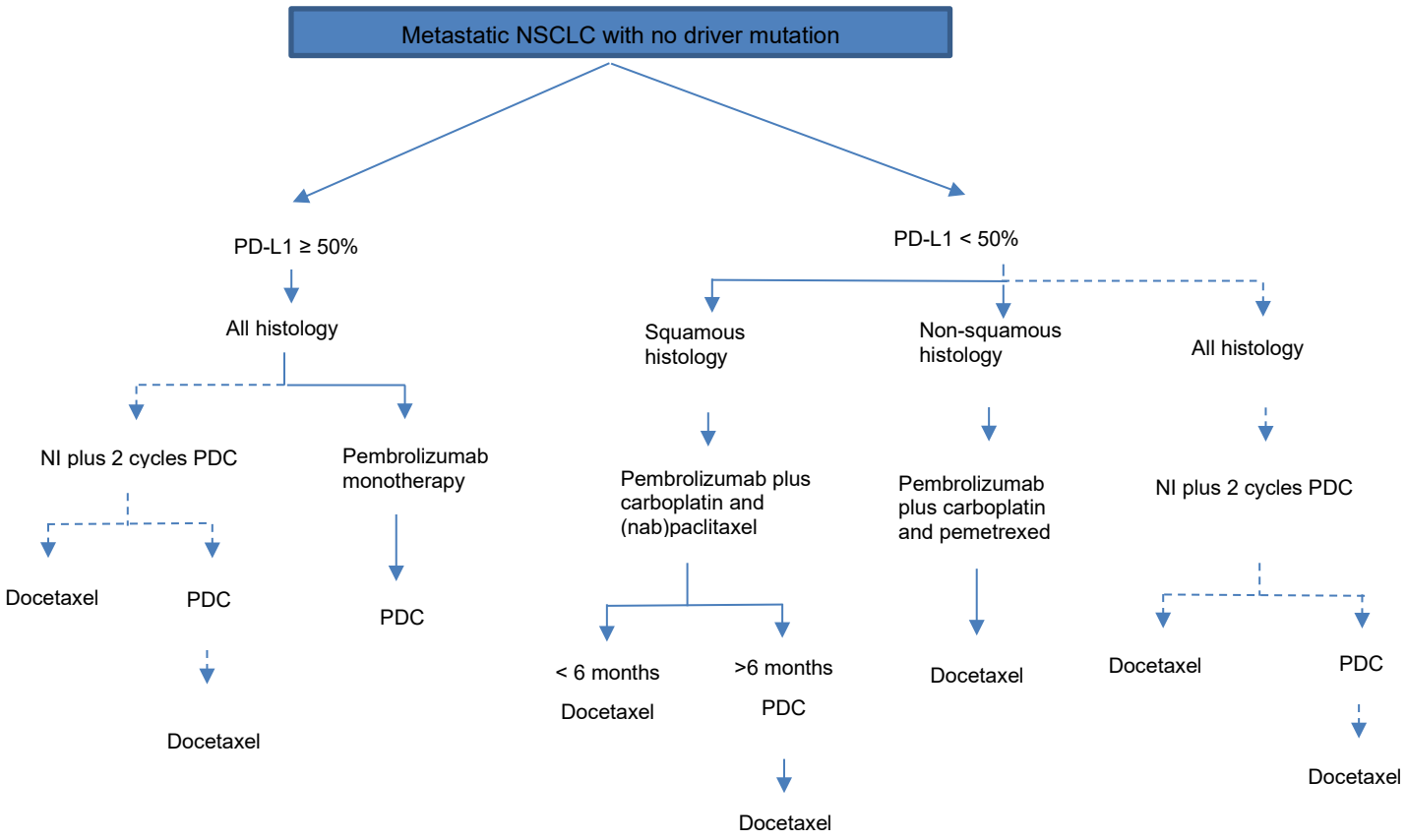


Table 4: Summary of Efficacy Outcomes in Trials of Immune Checkpoint Inhibitors in NSCLC

Trial	Treatment Groups	Median OS in mos	OS HR (95% CI)	1-year OS, %	2-year OS, %	3-year OS, %	Median PFS in mos	ORR, %	Median DOR, in mos
KEYNOTE-189[13,19]	Pembrolizumab plus PDC	22.0	0.56 (0.45–0.70)	69.8	45.7	32.0	9.0	48.3	11.2
	PDC	10.7		48.0	27.3	18.0	4.9	19.9	7.8
KEYNOTE-407[14,18]	Pembrolizumab plus PDC	17.1	0.71 (0.58–0.88)	64.7	37.5	NR	8.0	62.6	8.8
	PDC	11.6		49.6	30.6	NR	5.1	38.4	4.9
KEYNOTE-024[15,16]	Pembrolizumab	26.3	0.63 (0.47–0.86)	70.3	51.5	43.7	10.3	44.8	NR
	PDC	14.2		54.8	34.5	24.9	6.0	27.8	6.3
KEYNOTE-042 PD-L1 ≥1%[36]	Pembrolizumab	16.7	0.81 (0.71–0.93)	58.0	39.0	28.0	5.4	27.2	20.2
	PDC	12.1		50.0	28.0	15.0	6.6	26.5	8.4
KEYNOTE-042 PD-L1>50%[36]	Pembrolizumab	20.0	0.69 (0.56–0.85)	65.0	45.0	35.0	6.5	39.1	22.0
	PDC	12.2		50.0	30.0	20.0	6.4	32.0	10.8
CheckMate 227 PD-L1+[21,25]	NI	17.1	0.79 (0.67–0.93)	63.0	40.0	33.0	5.1	36.4	23.2
	PDC	14.9		56.0	33.0	22.0	5.6	30.2	6.7
CheckMate 227 PD-L1- [21,25]	NI	17.2	0.64 (0.51–0.81)	60.0	40.0	34.0	5.1	27.3	18.0
	PDC	12.2		51.0	23.0	15.0	4.7	23.1	4.8
CheckMate 9LA[2]	NI plus PDC	15.6	0.66 (0.55 – 0.80)	64.0	40.0	immature	6.8	38.0	11.3
	PDC	10.9		47.0	25.0	immature	5.0	25.0	5.6
IMpower110 TC3/IC3[24]	Atezolizumab	20.2	0.59 (0.40 – 0.89)	64.9	45.0	immature	8.1	38.3	NR
	PDC	13.1		50.6	25	immature	5.0	28.6	6.7

Trial	Treatment Groups	Median OS in mos	OS HR (95% CI)	1-year OS, %	2-year OS, %	3-year OS, %	Median PFS in mos	ORR, %	Median DOR, in mos
IMpower130[39]	Atezolizumab plus PDC	18.6	0.79 (0.64 – 0.98)	63.1	39.6	immature	7.0	49.2	8.4
	PDC	13.9		55.5	30.0	immature	5.5	31.9	6.1
IMpower131[37]	Atezolizumab plus carboplatin plus nab-paclitaxel	14.2	0.88 (0.73 –1.05)	58.0	32.5	immature	6.5	49.7	7.3
	Carboplatin plus nab-paclitaxel	13.5		58.0	26.6	immature	5.6	41.0	5.2
IMpower132[38]	Atezolizumab plus pemetrexed plus carboplatin or cisplatin	18.1	0.81 (0.644 – 1.025)	59.6	immature	immature	7.6	46.9	10.1
	Pemetrexed plus carboplatin or cisplatin	13.6		55.4	immature	immature	5.2	32.2	7.2
IMpower150[23,40]	Atezolizumab plus bevacizumab plus carboplatin plus paclitaxel	19.2	0.78 (0.64 – 0.96)	67.3	43.4	immature	8.3	63.5	9.0
	Bevacizumab plus carboplatin plus paclitaxel	14.7		60.6	33.7	immature	6.8	48.0	5.7

DOR = duration of response; HR = hazards ratio; NI = nivolumab plus ipilimumab; NR = not reported; ORR = objective response rate; OS = overall survival; PDC = Platinum doublet chemotherapy; PD-L1 = programmed cell death protein ligands 1; PFS = progression-free survival

It is clear that competing treatment options exist. Pembrolizumab monotherapy or in combination with platinum-based chemotherapy is currently funded or pending funding across Canada for patients with advanced/metastatic NSCLC. Among patients without EGFR mutations and ALK translocations, the addition of pembrolizumab to platinum-based chemotherapy improves OS, independent of PD-L1 status. In the absence of direct comparative data, pembrolizumab monotherapy is preferred in the majority of patients with PD-L1 strongly positive tumours (TPS ≥ 50%). However, available evidence would support additional treatment options with atezolizumab monotherapy, atezolizumab in combination with chemotherapy, NI, or NI plus two cycles of platinum-based chemotherapy. Differences exist in the populations studied including the magnitude of absolute survival benefits, ORR, and DOR. There are no direct comparative data for pembrolizumab monotherapy, or pembrolizumab plus platinum-based chemotherapy versus any of these other treatment options.

Based on the proportion of new cases of lung cancer in Canada that are NSCLC, approximately 30% of patients will receive some systemic therapy for advanced or metastatic NSCLC. Of these patients, approximately 30% are PD-L1 strongly positive and likely will receive first-line pembrolizumab monotherapy. Therefore, patients with either PD-L1 expression < 1% or 1-49%, would be eligible for NI plus PDC. Some patients may have contraindications to the use of immune checkpoint inhibitors, however, NI plus PDC would be an option for the majority of patients receiving first-line therapy for advanced or metastatic NSCLC, other than patients with EGFR mutations and ALK translocations. This population of patients is already eligible for therapy with pembrolizumab monotherapy or in combination with platinum-based chemotherapy. The Checkmate 9LA trial included patients with ECOG PS 0-1. However, physicians are likely to extrapolate the data to patients with ECOG 2 as well. Therefore, the population should be identifiable and the potential for indication creep low.

3 Summary of Patient Advocacy Group Input

The following patient groups provided input for the review of nivolumab plus ipilimumab (NI) plus two cycles of platinum doublet chemotherapy (PDC) for the first-line treatment of patients with metastatic or recurrent NSCLC with no EGFR or ALK genomic tumor aberrations and their input is summarized below: Lung Cancer Canada (LCC) and the Lung Health Foundation (LHF). Of note, the LHF was previously named "The Ontario Lung Association". LCC provided information from previously submitted input on pCODR reviews of chemotherapy and immunotherapy as treatment for NSCLC (pCODR reviews 10153 and 10176); an environmental scan of traditional and social media; surveys and interviews; and physician outreach. LCC also provided input from two patients treated with NI; both patients are female, located in Canada, and were diagnosed with stage 4 NSCLC. The LHF provided input from one phone interview completed in June 2020 with one female lung cancer patient living in Ontario who is over 60 years old. A summary of the information gathered from both patient groups is found in Table 5.

Fatigue, weight loss, severe cough, difficulty breathing, and pleural effusion were highlighted to be symptoms of concern. Patients reported receiving the following therapies for lung cancer: radiation, chemotherapy, immunotherapy, and chemotherapy plus immunotherapy. Radiation resulted in side effects including fatigue, low energy, loss of appetite, weight loss, headaches, and difficulty sleeping. Chemotherapy was reported to shrink tumours and allowed patients to reach remission; however, chemotherapy was also reported to exhibit poor treatment durability, potentially lower patients' immunity, and result in side effects such as nausea, vomiting, fatigue, and hair loss. Namely, chemotherapy-related side effects vary in severity depending on the dose and are experienced in a cyclic manner. Accordingly, patients feel ill and are unable to participate in life in the days following the infusion; subsequently, patients are able to resume normal activities for a few days before the next cycle but dread the upcoming cycle in anticipation. Immunotherapy was reported to be associated with fewer side effects compared to chemotherapy and most patients indicated that they felt good while receiving immunotherapy. Additionally, majority of patients reported the immunotherapy-related side effects to be mild, tolerable, and easily managed with little interference on daily life. Furthermore, the chemotherapy and immunotherapy combination, a pembrolizumab based regimen, was noted to improve symptoms (e.g. pleural effusion), reduce tumour size, control the disease, and be associated with manageable side effects. Moreover, LCC specified durability of treatment as an unmet need for NSCLC patients that are not treated with targeted therapies. Overall, patients value having enough energy to socialize with family and friends and to participate in leisure and physical activities; thus, the quality of life is particularly valued. Further, patients value treatments that reduce or eliminate side effects such as pain, fatigue, nausea, and shortness of breath; improve symptoms and quality of life to a state that enables patients to be independently functional throughout the day; and stop, slow, or delay disease progression.

Both patient groups were unable to contact patients with treatment experience with the combination under review; however, LCC reported on the experience of two patients treated with NI (i.e. NI not in combination with chemotherapy). One patient had to discontinue NI, following a year of treatment, due to health issues involving their pancreas but has remained stable and has not received treatment for their lung cancer since NI was discontinued. The other patient has only received radiation therapy for metastasis to the brain but is considered stable following discontinuation of NI. Both patients developed occasional fatigue that did not affect their daily activities and were able to be independent, functional, and physically active. Thus, NI elicited a good quality of life for both patients as they returned to their daily activities and established a new normal. Accordingly, LCC highlighted the durability of NI to be beneficial as this reduces the burden on caregivers and hospital resources. Namely, durable treatments can facilitate the patient and caregivers' ability to work, which also reduces the financial burden. Additionally, LCC emphasized that it is rare for lung cancer patients to remain stable without treatment; however, both these patients treated with NI responded quickly and established a new normal that has lasted for two years without any treatment specific to their lung cancer. Thus, the durability of NI is particularly favourable because for many patients treated with targeted therapies, they experience a good quality of life but remain on treatment.

Overall, caregivers may experience an emotional burden and negative psychological, behavioural, and physiological effects on their daily lives as a result of worrying about the patients' survival and the time dedicated to providing care and support. Namely, this stress can affect the caregivers' ability to fulfill their responsibilities at home and at work. LCC highlighted that longer durable treatments would help decrease the demand on caregivers; therefore, caregivers may be able to continue working (i.e. less of a need to take time off work for caregiving activities), which also reduces physical and financial burdens on the family.

LCC stated that despite medical advancements there is still a high unmet need for NSCLC patients particularly those with no known targetable mutations; specifically, there is a need for viable options in the first-line setting that provide longer-lasting survival benefits, a good quality of life, and delay disease progression. LCC stated that NI plus chemotherapy is a treatment option that fulfils the need for more effective first-line options and more durable options that promote quality of life. Namely, the reduced number of chemotherapy sessions combined with the durability of NI will likely be beneficial for the patients' and caregivers' quality of life. They elaborated that chemotherapy is associated with well documented side effects and is difficult to tolerate. LCC also noted that treatment combinations with a shorter duration of chemotherapy are favourable as they allow for patients to return to "normal life" faster (as chemotherapy is associated with side effects that are difficult to tolerate), are associated with less caregiver burden, and are less resource intensive (i.e. require less chemotherapy chair time). Additionally, LCC noted that clinical trial data demonstrate that responsive patients respond quickly (typical of patients responsive to immunotherapy), which aligns with patient and payer needs. Therefore, LCC believes this treatment combination has the potential to benefit patients' long term outcomes (i.e. chance at a longer life) and, if made available, can become the new standard and help extend the lives of patients with advanced NSCLC.

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

Table 5: Summary of Information Gathered by LCC and LHF

Patient Group	Information Gathering Method and Number of Respondents
LCC	1. **Environmental Scan: traditional and social media, surveys, interviews, and physician outreach** • **2 patient respondents (treatment experience with NI*)** ○ **Female** ○ **Diagnosed with stage 4 NSCLC** ○ **Located in Canada** 2. Previous LCC input on NSCLC patients treated with chemotherapy and immunotherapy submitted to pCODR • Pembrolizumab for the treatment of patients with metastatic squamous NSCLC in combination with carboplatin and either paclitaxel or nab-paclitaxel, in adults with no prior systemic chemotherapy treatment for metastatic NSCLC (10176) i. Faces of Lung Cancer Survey (National Survey; August 2015) ○ 91 patient respondents (all have or had lung cancer) ○ 72 caregiver respondents (all were currently caring for or previously cared for patients living with lung cancer) ii. Environmental scan ○ 2 patient respondents (one female and one male) ○ 3 caregiver respondents (all male) iii. Patient questionnaire ○ 2 patient respondents (all male) iv. One-on-one patient interviews ○ 1 patient respondent (male) v. Previous LCC submission for non-squamous NSCLC treated with pembrolizumab (Keytruda) in combination with chemotherapy • Pembrolizumab for metastatic non-squamous NSCLC in combination with pemetrexed and platinum chemotherapy (10153) i. Faces of Lung Cancer Survey (National Survey; August 2015) – see above for details ii. Environmental Scan of Online Forums ○ 9 patient respondents (6 females and 3 males) ○ 8 caregiver respondents (3 females and 5 males) iii. Previous LCC submission for pembrolizumab indicated for metastatic NSCLC whose tumours express PDL-1 (as determined by a validated test, after first-line chemotherapy) submitted in 2017.

Patient Group	Information Gathering Method and Number of Respondents
LHF	**1. Phone Interview (June 2020)** • **1 patient respondent (no experience with the treatment combination under review)** ○ **Female** ○ **Diagnosed with lung cancer** ○ **Located in Ontario**

*funding request under review: nivolumab, in combination with ipilimumab and 2 cycles of platinum-based chemotherapy for the first-line treatment of patients with metastatic or recurrent NSCLC with no EGFR or ALK genomic tumor aberrations.

Note: bolded information are the sources of information specifically submitted for this current CADTH review.

3.1 Condition and Current Therapy Information

3.1.1 Patients Experiences

The patient interviewed by the LHF stated that it took far longer than she would have preferred to receive an accurate diagnosis and develop a suitable treatment course; namely, she was aggravated by the number of appointments and the "*poor communication between her family doctor and all those involved with her testing and diagnosis*." Additionally, the experience was stressful and the uncertainty of *"not knowing"* was *"anxiety-producing."* She specified that speeding up the diagnosis process by shortening the time between appointments and improving communication between relevant parties would be particularly beneficial for patients. Furthermore, she reported that lung cancer has impacted several aspects of day-to-day life including the ability to socialize with family and friends and participate in leisure and physical activities. Due to fatigue, she feels physically and emotionally drained at times—as stated in her own words—"*my ability to do normal daily activities is reduced as I get tired so quickly now*."

LCC highlighted the national impact of lung cancer stating that it is the most commonly diagnosed cancer and the leading cause of death from cancer in Canada; namely, 29,800 Canadians are estimated to be diagnosed with lung cancer in 2020 and over 21,000 people die from the disease every year. Furthermore, the five-year survival rate is estimated to be 19% and is predicted to be even lower in advanced cases; notably, advanced cases represent about 50% of newly diagnosed lung cancer cases. Additionally, LCC noted that there may be unconscious attitudes (stigma) directed towards patients regarding a diagnosis with lung cancer. Please refer to Section 3.2.2 Patient Experiences to Date for experiences at the individual level; namely, two NSCLC patients.

3.1.2 Patients' Experiences with Current Therapy

At the time of the interview conducted by the LHF, the patient respondent was undergoing radiation and there was uncertainty whether additional treatments or medications would follow. Radiation resulted in side effects including fatigue, low energy, loss of appetite, weight loss, headaches, and difficulty sleeping for this patient.

LCC stated that chemotherapy, immunotherapy or a combination of both are current treatments for advanced NSCLC patients with no EGFR or ALK genomic tumor aberrations. Of note, patient and caregiver experiences with these aforementioned treatments are detailed below and retrieved from previous LCC submissions and interviews (pCODR reviews 10153 and 10176)—summary statements follow.

- Chemotherapy treats the cancer but has well known side effects.
- Immunotherapy is associated with fewer side effects compared to chemotherapy, and most patients report feeling good while treated with immunotherapy.
- Chemotherapy in combination with immunotherapy controls the disease by improving symptoms and reducing tumour sizes (reported specifically on pembrolizumab plus chemotherapy).

Chemotherapy

The use of chemotherapy for the treatment of lung cancer is well documented; chemotherapy has been reported to shrink tumors (one patient reported a reduction from 8 cm to 4 cm) and allows patients to reach remission and to participate in various activities such as bowling and golfing. However, chemotherapy is associated with side effects such as nausea, vomiting, and fatigue, which

vary in severity depending on the dose; for instance, some patients on higher doses start to feel unwell during the infusion. Namely, some patients experience minimal side effects; one patient reported that her hair fell out and she was a bit sick but it was quite manageable, and one caregiver reported that his mother did not complain of any side effects and the chemotherapy is *"slowing brought his mother back to life.*" Alternatively, one patient reported feeling very sick and was bedridden for two months and described the experience as *"awful."* Patients commonly allude to the cyclical side effect schedule; namely, patients feel ill and are unable to participate in life in the days following the infusion. Patients are then able to resume normal activities for a few days before the next cycle but dread the upcoming cycle in anticipation. This affects their ability to participate in life, take care of themselves, and increases caregiver burden. Additionally, the durability of treatment is a concern as many patients respond to chemotherapy but subsequently progress and require additional treatment (e.g. more chemotherapy). Furthermore, chemotherapy can also lower patient's immunity, and in some cases, the treatment heavily depletes patients' white and red blood cells, which may limit the ability to go out, return to work, have visitors, and spend quality time with family and loved ones. Thus, many patients do not want to undergo chemotherapy longer than necessary. Nevertheless, chemotherapy has been a long-standing standard of care and is still a viable option for lung cancer patients.

Immunotherapy

Of note, the patient input reported in this Immunotherapy Section is not based on the NI combination. Immunotherapy has been reported to be associated with fewer side effects compared to chemotherapy and most patients feel good while receiving immunotherapy. According to LCC, it has been over two years since the first IO therapy was launched for treatment of lung cancer and has proven to be efficacious and tolerable. Patients report that IO has improved lung cancer symptoms; many of the patients indicate that they went from feeling quite sick before starting treatment to feeling better within days of their first treatment. Namely, one patient had a severe cough and also lost weight; after treatment with immunotherapy, his cough slowly went away and it had allowed him to have a more normal family life, in his words, *"it has allowed me to live."* Additionally, the majority of patients reported that side effects were mild and easily managed. In a few cases, there were reports of stronger side effects that had to be managed either by over-the-counter or prescription drugs; however, were still noted to be tolerable and did not interfere with daily life. Thus, immunotherapy has allowed patients to be more functional and physically active (e.g., spend more time with family, travel, and be more involved in daily activities).

Chemotherapy and Immunotherapy Combination Therapy

Of note, input in this Chemotherapy and Immunotherapy Combination Therapy Section reports on experiences of patients treated with pembrolizumab plus chemotherapy. Overall, the pembrolizumab plus chemotherapy combination was reported to improve symptoms and reduce tumour size, which helped to control the disease. LCC highlighted that the duration of chemotherapy for the pembrolizumab-chemotherapy combination is longer than the chemotherapy portion for the NI plus PDC combination under review (two cycles).

For one patient, surgery and radiation were not viable treatment options due to the location of the tumor; thus, pembrolizumab plus chemotherapy was administered and controlled the disease (i.e. cancer was termed stable). She reported that the treatment combination felt like a lifeline as she survived and lived to talk about it. For another patient, they initially received immunotherapy as a first-line treatment; however, the cancer progressed, which resulted in the treatment switch to chemotherapy plus immunotherapy. Within a week, he noticed improvement in his breathing and coughing and the pleural effusion thoracentesis he was experiencing for months resolved. Additionally, the tumors reduced in size by 30 to 40% and metastases were no longer visible on follow-up scans. Other patients also reported similar significant improvements including reduced symptoms, resolved pleural effusion, tumor shrinkage, and stable metastases. Another two patients returned to work with one reporting full-time work, and one noted their ability to garden and play with their grandkids after treatment.

Overall, patients reported side effects to be manageable. One NSCLC patient said "*it wasn't awful when I went on the combo. I had more fatigue and some nausea but I was able to work full time*". *Getting through the four cycles that included chemotherapy was the most challenging but totally doable for me*." However, two patients reported needing to take a treatment break. One patient did so when his tumors had all shrunken by 60-80%; the break allowed him to put on weight, become very energetic, and complete more tasks throughout the day since he was not fatigued and sleeping all the time. Another patient stopped treatment due to developing diverticulitis and was subsequently treated with prednisolone and antibiotics.

3.1.3 Impact on Caregivers

LCC highlighted mental stress, anxiety, and depression to be the most significant impacts on caregivers as a result of worrying about the patients' survival and the time dedicated to providing care and support as the diagnosis is commonly a shock to the family. In some cases, caregivers feel just as much stress as the patient or even more, which can affect the caregivers' ability to fulfill their role at home and at work. Caregivers may also experience stigma as a result of the negative implications associated with lung cancer. There may be unconscious attitudes directed towards caregivers resulting in emotional burden and negative psychological, behavioural, and physiological effects. LCC noted that longer durable treatments would also help decrease the demand on caregivers; therefore, caregivers may be able to continue working (i.e. less of a need to take time off work for caregiving activities), which also reduces physical and financial burdens on the family. To provide context, LCC noted that one caregiver emphasized that they were not ready to lose their husband, partner, and best friend to lung cancer and another caregiver described the journey as "*scary and challenging*."

3.2 Information about the Drug Being Reviewed

3.2.1 Patient Expectations for New Therapies

Overall, key treatment outcomes highlighted in both inputs include delaying disease progression, reducing side effects, and improving symptoms and quality of life to a state that enables patients to be independently functional throughout the day. Namely, the patient interviewed by the LHF reported the following key treatment outcomes: stopping or slowing disease progression; reducing or eliminating side effects such as pain, fatigue, nausea and shortness of breath; and improving appetite. Further, she greatly values the quality of her life, not just the extension of life, which was consistently portrayed throughout her responses in addition to having more energy to complete more daily tasks before becoming exhausted. LCC highlighted that treatment options differ in terms of patient response and side effects. Namely, patients identified the following as improved outcomes: improved symptoms; prolonged survival; a good quality of life that allows patients to be functional, independent, and physically active; manageable side effects; longer lasting, durable treatment; and delayed disease progression. Additionally, they highlighted that despite treatment advancements, a high unmet need still exists for viable options in the first-line setting that provide longer-lasting survival benefits, allow patients to have a good quality of life, and delay progression. Namely, durability of treatment is an area of unmet need for patients that are not treated with targeted therapies.

3.2.2 Patient Experiences to Date

The patient interviewed by the LHF had no experience with the treatment combination under review—she has only been treated with radiation. LCC expressed their difficulty in contacting patients that match the population in the funding request under review (NI plus two cycles of PDC for the first-line treatment of patients with metastatic or recurrent NSCLC with no EGFR or ALK genomic tumor aberrations). Nevertheless, LCC stated that the combination of NI plus chemotherapy is a treatment option that fulfils the need for more effective first-line options and more durable options that promote quality of life. Namely, the need for less chemotherapy sessions combined with the durability of NI will likely be beneficial for patient quality of life. Additionally, LCC highlighted that this treatment combination has been approved for the treatment of melanoma and patients have reported very little side effects. The remainder of this section details the input provided by LCC from two female patients who received NI (not in combination with chemotherapy) as first-line treatment through participation in a clinical trial (referred to below as LL and CC). Overall, treatment with NI resulted in durable disease control.

LL was diagnosed with NSCLC in 2017 and treated with NI; LL responded quite well as most of the tumors disappeared and the small number that remained were considered stable. Namely, LL indicated that her response to treatment was very quick. However, following a year of treatment with NI, it affected her pancreas and treatment had to be discontinued. Nevertheless, she has remained stable since her last treatment in 2018. CC was diagnosed with NSCLC in 2016 and was enrolled into the two-year trial for NI. CC's tumors shrunk remarkably and symptoms such as tiredness improved. CC's last treatment was in November 2018 as CC had reached the end of the trial, since then, CC has not received any treatments apart from radiation therapy for brain metastasis but is still considered to be stable. Regarding side effects, both patients developed occasional fatigue, which did not affect their daily activities. For LL, her livelihood post-treatment was very similar to pre-treatment as a result of very few side effects that did not affect her functionality and independence. LCC also reported that NI elicited a good quality of life for both patients as they were able to be

independent, functional, and physically active; in other words, they returned to their daily activities and established a new normal. Namely, these patients enjoy and spend lots of time gardening and playing golf. As a result of the patients establishing a new, durable normal, the caregivers have been able to do the same.

Both these cases demonstrate that treatment with NI is durable as both patients have not received treatment for their lung cancer for the two years since they stopped the treatment combination. For two years, they have established a new normal and participated in life; thus, their lung cancer is well controlled and stable as demonstrated by routine follow-up scans. Namely, CC expressed that she is extremely grateful to have had access to NI, in her words, *"I don't believe I would be here if it wasn't for the treatment. It is a miracle."* Accordingly, CC hopes other patients are able to access NI. Furthermore, the durability of NI is highly significant as this reduces the burden on the caregiver; for instance, the caregiver can take less time off work to take the patient to treatment. Additionally, this reduces the burden on hospital resources as these patients are not occupying chemotherapy chairs. Of note, the treatment under review involves a reduced number of platinum-based chemotherapy cycles (two cycles); therefore, this treatment combination would also reduce the burden on the caregiver and hospital resources (e.g. need for chair time). LCC emphasized that it is rare for lung cancer patients to remain stable without treatment—as stated—both patients responded quickly and established a new normal that has lasted for two years without any treatment. Thus, the durability of NI is significant because for many patients treated with targeted therapies, they experience a good quality of life but they remain on treatment.

3.3 Companion Diagnostic Testing

None to report.

3.4 Additional Information

LCC stated that there is an unmet need for NSCLC patients particularly those with no known targetable mutations due to the lack of pERC recommendations for reimbursement amongst recent submissions. They specified that in recent years there have been new advances for the treatment of NSCLC but many of these have been targeted therapies, which benefits only about 20% of lung cancer patients. Accordingly, options are still limited for the remaining 80% who do not exhibit a driver mutation or have a driver mutation that does not have an approved treatment. Therefore, despite the advancements, a high unmet need still exists for viable options in the first-line setting that provide longer-lasting survival benefits, allow patients to have a good quality of life, and delay progression.

Furthermore, they highlighted that chemotherapy is associated with well documented side effects and is difficult to tolerate. Thus, treatment combinations that allow for a shorter duration of chemotherapy are beneficial as they allow for patients to return to "normal life" faster and are associated with less caregiver burden. Additionally, they noted that the data demonstrate that responsive patients respond quickly, which aligns with patient and payer needs. Overall, LCC hopes pERC makes a positive recommendation as this would enable patient access through public payers. This treatment combination has the potential to impact patients' long term outcomes (i.e. chance at a longer life) and clinical trial data demonstrate treatment benefit. Accordingly, there would be potential for this treatment combination to become the new standard and to help extend the lives of patients with advanced NSCLC. Of note, LCC also highlighted the survival data from the phase 3 CheckMate 227 trial (*An Investigational Immuno-therapy Trial of Nivolumab, or Nivolumab Plus Ipilimumab, or Nivolumab Plus Platinum-doublet Chemotherapy, Compared to Platinum Doublet Chemotherapy in Patients With Stage IV Non-Small Cell Lung Cancer (NSCLC)*); namely, an OS of 14.9 months with a long-term follow-up of three years.

4 Summary of Provincial Advisory Group (PAG) Input

The PAG 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 CADTH 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:

- Place in therapy and sequencing with currently available treatments
- Use after adjuvant/consolidation therapy

Economic factors:

- Discontinuation rules for one or both drugs
- Sizeable budget impact

Please see below for more details.

4.1 Currently Funded Treatments

The standard of care in first-line NSCLC with no EGFR or ALK genomic tumour aberrations varies based on PD-L1 level and histology. For tumours with expression of any or unknown PD-L1, platinum doublet and pembrolizumab plus chemotherapy can be offered, although the latter is not yet funded by provinces. Pembrolizumab monotherapy is an additional funded option for those with PD-L1 ≥ 50%. In non-squamous NSCLC, the chemotherapy regimens complementing pembrolizumab consist of platinum agents plus pemetrexed, whereas carboplatin plus paclitaxel are used for squamous NSCLC.

PAG noted that the CheckMate 9LA trial compared NI plus two two cycles of platinum doublet chemotherapy (PDC) to PDC alone. PAG seeks additional comparison of NI plus PDC against pembrolizumab-based regimens.

4.2 Eligible Patient Population

The reimbursement request of NI plus platinum-based chemotherapy is the first-line treatment of patients with metastatic or recurrent NSCLC with no EGFR or ALK genomic tumour aberrations. In view of the characteristics of the patient population in the trial, PAG is seeking clarity on whether the following patients would be eligible for treatment with NI plus platinum-based chemotherapy:

- Patients with ECOG performance score ≥ 2
- Patients with no PD-L1 results
- Patients with untreated CNS metastases
- Patients with stage IIIB NSCLC
- Patients with non-metastatic or non-recurrent disease that is not amenable to resection
- Patients who have experienced disease progression on anti-PD-L1 therapy (e.g., durvalumab) for stage III NSCLC, or who have experienced disease progression on chemotherapy for stage III NSCLC within 6 months of completion, or for stage III NSCLC have experienced disease progression after 6 months of completion
- Patients who progressed on maintenance pemetrexed in the non squamous setting
- Patients with rare subtypes of lung cancer (e.g., typical or atypical carcinoid)

PAG seeks guidance on whether specific subgroups of patients defined by PD-L1 expression (≥ 50%, any, unknown or other) or histology (squamous versus non-squamous) should be treated differently. Additionally, PAG would like confirmation that other driver mutations (e.g., ROS-1, NTRK) should also be excluded when results are available. Although out of scope of the review, PAG is seeking information on the use of NI in combination with other chemotherapy regimens (e.g. non-platinum-based regimens).PAG identified a potential time-limited need to switch patients who initiated first-line chemotherapy or pembrolizumab, and have not progressed, to NI plus platinum-based chemotherapy. In particular, for patients having initiated platinum chemotherapy, PAG would like confirmation that they should discontinue chemotherapy after two additional cycles in combination with NI. PAG noted potential indication creep to patients who failed first line therapy (with or without an immune checkpoint inhibitor) and patients with non-metastatic or non-recurrent disease.

4.3 Implementation Factors

Nivolumab is to be administered with ipilimumab, plus two cycles of histology-based PDC. After two cycles of induction treatment, NI treatment (nivolumab 360 mg every three weeks and ipilimumab 1 mg/kg every six weeks) will continue until progression, unacceptable toxicity, or other reasons. PAG would like clarification of “disease progression” and “other reasons” for discontinuation. PAG noted that patients in the CheckMate 9LA trial were treated with NI for a maximum of two years. PAG is looking for confirmation that the patient must be a suitable candidate for two cycles of platinum chemotherapy before being considered for NI therapy.

PAG also highlighted the potential for medication errors due to the new dosing schedule. PAG seeks guidance on the adequacy of alternate weight-based dosing for nivolumab (4.5 mg/kg) with or without a cap of 360 mg. PAG noted that Q3W dosing and the 360 mg fixed dose both differ from approved nivolumab monotherapy regimens (flat 240/480 mg every 2/4 weeks) and may cause confusion. Variable dosing with ipilimumab (and potentially nivolumab) may minimize costs but also lead to wastage of drugs unless vial sharing is realized. Implementation of the latter is challenging in smaller centres. PAG added that the high prevalence of NSCLC combined with the high cost drug combination may have a substantial impact on drug program budgets.

NI plus PDC is aiming to replace some chemotherapy regimens in the same setting; it may therefore require additional healthcare resources such as nursing, pharmacy, clinic visits given treatment is every three weeks, chair time, and supportive care. Additional resources would be required for pre-medication, drug preparation, drug administration, and monitoring and management of adverse effects (infusion related reactions, immune-related adverse events). PAG noted that both drugs are known to clinicians and are used together for other indications, but since the combination is new to the NSCLC space, treating lung clinicians may not be familiar with some of the adverse effects. Greater monitoring would also be required as significant toxicities are likely in the presence of both immunotherapy drugs. PAG is seeking guidance on dose adjustment and/or discontinuation of one of the drugs in the event of such toxicity. PAG is seeking guidance on whether there are any special considerations for older patients with comorbidities.

PAG seeks to clarify whether pseudoprogression is recognized or likely with this treatment. If so, PAG noted that prompt access to more frequent imaging may be required to re-assess.

Nivolumab, ipilimumab, and PDC, being intravenous drugs, would be administered in an outpatient chemotherapy centre for appropriate administration and monitoring of toxicities. Intravenous oncology drugs would be fully funded in all jurisdictions for eligible patients, which is an enabler for patients. However, in some areas, patients would need to travel far to an outpatient chemotherapy center, which would be a barrier to for these patients.

4.4 Sequencing and Priority of Treatments

PAG is seeking to confirm the place in therapy and sequencing with NI plus PDC, including the scenarios below:

- Factors justifying the preferential use of NI plus PDC, pembrolizumab monotherapy, or pembrolizumab plus chemotherapy.
- Confirmation that subsequent anti-PD-1/PD-L1 cannot be given upon progression while on NI plus PDC.
- Suitability of re-treatment with NI plus PDC or treatment with pembrolizumab (and timing thereof) upon relapse after the two-year treatment.
- Addition of NI to any ongoing first-line chemotherapy regimen, and termination of the latter after two additional cycles (i.e., induction).

- Optimal choice of next line chemotherapy upon disease progression.
- In the next line setting, appropriateness of full platinum chemotherapy despite the two cycles of platinum given in the NI plus PDC induction phase.
- Appropriateness of re-treatment with agents used in PDC during the NI plus PDC induction phase (e.g. pemetrexed, paclitaxel, cisplatin, carboplatin)

4.5 Companion Diagnostic Testing

PAG would like confirmation that PD-L1 testing is not required.

4.6 Additional Information

None.

5 Summary of Registered Clinician Input

A total of two registered clinician inputs were provided for the review of nivolumab plus ipilimumab (NI) plus two cycles of platinum doublet chemotherapy (PDC) for the first-line treatment of patients with metastatic or recurrent NSCLC with no EGFR or ALK genomic tumor aberrations: two clinicians provided input on behalf of Cancer Care Ontario (CCO) Lung Drug Advisory Committee (DAC) and 15 clinicians provided input on behalf of LCC.

The standard of care in first-line NSCLC patients with no EGFR or ALK genomic tumor aberrations varies based on PD-L1 level and histology and may be administered for up to two years. For tumours with unknown PD-L1 expression or PD-L1 expression of any level, PDC (four to six cycles) plus pembrolizumab is typically administered. For squamous histologies, carboplatin and paclitaxel (PDC) are followed by pembrolizumab maintenance. For non-squamous histologies, cisplatin or carboplatin plus pemetrexed are followed by pembrolizumab (PDC) and pemetrexed maintenance. For tumours with PD-L1 expression of ≥ 50%, pembrolizumab monotherapy is another funded treatment option. Of note, pembrolizumab is not yet funded in all provinces. For the present review, the LCC clinicians stated that a chemotherapy and immunotherapy combination is the most appropriate comparator. The CCO and LCC clinicians indicated that NI plus PDC (two cycles) serves as an alternative first-line treatment option for newly diagnosed metastatic NSCLC patients without a driver mutation or patients with contraindications to immunotherapy. Namely, the treatment combination under review would replace the use of chemotherapy or pembrolizumab based regimens in the first-line setting (e.g., pembrolizumab monotherapy or pembrolizumab plus chemotherapy). The LCC clinicians further specified that this treatment combination (NI plus PDC) would be followed by treatment with PDC with pemetrexed maintenance therapy (for patients with non-squamous histology) or without pemetrexed maintenance therapy in the second-line setting and docetaxel in the third-line setting. Additionally, the LCC clinicians noted that chemotherapy plus immunotherapy, whether the immunotherapy is a single agent or doublet, remains a treatment best suited for patients with a performance status of 0 or 1. The LCC clinicians are most interested in offering this combination to the PD-L1 negative patient population. The CCO clinicians would like to administer this treatment combination in patients pre-treated with durvalumab and would not follow some of the trial criteria such as excluding patients with HIV or steroid use at baseline. When asked if there is evidence to suggest that regimens other than the one used in the trial can be effectively combined with NI in the induction phase; the LCC clinicians stated that in the Canadian Cancer Trials Group IND.226 and BR.34 trials, they evaluated similar compounds (durvalumab and tremelimumab) plus chemotherapy. These trials generated safety data with pemetrexed/platinum, gemcitabine/platinum as well as taxane platinum. Based on this data, the LCC clinicians noted that any of these common platinum doublets could be safely combined with immunotherapy. Alternatively, the CCO clinicians stated that they would not use NI with other chemotherapy agents.

Both inputs highlighted the favourability of this treatment combination for patients seeking to minimize the duration and associated toxicity of chemotherapy due to the reduced number of chemotherapy cycles. Additionally, the LCC clinicians highlighted that this combination is particularly favourable in the era of COVID-19 during which, options that limit the immune suppressive effects of chemotherapy are particularly advantageous. The LCC clinicians stated they do not know if NI plus limited PDC is superior, with respect to efficacy or toxicity, to pembrolizumab plus chemotherapy as no direct comparison exists. However, they noted that the side effect/ toxicity profile is similar when comparing the nivolumab plus PDC arm of the CheckMate 227 trial and data from pembrolizumab/chemotherapy trials to the experimental arm of the pivotal trial (CheckMate 9LA). Further, when comparing NI to nivolumab monotherapy or in combination with chemotherapy, the treatment discontinuation rate was reported to be slightly higher. This suggests there is a modest increase in immune-related toxicity from doublet immunotherapy; the LCC clinicians noted this increase in immune-related toxicity from the addition of a CTLA-4 inhibitor (ipilimumab) is well-established. Regarding preferential use of NI, pembrolizumab monotherapy, or pembrolizumab plus chemotherapy for first-line treatment of NSCLC; the CCO clinicians specified that patient choice and desire to avoid an additional two cycles of chemotherapy would be justifying factors for preferential administration. The LCC clinicians stated that most clinicians would administer pembrolizumab monotherapy to patients with tumours that have PD-L1 expression ≥ 50%. However, an exception to this practice may include patients with a heavy disease burden where achieving an objective response early in the treatment course is highly desirable (where both pembrolizumab and pembrolizumab plus chemotherapy are available in the PD-L1 highly expressing patient population). Patients with tumours that have PD-L1 expression < 50%, would be administered chemotherapy plus immunotherapy for benefits of the latter. Notably, patients and clinicians value sparing chemotherapy when possible for patients of all NSCLC sub-types.

The CCO and LCC clinicians did not strongly support the practice of administering other PD-1/PD-L1 inhibitors in subsequent lines of therapy. Namely, the LCC clinicians would re-treat with PDC as two cycles would not be considered adequate exposure to induce resistance. The CCO and LCC clinicians noted that there is no evidence at this time to inform whether patients who experienced disease progression on or shortly after "curative intent" treatment (with or without durvalumab consolidation) for stage III NSCLC are eligible for treatment with NI plus chemotherapy at the time of disease recurrence. However, the CCO clinicians stated that it would be reasonable to administer the treatment under review to these patients as a final effort to provide treatment when options are limited. The LCC clinicians would re-challenge with PDC if there was at least a six-month interval between completion of chemotherapy and radiation for stage III NSCLC as this is the same interval used to address progression after completion of durvalumab. Further, they stated that most clinical trials would exclude patients who had progressed while on consolidation immunotherapy or had completed consolidation immunotherapy within the previous six months. Moreover, the CCO clinicians were unaware of evidence to inform the suitability of re-treatment with nivolumab-ipilimumab-platinum or treatment with pembrolizumab upon relapse after two years of treatment but specified that this practice is typical with other immunotherapies with limited treatment duration. The LCC clinicians stated that there is evidence from other clinical trials, of up front immunotherapy, that demonstrate that re-challenging can be a successful strategy. However, the pivotal trial did not allow for re-challenging of patients who progressed after completion of two years of treatment; thus, there is no data on if this specific strategy would be efficacious. The LCC clinicians would recommend review of these requests on a patient basis as numbers would be quite small; if progression was six months or greater from discontinuation for completion of two years of treatment then re-challenge with PD-1/L1 should be considered if performance status remains adequate.

Please see below for details from the clinician inputs.

5.1 Current Treatment(s)

The CCO and LCC clinicians indicated that the standard of care in first-line NSCLC patients with no EGFR or ALK genomic tumor aberrations varies based on PD-L1 level and histology. The LCC clinicians stated that the chemotherapy and immunotherapy combination is the most appropriate comparator.

- For tumours with unknown PD-L1 expression or PD-L1 expression of any level: PDC plus pembrolizumab.
  - Squamous histology: carboplatin and paclitaxel (four to six cycles) plus pembrolizumab followed by pembrolizumab maintenance (treatment duration is up to two years).
  - Non-squamous histology: cisplatin or carboplatin plus pemetrexed (four to six cycles) followed by pembrolizumab and pemetrexed maintenance (treatment duration is up to two years).
- For tumours with PD-L1 expression of ≥ 50%: pembrolizumab monotherapy is an additional funded treatment option (treatment duration is up to two years).
- Of note, pembrolizumab is not yet funded in all provinces.

5.2 Eligible Patient Population

The CCO and LCC clinicians indicated that NI plus chemotherapy serves as an alternative treatment option. Namely, the CCO clinicians stated that the treatment combination does not meet an unmet need, and the LCC clinicians specified that this would be an alternative treatment option for the patient population that is eligible for pembrolizumab plus chemotherapy. Both inputs highlighted the reduced number of chemotherapy cycles in this treatment combination; accordingly, the bulk of this treatment combination is immunotherapy as it only administers two cycles (six weeks) of PDC at the very beginning. Thus, the LCC clinicians noted that this treatment combination is appealing for patients seeking to minimize the duration and associated toxicity of chemotherapy. Notably, this treatment combination is of particular interest to patients and physicians in the era of COVID-19 during which, options that limit the immune suppressive effects of chemotherapy are particularly advantageous.

5.2.1 Is there evidence to inform whether patients who experienced disease progression on or shortly after "curative intent" treatment (with or without durvalumab consolidation) for stage III NSCLC are eligible for treatment with NI plus chemotherapy at the time of disease recurrence?

The CCO and LCC clinicians noted that there is no evidence to inform this practice at this time. However, the CCO clinicians stated that it would be reasonable to administer NI plus chemotherapy to these patients as a final effort to provide treatment when options are limited. Namely, the CCO clinicians stated in their own words "*nivo/ipi/chemo would be reasonable hail mary in this situation.*" The LCC clinicians stated that in clinical practice, they would re-challenge with PDC if there was at least a six-month interval between completion of chemotherapy and radiation for stage III NSCLC as this is the same interval used for durvalumab. Namely, when a patient progresses six months or more after completion of durvalumab, front-line treatment with pembrolizumab or pembrolizumab plus chemotherapy would be recommended—presuming ongoing patient eligibility for both chemotherapy and immunotherapy. Further, they stated that most clinical trials would exclude patients from participating who had progressed while on consolidation immunotherapy or had completed consolidation immunotherapy within the previous six months.

5.3 Relevance to Clinical Practice

The CCO clinicians did not specify if they had experience administering the treatment combination under review. Some of the clinicians who contributed to the input on behalf of LCC reported having experience administering the treatment combination under review through clinical trials. Namely, the majority of the LCC clinicians had experience administering the combination of PDC with double immunotherapy (anti-CTLA-4 and anti-PD-1/L1) through participation in similar clinical trials such as the IND.226 and BR.34 trials conducted through the Canadian Cancer Trials Group (CCTG), which combined similar agents.

The LCC clinicians noted that double immunotherapy and PDC can be safely delivered to Canadian patients. They specified that the treatment combination under review would be an option for any patient with newly diagnosed metastatic NSCLC without a driver mutation that does not have a contraindication for immunotherapy. Namely, the LCC clinicians stated that they are most interested in offering the double immunotherapy and chemotherapy combination to the PD-L1 negative patient population. Additionally, they specified that chemotherapy plus immunotherapy, whether the immunotherapy is a single agent or doublet, remains a treatment best suited for patients with a performance status of 0 or 1. The LCC clinicians stated that there are no new contraindications to this combination as there have always been contraindications for immunotherapies as a therapeutic class. Namely, the contraindications do not differ when adding ipilimumab to the combination.

Further, the LCC clinicians noted that NI plus limited chemotherapy has not been directly compared with pembrolizumab plus chemotherapy; thus, they do not know if one regimen is superior with respect to efficacy or toxicity. Nevertheless, they alluded to various CheckMate and KEYNOTE trials to compare the treatment combination under review with other nivolumab, ipilimumab, pembrolizumab, and chemotherapy based regimens. The LCC clinicians noted that the side effect/ toxicity profile is similar when comparing the nivolumab plus PDC arm of the CheckMate 227 trial and data from pembrolizumab/chemotherapy trials to the experimental arm of the pivotal trial (CheckMate 9LA). Further, when comparing NI to nivolumab monotherapy or in combination with chemotherapy, the treatment discontinuation rate was reported to be slightly higher. The LCC clinicians stated that this suggests there is a modest increase in immune-related toxicity from doublet immunotherapy; however, the increase in immune-related toxicity from the addition of a CTLA-4 inhibitor (ipilimumab) has been well-established. Regarding efficacy, the LCC clinicians primarily alluded to the CheckMate 227 trial due to the longer follow-up period of three years compared to the one year follow up of the CheckMate 9LA pivotal trial. According to the CheckMate 227 trial; more patients were alive at three years when treated with double immunotherapy compared to patients who received PDC alone; the difference between the three-year survival was small in the PD-L1 positive population when comparing NI to nivolumab monotherapy; and the difference was greater in the PD-L1 negative population when comparing NI to nivolumab plus chemotherapy. Please see Section 5.7 Additional Information for a detailed discussion, supported by comparisons of the CheckMate and KEYNOTE trials, of how the treatment combination under review compares with other nivolumab, ipilimumab, pembrolizumab, and chemotherapy based regimens with respect to safety, tolerability, and efficacy.

5.4 Sequencing and Priority of Treatments with New Drug Under Review

The LCC clinicians specified that NI plus two cycles of PDC would be administered in the first-line setting; followed by PDC with or without pemetrexed maintenance therapy specifically for those with a non-squamous histology in the second-line setting and docetaxel in the third-line setting. The LCC and CCO clinicians stated that the treatment combination under review would replace the use of chemotherapy or pembrolizumab in the first-line setting. Namely, the LCC clinicians stated that the combination under review

would replace pembrolizumab monotherapy or pembrolizumab plus chemotherapy, and the CCO clinicians specified they would administer the combination under review in patients when tolerability of additional immunotherapy is worth the reduction of chemotherapy.

5.4.1 Are there factors that would justify the preferential use of NI, pembrolizumab monotherapy, or pembrolizumab plus chemotherapy in the first-line treatment of NSCLC?

The CCO clinicians specified that patient choice and desire to avoid an additional two cycles of chemotherapy would be justifying factors for preferential administration. The LCC clinicians stated that most clinicians would administer pembrolizumab monotherapy to patients with tumours that have PD-L1 expression ≥ 50%; however, an exception to this practice may include patients with a heavy disease burden where achieving an objective response early in the treatment course is highly desirable (where both pembrolizumab and pembrolizumab plus chemotherapy are available in the PD-L1 highly expressing patient population). Both patients and clinicians value sparing chemotherapy when possible for patients throughout all NSCLC sub-types. The most notable differences of the treatment combination under review are 1) the reduced duration of chemotherapy (two cycles versus four to six cycles) and 2) the elimination of chemotherapy maintenance in the first-line setting specifically for non-squamous patients. Thus, chemotherapy sparing combinations align with patient values. While the PD-L1 ≥ 50% patient population can access pembrolizumab as a single agent, patients with tumours that are PD-L1 < 50% need to receive chemotherapy plus pembrolizumab to access the upfront benefits of immunotherapy. As mentioned, limiting chemotherapy is particularly favourable during the era of COVID-19 when administering treatments with a reduced chance of suppressing the immune system is particularly advantageous.

5.4.2 Can other PD-1/PD-L1 inhibitors be given in subsequent lines of therapy, and if so, under what circumstances?

The CCO and LCC clinicians did not strongly support the practice of administering other PD-1/PD-L1 inhibitors in subsequent lines of therapy. The CCO clinicians said this practice would be unlikely and further stated that the "*bigger question is what to do at progression;"* namely, questioning if doublet chemotherapy would be administered again. The LCC clinicians stated that after progression on the treatment combination under review, they would not re-treat with PD-1/PD-L1 inhibitors given the current level of evidence outside of clinical trials. Instead they would re-treat with PDC because two cycles (of PDC) would not be considered adequate exposure to induce resistance. For progression after completion of the treatment combination under review refer to Section 5.4.3.

5.4.3 Is there evidence to inform the suitability of re-treatment with nivolumab-ipilimumab-platinum or treatment with pembrolizumab (and timing thereof) upon relapse after the 2-year treatment?

The CCO clinicians stated that they are unaware if there is informing evidence of this practice; however, this practice is typical with other immunotherapies with limited treatment duration. Alternatively, the LCC clinicians stated that there is evidence from other clinical trials of up front immunotherapy that demonstrate that re-challenging can be a successful strategy. However, the pivotal trial did not allow for re-challenging of patients who progressed after completion of two years of treatment so there is no data on if this specific strategy would be efficacious. Therefore, the LCC clinicians would recommend review of these requests on a patient basis as numbers would be quite small. If progression was six months or greater from discontinuation for completion of two years of treatment then re-challenge with PD-1/L1 should be considered if performance status remains adequate.

5.5 Companion Diagnostic Testing

None to report.

5.6 Implementation Questions

5.6.1 Is there evidence to suggest that regimens other than the one used in the trial can be effectively combined with NI in the induction phase?

The LCC clinicians stated that in the Canadian Cancer Trials Group IND.226 and BR.34 trials, they evaluated similar compounds (durvalumab and tremelimumab) plus chemotherapy. These trials generated safety data with pemetrexed/platinum, gemcitabine/platinum as well as taxane platinum. Based on this data, the LCC clinicians noted that any of these common platinum doublets could be safely combined with immunotherapy. Alternatively, the CCO clinicians stated that they would not use NI with other chemotherapy agents and they do not foresee there being a cost issue for two cycles of chemotherapy.

5.7 Additional Information

The LCC clinicians noted that the appropriate dosing and scheduling of NI administration, for tolerability, was identified through multiple iterations of the CheckMate 012 trial while the side effect profile with the nivolumab 3 mg/kg and ipilimumab 1 mg/kg regimen was established in the CheckMate 227 trial. When comparing the nivolumab plus PDC arm of CheckMate 227 to the limited chemotherapy plus NI arm of the pivotal trial (CheckMate 9LA), the side effect profile is similar with 92% of patients in both trials experiencing treatment-emergent AEs and approximately 50% of patients experiencing grade 3 or 4 AEs. They highlighted that this toxicity profile is similar to published data from the pembrolizumab/chemotherapy trials. When comparing NI to nivolumab monotherapy or in combination with chemotherapy, there is a slightly higher treatment discontinuation rate (18% vs. 12-14%). The LCC clinicians stated that this suggests there is a modest increase in immune-related toxicity from doublet immunotherapy and that the increase in immune-related toxicity from the addition of a CTLA-4 inhibitor (ipilimumab) has been well-established. Of note, they highlighted that an investigation of both double immunotherapy and chemotherapy in the same trial as single agent immunotherapy or platinum doublet plus immunotherapy does not exist.

Further, the LCC clinicians commented on the efficacy of NI for treatment of NSCLC based on comparisons between the CheckMate and KEYNOTE trials. They highlighted that the CheckMate trials included both squamous and non-squamous patients in the same trial; whereas, the KEYNOTE trials were conducted separately for each histologic category. Additionally, they noted that they were unable to make a comprehensive comparison because they did not have access to the data investigating subgroups by both histology and PD-L1 status from the CheckMate trials. Nevertheless, they noted that squamous patients have a poorer prognosis than non-squamous patients as demonstrated by the pembrolizumab plus chemotherapy arms of the KEYNOTE 189 and 407 trials, and that the CheckMate 9LA and 227 trials were comprised of 31% and 28% of squamous patients, respectively. The LCC clinicians also stated that the addition of a CTLA-4 inhibitor (ipilimumab) has been theorized to improve long term survival. Thus, they reported that 33-34% of patients are still alive at three years with double immunotherapy in contrast to 15-22% of patients who received PDC alone in the CheckMate 227 trial. Furthermore, the difference between the three-year survival was small in the PD-L1 positive population (33% vs. 29%) when comparing NI to nivolumab monotherapy; however, the difference was greater in the PD-L1 negative population (34% vs. 20%) when comparing NI to nivolumab plus chemotherapy. Of note, they reported the CheckMate 227 trial results instead of those of the pivotal trial (CheckMate 9LA) due to the longer follow-up; follow-up for the CheckMate 227 and 9LA trials are three years and one year, respectively. They also noted that the CheckMate 227 trial does not have the added potential benefit of the addition of the two cycles of induction chemotherapy. Furthermore, the LCC clinicians reported the final OS results of the KEYNOTE 189 trial, which were presented at ASCO 2020 (most recent update at the time of the input). Namely, based on a minimum follow-up of 26.5 months, the PD-L1 ≥ 50% population demonstrated a clear flattening of the survival curve; whereas, the survival curves did not appear to flatten for the PD-L1 low (1-49% expression) and negative (0% expression) subgroups. Of note, the LCC clinicians noted that the pembrolizumab trials have a shorter duration of follow up available.

6 Systematic Review

6.1 Objectives

To evaluate the efficacy and safety of NI and two cycles of PDC for the first-line treatment of adult patients with metastatic or recurrent NSCLC with no known EGFR or ALK genomic tumour aberrations.

Supplemental Issue: The CheckMate 9LA trial compared NI and two cycles of PDC to PDC alone in patients with stage IV metastatic or recurrent NSCLC. In the absence of direct trial evidence comparing NI and two cycles of PDC to other relevant comparators, the Sponsor provided an indirect treatment comparison (ITC) that compared the efficacy of NI plus PDC to:

- Pembrolizumab monotherapy
- Pembrolizumab plus platinum-based chemotherapy and pemetrexed
- Pembrolizumab plus platinum-based chemotherapy and paclitaxel/nab-paclitaxel

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the CGP and the CADTH Methods Team. Studies were chosen for inclusion in the review based on the criteria in the Table 6. Outcomes considered most relevant to patients, based on input from patient advocacy groups, are those in bold. The literature search strategy and detailed methodology used by the CADTH Methods Team are provided in Appendix A.

Table 6: Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Published or unpublished RCTs In the absence of RCT data, fully published clinical trials investigating the safety and efficacy of NI with two cycles of PDC should be included.	Untreated patients with metastatic or recurrent NSCLC with no EGFR mutations or ALK translocations • Subgroups ○ PD-L1 (<49% vs. ≥50%) ○ Sex (male vs. female) ○ Histology (squamous vs. non-squamous)	NI plus PDC (2 cycles)	• Pembrolizumab monotherapy • Pembrolizumab + platinum + pemetrexed • Pembrolizumab + platinum-based chemotherapy • Platinum-based chemotherapy • Platinum + pemetrexed • Atezolizumab + bevacizumab + carboplatin + paclitaxel[a] • Atezolizumab + platinum-based chemotherapy[b] • NI[c]	• **OS** • **PFS** • DOR • ORR • **HRQoL** **Safety** • AEs including irAEs • SAEs

AE = adverse event; DOR = duration of response; HRQoL = health related quality of life; irAE = immune related adverse event; NI = nivolumab plus ipilimumab; NSCLC = non-small cell lung cancer; ORR = objective response rate; OS = overall survival; PDC = platinum doublet chemotherapy; PFS = progression-free survival; RCT = randomized controlled trial; SAE = serious adverse event.

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

[a] Atezolizumab has been issued market authorization in combination with bevacizumab, paclitaxel and carboplatin for the first-line treatment of adult patients with metastatic NSCLC with no EGFR or ALK genomic tumour aberrations, and no prior systemic chemotherapy treatment for metastatic non-squamous NSCLC.

[b] Atezolizumab has been issued market authorization in combination with nab-paclitaxel and carboplatin for the first-line treatment of adult patients with metastatic NSCLC who do not have EGFR or ALK genomic tumour aberrations.

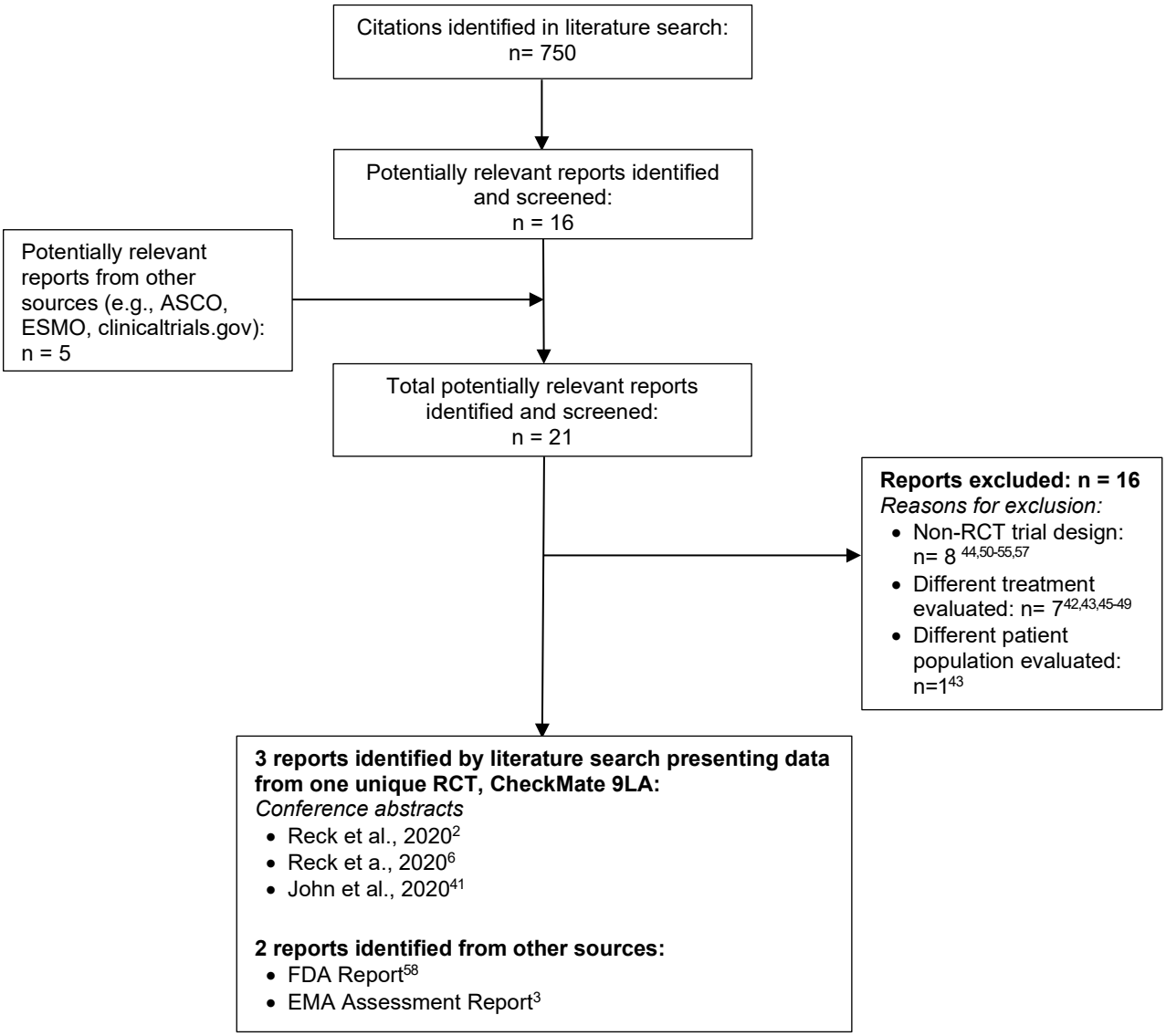
[c] During development of the protocol for the systematic review, NI did not have marketing authorization for first-line treatment of patients with metastatic or recurrent NSCLC. However, based on input from the CGP, the CADTH Methods Team included this treatment regimen as a relevant comparator. On December 3, 2020, NI received marketing authorization. NI has not been reviewed by CADTH.

6.3 Results

6.3.1 Literature Search Results

Of the 21 potentially relevant reports identified, three reports[2,6,41] representing one trial were included in the pCODR systematic review. Of these reports, one[41] was not discussed in this report since the results pertain to an Asian subpopulation of the CheckMate 9LA trial. A total of 16 reports[42-57] were excluded. Additional information on the included trial was obtained from a FDA report[58] and a European Medicines Agency (EMA) Assessment Report.[3] Reports were excluded for various reasons that included evaluation of a different treatment regimen, patient population, or trial design (Figure 2).

Figure 2: Flow Diagram for Study Selection



Note: Additional data related to CheckMate 9LA were obtained through requests to the sponsor: Clinical Study Report,[4,8] Study Protocol,[59] Statistical Analysis Plan,[60] and Checkpoint Meeting Responses[5,61,62]

6.3.2 Summary of Included Studies

One phase III trial was identified that met the systematic review protocol criteria—CheckMate 9LA. Key characteristics of the CheckMate 9LA trial related to study design, eligibility criteria, interventions, and trial outcomes are summarized in Table 7.

6.3.2.1 Detailed Trial Characteristics

Table 7: Summary of Trial Characteristics of the Included Studies

Trial Design	Inclusion and Exclusion Criteria	Intervention and Comparator	Trial Outcomes

CheckMate 9LA[59,4]
 	
NCT03215706
 	
Phase III randomized (1:1) open-label study comparing NI plus PDC to PDC in patients with stage IV or recurrent NSCLC
 	
N enrolled = 1,150; N randomized = 719; n treated = 707
 	
Number of centres and number of countries
 	
103 sites in 19 countries (Argentina, Australia, Belgium, Brazil, Canada, Chile, China, France, Germany, Ireland, Italy, Japan, Mexico, Poland, Romania, Russian Federation, Spain, United Kingdom, and United States)
 	
Patient Enrolment Dates
 	
Study initiation date: August 24, 2017
 	
Study completion date: August 16, 2019 (last patient last visit and clinical cut-off)
 	
Primary analysis: October 3, 2019
 	
Updated analysis: March 9, 2020
 	
Funding: Bristol-Myers Squibb
	Key Inclusion Criteria:**
	
	• Adult (≥18 years) patients with histologically confirmed stage IV or recurrent NSCLC of squamous or non-squamous histology as per the 7th International Association for the Study of Lung Cancer classification (IASLC)
	• Measurable disease by CT or MRI per RECIST v1.1 criteria and radiographic tumour assessment performed within 28 days before treatment
	• No sensitizing EGFR mutations or known ALK alterations
	• ECOG PS 0-1
	• PD-L1 IHC testing performed by a central laboratory during the screening period
	• Life expectancy of ≥3 months
	• Prior definitive chemoradiation for locally advanced disease was permitted so long as the last administration of chemotherapy or radiotherapy occurred at least six months prior to enrollment. Patients with locally advanced disease with recurrence after chemoradiation therapy (stage IIIB disease, refers specifically to patients with no curative options) were eligible.
	• [redacted]. Patients with symptomatic tumour lesions at baseline which may have required palliative radiotherapy within 4 weeks of first study treatment were strongly encouraged to receive palliative radiotherapy prior to initiating study treatment.
	• Prior adjuvant or neoadjuvant chemotherapy was permitted for early stage cancer so long as treatment was completed ≥six months prior to enrollment
	• Appropriate screening laboratory values: white blood cell (≥2000/μL), neutrophils (≥1500/ μL), platelets (≥100x10^3/ μL), hemoglobin (≥9.0 g/dl), serum creatinine (≤1.5xULN) or calculated creatinine clearance (≥50mL/min using the Cockroft Gault formula)*, AST/ALT (≤3.0xULN,
		Intervention: NI plus 2 cycles of PDC
		
		Nivolumab (IV) – 360mg every 3 weeks until progression, unacceptable toxicity or other reasons, up to 24 months
		
		Ipilimumab (IV) – 1mg/kg every 6 weeks until progression, unacceptable toxicity or other reasons, up to 24 months
		
		Histology-based PDC: (every three weeks for 2 cycles)
		SQ histology: carboplatin + paclitaxel;
		NSQ histology: carboplatin or cisplatin + pemetrexed
		
		Comparator: PDC
		
		Histology-based PDC: (every three weeks for 4 cycles)
		
		SQ histology: carboplatin + paclitaxel
		
		NSQ histology: carboplatin or cisplatin + pemetrexed
			Primary:
			• OS
			
			Secondary:
			• PFS by BICR
			• ORR by BICR
			• Efficacy by tumour PD-L1 expression: ORR and PFS by BICR, and OS in participants with different PD-L1 levels
			
			Tertiary:
			• Safety
			• AEs
			• Drug-related AEs
			• irAEs
			• SAEs
			• TMB association with ORR, PFS and OS
			
			Exploratory:
			• HRQoL
			  ○ LCSS ABSI
			  ○ LCSS 3-IGI
			  ○ EQ-5D VAS
			  ○ EQ-5D-3L UI

Trial Design	Inclusion and Exclusion Criteria	Intervention and Comparator	Trial Outcomes
	or ≤5xULN if liver metastases are present), and total bilirubin (≤1.5xULN except for patients with Gilbert Syndrome who must have had total bilirubin level of <3.0 mg/dL) **Key Exclusion Criteria:** • Patients with known EGFR mutations or ALK translocations sensitive to targeted inhibitor therapy • CNS metastases, unless it was adequately treated and if neurologic findings had returned to baseline (except for residual signs or symptoms related to CNS treatment) ≥2 weeks prior to receipt of first study treatment. • Prior systemic anti-cancer therapy for advanced or metastatic disease • Prior treatment with anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA-4 or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways • History of allergy or sensitivity to study drug components • HBV, HCV, [redacted]		

3-IGI=3-item global index; AE = adverse event; ALK = anaplastic lymphoma kinase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BICR = blinded independent central review; CNS = central nervous system; ECOG PS = Eastern Cooperative Oncology Group performance status; EQ-5D VAS = EuroQoL Five Dimensions Visual Analogue Scale; EQ-5D-3LUI = EuroQoL Five Dimensions-3 Level Utility Index; HBV = hepatitis B virus; HCV = hepatitis C virus; irAE = immune related adverse event; LSCC ASBI = Lung Cancer Symptom Scale Average Symptom Burden Index; NSCLC = non-small cell lung cancer; NSQ = nonsquamous; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; SAE = serious adverse event; SQ = squamous; TMB = tumour mutational burden; ULN = upper limit of normal.

*Female CrCl = (140 - age in years) x weight in kg x 0.85/ 72 x serum creatinine in mg/dL; Male CrCl = (140 - age in years) x weight in kg x 1.00/ 72 x serum creatinine in mg/dL

**this study allowed for re-enrollment of participants who had discontinued the study due to pre-treatment failure (e.g., patient was not treated or randomized). Re-enrolled patients must have re-consented, and retesting of laboratory assessments and/or other assessments within a single screening were permitted; the most current screening values prior to randomization were the values by which study inclusion was assessed.

Sources: Clinical Study Report,[4] Study Protocol,[59] EMA Assessment Report,[3] CADTH Submission.[7]

(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed)

a) Trial

CheckMate 9LA is an ongoing international, open-label, randomized, active-controlled, phase III trial evaluating the efficacy and safety of NI and two cycles of PDC compared to PDC alone in patients with stage IV metastatic or recurrent NSCLC.[3] The trial was conducted in 103 sites across 19 countries that included four sites (six patients) in Quebec, Canada.[3,22] The majority of trial patients (59.1%) were from Europe, with the remainder were from North America (8.9%), Asia (8.1%), and the rest of the world (23.9%) which

included Argentina, Australia, Brazil and Chile.[4] The trial was conducted according to the Declaration of Helsinki and the International standards of Good Clinical Practice. Each participating centre approved the CheckMate 9LA trial protocol through their independent ethics committee or institutional review board.[7]

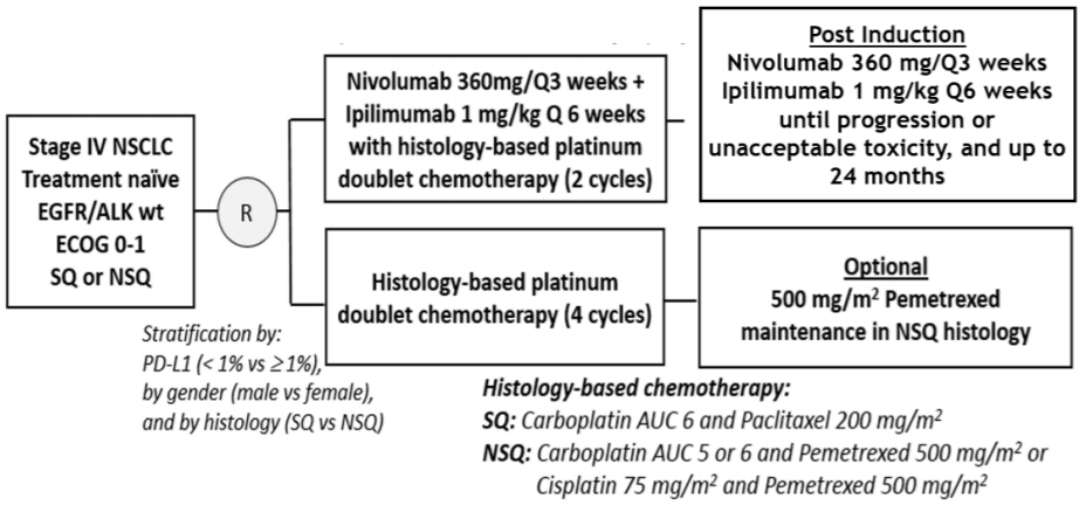
Funding

The CheckMate 9LA trial was designed and analysed by the sponsor, Bristol Myers Squibb, along with a steering committee. The sponsor oversaw all aspects of trial conduct including design and data analysis.[7]

Trial Design

Screening, Eligibility Criteria, and Randomization: The key eligibility criteria used in the CheckMate 9LA trial are summarized in Table 7. Briefly, eligible patients were adults (≥18 years) with stage IV metastatic or recurrent NSCLC without the presence of EGFR mutations or known ALK alterations, with an ECOG PS of 0-1, and no prior history of systemic therapy for advanced or metastatic disease. Patients were eligible regardless of their histology (squamous or non-squamous) or PD-L1 expression status. Testing of tumour tissues for PD-L1 status was conducted during the screening period (before randomization) and performed by a central laboratory.[3] Figure 3 depicts the study design of the CheckMate 9LA trial.

Figure 3: Study Design Schematic of CheckMate 9LA



Abbreviations: ALK - anaplastic lymphoma kinase, AUC - area under the plasma drug concentration-time curve, ECOG - Eastern Cooperative Oncology Group, EGFR - epidermal growth factor receptor, NSQ - non-squamous, PD-L1 - programmed death ligand 1, Q3 - every 3, Q6 - every 6, R - randomization, SQ - squamous

Source: EMA Assessment Report[3]

Eligible patients were enrolled via an interactive web response system (IWRS). Patients were randomized 1:1 to receive either NI plus PDC or PDC alone and were stratified based on the following factors: histology (squamous, non-squamous), sex (male, female) and PD-L1 status (<1%, ≥1%).[3] Patients whose PD-L1 status was recorded as "not quantifiable" were stratified into the PD-L1 <1% category. An enrollment cap was imposed so that subjects with a PD-L1 status of "not quantifiable" did not exceed 10% of the total randomized population. For patients with non-squamous histology, an investigator decided before randomization if patients would receive carboplatin or cisplatin therapy based on eligibility criteria for cisplatin.[3,59] As this was an open-label study, there was no blinding of investigators or patients.[4] Therefore, an independent data monitoring committee (IDMC) was responsible with general trial oversight and safety considerations. The IDMC served in an advisory capacity to the sponsor by monitoring patient safety data and overall conduct of the trial (i.e. managing communication of study data), providing guidance regarding continuation or termination of the trial, and determining whether protocol amendments or changes to study conduct were necessary. The sponsor remained blinded

to aggregate treatment group information until DBL; however, select members of the sponsor's clinical team remained unblinded to treatment group assignment of patients to monitor patient's safety.[3]

Disease Assessments

Tumour assessments and disease progression per RECIST 1.1 criteria were determined via BICR.[3] For analyses of PFS and ORR, tumour images were reviewed in all treated patients by BICR to determine response per RECIST v1.1 criteria.[59] Screening tumour assessments at baseline were performed within 28 days of randomization.[59] Radiographic tumour assessments were conducted via CT or MRI scans at baseline, at week six following the first dose of study drug (±seven days) and were then performed every six weeks (±seven days) until week 48 in both treatment groups. Thereafter, tumour assessments were performed every 12 weeks (±seven days) until BICR-assessed progression.[3]

As efficacy outcomes were also analysed by PD-L1 status, baseline assessments included central testing for this biomarker. PD-L1 was assessed centrally using the Dako PD-L1 IHC 28-8 pharmDx assay and defined PD-L1 status as the percentage of tumour cells with membrane staining in a minimum of 100 evaluable tumour cells.[4]

Sample Size

For the assessment of the primary endpoint of the trial, OS, approximately 700 randomized patients were deemed required (402 deaths) to provide 81% power to detect an average HR of 0.75 with a type 1 error of 0.05 (two-sided) via the log-rank test. The averaged HR of 0.75 was determined based on a target HR of 1.00 for the initial three months from randomization, and a targeted HR of 0.68 for the time beyond three months from randomization to allow for a delayed treatment effect for the NI plus PDC group, which has been observed with other PD-1/PD-L1 inhibitor plus chemotherapy regimens.[3,13,14] The average HR corresponded to a 33% increase in median OS with NI plus PDC (median OS of 18.57 months in the NI plus PDC treatment group versus 13.93 months in the PDC group).[3]

It was estimated that approximately 15 months would be required to accrue 700 randomized patients assuming a piecewise accrual rate of five patients in the first two months, 23 patients in the next three months, 47 patients in the next three months, and 70 patients per month thereafter beginning at the eighth month.[60]

Study Endpoints and Statistical Analyses

The patient population datasets used for analyses in the CheckMate 9LA trial are summarized in Table 8. The All Randomized Population included all patients who were randomized to either treatment group in the trial; this set of patients is consistent with intent-to-treat (ITT) principle in clinical trials, which includes every randomized patient who is analyzed according to their randomized treatment assignment rather than the treatment actually received.[63]

Table 8: Analysis Sets for the Evaluation of Outcomes in CheckMate 9LA

Population Set	N	Description	Analysis
All Randomized Population	719	Included all patients randomized into either treatment group of the trial	This dataset was used for analyses of demography, protocol deviations, baseline characteristics, efficacy, and other outcomes.
Treated Population	707	Included all patients who received at least one dose of any study drug.	This dataset was used for analyses of dosing and safety.

N/A = not applicable.

Source: EMA Assessment Report[3]

Primary Endpoint – Overall Survival

The primary endpoint was OS as assessed by investigator. OS was defined as the time from randomization to the date of death from any cause. Follow-up for survival was conducted continuously while patients were on study treatment, approximately 35 and 115 days after the last dose of study drug, and every three months thereafter.[3,60]

A log-rank test stratified by PD-L1, histology, and sex was conducted to compare OS between treatment groups, with an overall significance P value of 0.05.[3] A group sequential testing procedure was applied to control for overall type I error for the interim and

final analyses of OS.HRs and corresponding two-sided 95% CIs were estimated using a Cox proportional hazard model with treatment group as a covariate and stratified by PD-L1, histology, and sex.[3] OS was displayed graphically and estimated using the KM product limit method, generating OS curves, OS medians with 95% CIs, and OS rates with 95% CIs at 6, 12, 18, 24, 36, and 48 months.[59,60] Censoring for OS occurred on the last date a participant was known to be alive.[60]

Secondary Endpoints

Secondary endpoints included PFS by BICR, ORR by BICR, and efficacy by tumour PD-L1 expression. Statistical analyses for PFS and ORR were performed hierarchically; therefore, these endpoints were only analysed if the primary endpoint (OS) demonstrated statistical significance at the interim or final analysis.[3]

Progression-Free Survival: PFS was measured using two definitions. The primary definition of PFS was the time from the date of randomization to the date of first documented tumour progression based on BICR assessment per RECIST v1.1 criteria or death from any cause, whichever occurred first. Patients without a reported progression prior to death were considered to have progressed on the date of their death. Censoring occurred for patients during the following circumstances:[3]

- For patients who did not experience progression or death, censoring occurred on the date of their last evaluable tumour assessment.
- For patients without any tumour assessments during the trial and who did not die, censoring occurred on the date of their randomization.
- For patients who began palliative local therapy or subsequent anticancer therapy without a reported progression, censoring occurred on the date of their last evaluable tumour assessment prior to initiation of palliative local therapy or subsequent anticancer therapy, whichever occurred first.

Comparison of PFS was based on a two-sided long rank test (alpha of 0.05) stratified by PD-L1, histology, and sex. A cox proportional hazard model with treatment group as a covariate and stratified by PD-L1, histology, and sex was used to calculate HRs and corresponding two-sided 95% CIs.[3] PFS curves, PFS medians with 95% CIs, and PFS rates with 95% CIs at 6, 12, 18, 24, 36, and 48 months were calculated using the KM method.[60]

The secondary definition of PFS did not consider the receipt of subsequent therapy. The analysis of PFS using this secondary definition was conducted using the same methods described for the primary definition of PFS.[60]

Objective Response Rate: ORR was defined as the number of randomized patients with a best overall response (BOR) of confirmed CR or PR based on BICR assessment per RECIST v1.1 criteria, divided by the total number of randomized patients.[3] BOR was recorded between the date of randomization and the date of objectively documented disease progression or the date of initiation of either palliative local therapy or subsequent anticancer therapy, whichever occurred first. The response designations of all patients without progression or initiation of palliative local therapy or subsequent anticancer therapy contributed to the determination of BOR. For determination of BOR in patients who continued treatment beyond progression, response designations were recorded up to the time of initial disease progression per RECIST v1.1 criteria. CR or PRs were confirmed only if criteria for each were met at a subsequent assessment time point of ≥four weeks later.[60]

Time to response (TTR) and duration of response (DOR) endpoints were also assessed to characterize response and were based on maximum tumour shrinkage in target lesions.[60] DOR and TTR were evaluated in patients who achieved a confirmed CR or PR, and were defined as follows:

- DOR: the time between the date of first confirmed documented response (CR or PR) and the date of first documented tumour progression based on BICR assessment per RECIST v1.1 criteria.[3]
- TTR: the time from the date of randomization to the date of first confirmed response (CR or PR) based on BICR assessment.[3]

The difference in ORR between treatment groups (and 95% CI) was assessed using a two-sided Cochran-Mantel-Haenszel test stratified by PD-L1, histology, and sex. The proportions of patients with a BICR assessed CR, PR, SD, and PD were presented by treatment group. The Clopper-Pearson method was used to estimate the ORR and associated two-sided 95% CI by treatment group.[3]

Efficacy outcomes, including OS, PFS, and ORR, were also evaluated by PD-L1 expression level.

Subgroup Analyses

Exploratory subgroup analyses were conducted for OS, PFS, and ORR among all randomized patients.[3] [redacted]. *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed)* Subgroup analyses were considered descriptive in nature and summarized using 95% CIs. The following subgroups were pre-specified in the trial protocol:[60]

- Age category (<65, ≥65 and <75, ≥75 and <85, ≥85, ≥75, ≥65)
- Sex (male versus female)
- Race (White, Black, Asian, other)
- Region (Europe, North America, Rest of World, Asia)
- ECOG PS (0, ≥1)
- Baseline histology (squamous, non-squamous)
- Smoking status (current/former, never smoked, unknown)
- PD-L1 status (<1%, ≥1%, 1-49%, ≥50%)
- Disease stage (stage IV, metastatic to recurrent)
- CNS, liver, and bone metastasis (yes versus no for each)
- Tumour tissue TMB evaluable (≥10 Mut/MB, <10 Mut/MB, Overall)
- Tumour tissue TMB not evaluable
- Blood TMB evaluable (≥16 Mut/MB, <16 Mut/MB, ≥20 Mut/MB and <20 Mut/MB, Overall)
- Blood TMB not evaluable

Exploratory Endpoints

Exploratory endpoints included the evaluation of biomarkers and their association with clinical outcomes, pharmacokinetics of nivolumab and ipilimumab, assessment of healthcare resource utilization of patients, safety and patient-reported HRQoL outcomes.[60] Only safety and QoL endpoints are discussed in this report.

Safety Outcomes: The analysis of safety in the CheckMate 9LA trial was based on the frequency of AEs, irAEs and SAEs, the AEs leading to dose modification or discontinuation of study drug, and deaths.[60]

Data on AEs were collected and assessed at baseline, while on treatment (before each dosing cycle) and during follow-up (at 35 days and 115 days from the last dose of study drug); AEs and SAEs were collected continuously from the screening period and within 100 days of discontinuation of dosing. AEs were graded for severity based on NCI CTCAE version 4.0 and coded using the MedDRA version 22.1. Analyses of safety were conducted using the 30-day and/or 100-day safety window from the last dose received by patients. Clinical laboratory assessments and vital sign measurements were also included as part of the safety analyses.[60]

Patient Reported Outcomes – LCSS ASBI and 3-IGI, EQ-5D-3L Utility Index and EQ-5D VAS: The overall health status of patients was measured using the EuroQoL, 5-dimension, 3-level (EQ-5D-3L) UI and VAS. Within the descriptive system of the EQ-5D-3L the following health dimensions are captured: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The dimensions are measured on a three-point scale from “no health problems” (level 1) to “extreme health problems” (level 3). The proportion of patients in each problem level (level 1 to level 3) was summarized by treatment group according to ITT.[4] A clinically meaningful change in EQ-5D-3L UI scores was defined as of 0.08 points.[6] The VAS is a score where patients rate their current state of health; the score ranges between 0 (“worst imaginable health”) and 100 (“best imaginable health”). Patient’s responses to the EQ-5D VAS were summarized using descriptive statistics (N, mean, median, SD, 25th and 75th percentiles, and 95% CI) by treatment group.[59] A clinically meaningful change in EQ-5D-3L VAS scores was defined as seven points.

The LCSS ASBI measures patients' lung cancer symptoms and HRQoL. The questionnaire includes nine items overall; six symptom related items (appetite, fatigue, cough, shortness of breath, hemoptysis, pain) and three additional items (overall symptom burden, disease related functional limitations and global HRQoL). The questionnaire relies on a 24-hour recall period. Each questionnaire item captures a patient's response using a scale that ranges between 0 (no symptomology) and 100 (worse symptomology). The ASBI score is derived by taking the average of the individual scores for the six symptom items. A clinically meaningful change in the ABSI score was defined as 10 points by the sponsor. The change from baseline in the ABSI score was summarized using descriptive statistics (N, mean, median, SD, 25th and 75th percentiles, and 95% CI) by treatment group as randomized during each assessment point.[59] The LCSS 3-IGI scale includes three items: symptom distress, interference with activity level, and HRQoL. Items on this scale are assessed using a VAS between 0 ("worst") to 300 ("best"). The 3-IGI is calculated by taking the sum of the three items of this scale. A clinically meaningful change for the LCSS 3-IGI was defined as 30 points.[6]

A TTD analysis was also conducted for the LCSS and EQ-5D-3L questionnaires and their subscales. TTD was defined as the time from randomization to the first deterioration that met or exceeded the MID of each scale, provided that all subsequent assessments also met or exceeded the MID.[6]

PFS2: PFS2 was defined as the time from randomization to the date of investigator-defined documented disease progression after next line of treatment or death due to any cause, whichever came first. Patients who did not progress after their next line of treatment, or who did not die were censored on the date of their last tumour assessment or last follow-up for progression/subsequent therapy. Clinical deterioration on its own was not considered disease progression. Patients without post-baseline tumour assessments or who did not die were censored on the date of their randomization.[3]

Interim and Final Analyses

One formal interim analysis was prespecified to test for superiority of OS and was monitored and carried out by the IDMC. The interim analysis was planned to be performed in the All Randomized Population when approximately 80% of the total number of deaths was observed (i.e. 322 deaths)[3]; this was expected to occur approximately 24 months after study initiation.[4] The boundary for declaring superiority of OS at the interim analysis was a P value <0.033, based on the Lan-DeMets alpha spending function with O'Brien-Fleming stopping boundaries.[3] It was estimated to take approximately 24 and 29 months from randomization of the first patient to observe the required number of events for the interim and final analyses of OS, respectively.[60] The IDMC reviewed efficacy and safety data at the time of the interim analysis. The IDMC also had access to periodic unblinded reports of efficacy and safety to allow for risk/benefit assessment.[60] Testing of secondary endpoints at the interim analysis was to be conducted hierarchically at prespecified significance levels, which were adjusted for the primary endpoint to preserve the overall type 1 error rate (0.0252 for PFS and 0.025 for ORR).[3] Alpha for the CI was the same as the nominal significance level for hypothesis testing. Analyses of endpoints that were not part of the statistical hierarchy were considered descriptive and summarized using two-sided 95% CIs. At the time of the interim analysis, 351 deaths out of the 401 required for the final analysis (87%) had occurred.[7]

An updated efficacy analysis was also conducted (DBL: March 9, 2020) providing an additional 4.6 months of follow-up for patients.[3] At the time of this updated DBL, the study had reached 60% maturity.[7] Analyses conducted at the March 9, 2020 DBL were not pre-specified in the original statistical analysis plan; therefore, these analyses are considered exploratory. [redacted].[61] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed)*

The final analysis of OS is expected to be performed when at least 420 events have been observed. All secondary endpoints are planned to be analysed at the time of the final analysis. According to the trial protocol, If the interim analysis demonstrated superiority of OS for NI plus PDC over PDC, then the final analysis of OS could be performed before the required 420 deaths are accrued.[60]

Protocol Amendments

The CheckMate 9LA trial protocol was amended a total of four times; a summary of these amendments is provided in Table 9.[3] The most significant of the amendments was amendment number 4 (March 8, 2019), which involved a change in the number of planned interim analyses from two to one interim analysis. This amendment was informed by data published after the design of the

CheckMate 9LA trial, which demonstrated superior treatment efficacy with PD-L1 inhibitors plus chemotherapy compared to chemotherapy alone but showed a delayed treatment effect in OS with a late separation of survival curves. Accordingly, the statistical analysis plan was revised to update the assumptions for the interim and final analyses to allow for sufficient power for detection of a delayed survival benefit (e.g., number of events, HRs, and projected time of events). Specifically, the number of events at the interim and final analyses were updated as well as the projected timing of events.[3]

Table 9: Summary of Protocol Amendments in the CheckMate 9LA Trial

Document	Date of issue	Summary of change
Revised protocol 04	08-Mar-2019	• Updated the two planned interim analyses to one single interim analysis • The interim and final analyses were updated with number of events, power, hazard ratios, and projected timing of events, • Blood TMB moved to secondary endpoint from exploratory endpoint
Revised protocol 03	24-Jan-2019	• Updated appendix 3: Adverse Events and Serious Adverse Events: Definitions and procedures for recording, evaluating, follow up and reporting • Updated appendix 4: woman of childbearing potential definition and methods of contraception • Updated appendix 6 for management of algorithms for immuno-oncology use • Excluded vaccine use
Revised protocol 02	02-Jul-2018	• Removed 1-year re-treatment after progression • Provided updated safety data from CA 209568 safety lead in study • Expanded study sample size, updated study endpoints • Updated document with program standards and corrected internal inconsistencies
Administrative letter 01	09-Oct 2017	• Added neurological adverse event management in algorithm
Revised protocol 01	10-Aug 2017	• Confirmed dosing language in study • Provided updated safety data from CA 209568 safety lead in study • Biomarker objective was clarified • Typographical and formatting errors were corrected
Original protocol	10-May 2017	• Not applicable

Source: EMA Assessment Report[3]

b) Populations

Demographic and Disease Characteristics

The baseline characteristics of patients in the CheckMate 9LA trial are summarized in Table 10. A total of 719 patients were randomized: 361 to the NI plus PDC group and 358 to the PDC group. Demographic and disease characteristics appeared balanced between the treatment groups except for presence of liver metastases, which was lower in the NI plus PDC group (18.8%) compared to the PDC group (24.3%). The median age of patients in both groups was 65.0 years. Most patients were white (88.7%), male

(70.1%), from Europe (59.1%), had an ECOG PS of 1 (68.4%), were classified as current or former smokers (86.2%), had non-squamous NSCLC (68.8%), and stage IV disease (92.9%; NI plus PDC group: 91.4%; PDC group: 94.4%).[3-5] In terms of PD-L1 expression, the percentage of patients with PD-L1 expression <1%, 1 to 49%, and ≥50% were 36.7%, 32.4%, and 24.1%, respectively.[3]

The baseline characteristics presented in Table 10 are based on the updated analysis DBL of March 9, 2020, which incorporates minor changes in patient's PD-L1 status compared to the primary analysis DBL of October 3, 2019. [redacted]. *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed)* Most trial patients had quantifiable PD-L1 status at baseline; there were 46 patients (6.4%) who had non-quantifiable PD-L1 status including 21 (5.8%) in the NI plus PDC group and 25 (7.0%) in the PDC group.[4]

Table 10: Baseline Characteristics in All Randomized Patients

	Nivo+Ipi+Chemo (N = 361)	Chemo (N = 358)	Total (N = 719)
Age (years)			
Median	65.0	65.0	65.0
< 65 (n, %)	176 (48.8)	178 (49.7)	354 (49.2)
≥ 65 and < 75 (n, %)	148 (41.0)	147 (41.1)	295 (41.0)
≥ 75 (n, %)	37 (10.2)	33 (9.2)	70 (9.7)
≥ 85 (n, %)	0	2 (0.6)	2 (0.3)
Male (n, %)	252 (69.8)	252 (70.4)	504 (70.1)
Race (n, %)			
White	322 (89.2)	316 (88.3)	638 (88.7)
Black	5 (1.4)	4 (1.1)	9 (1.3)
Asian (including Chinese & Japanese)	30 (8.3)	30 (8.4)	60 (8.3)
All other	4 (1.1)	8 (2.2)	12 (1.7)
Tumor Histology (n, %)			
SQ Carcinoma	113 (31.3)	111 (31.0)	224 (31.2)
NSQ Carcinoma	248 (68.7)	247 (69.0)	495 (68.8)
Metastasis Site			
Liver	68 (18.8)	87 (24.3)	155 (21.6)
CNS	63 (17.5)	58 (16.2)	121 (16.8)
Bone	96 (26.6)	110 (30.7)	206 (28.7)
ECOG PS (n, %)			
0	113 (31.3)	112 (31.3)	225 (31.3)
1	247 (68.4)	245 (68.4)	492 (68.4)
Not Reported	1 (0.3)	1 (0.3)	2 (0.3)
Smoking Status (n, %)			
Current/Former	315 (87.3)	305 (85.2)	620 (86.2)
Never smoker	46 (12.7)	53 (14.8)	99 (13.8)
PD-L1 Level (n, %)			
Quantifiable			
< 1%	135 (37.4)	129 (36.0)	264 (36.7)
≥ 1%	203 (56.2)	203 (56.7)	406 (56.5)
1 - 49%	127 (35.2)	106 (29.6)	233 (32.4)
≥ 50%	76 (21.1)	97 (27.1)	173 (24.1)
Not Quantifiable	21 (5.8)	25 (7.0)	46 (6.4)
Not Reported	2 (0.6)	1 (0.3)	3 (0.4)

Abbreviations: CNS - central nervous system, ECOG PS - Eastern Cooperative Oncology Group performance status, NSQ - non-squamous, PD-L1 - programmed death ligand 1, SQ - squamous.

Source: EMA Assessment Report[3]

Prior Therapies

The prior systemic treatment history of trial patients is summarized in Table 11. Most patients (93.5%) had not received any prior systemic therapy for their cancer. A total of 47 patients (6.5%) had received one prior systemic cancer regimen in either the adjuvant ([redacted]%) or neo-adjuvant ([redacted]%) treatment setting. [redacted]. As per the trial eligibility criteria, no patients in the trial had received prior systemic therapy for metastatic NSCLC. Eligibility criteria of the CheckMate 9LA trial allowed treatment with chemoradiation for locally advanced disease so long as administration (of either chemotherapy or radiotherapy) occurred at least six months prior to trial enrollment. [redacted].[4] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed)*

A breakdown of the prior chemotherapy regimens received by trial patients is provided in Table 12. Overall, the frequency and types of prior systemic therapies received by patients in each treatment group were similar. Patients had received either platinum-based chemotherapy ([redacted]% in the NI plus PDC group and [redacted]% in the PDC group) or non-platinum chemotherapy ([redacted]% and [redacted]%, respectively).[4] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed)*

Table 11: Prior Systemic Cancer Therapies Summary in All Randomized Patients

[redacted]

Source: Clinical Study Report[4]

(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed)

Table 12: Summary of Prior Systemic Chemotherapy in All Randomized Patients

Source: Clinical Study Report[4]

(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed)

c) Interventions

Treatment

The treatments administered to patients in each treatment group of the CheckMate 9LA trial are provided in Table 13.

The dosing schedule for NI plus PDC in the CheckMate 9LA trial was selected based on the safety lead-in phase of the CheckMate 568 trial.[47] CheckMate 568 was a phase II, single group trial (N=36) that evaluated the safety and tolerability of first-line NI plus PDC in patients with stage IV NSCLC.[3] Patients in the CheckMate 9LA trial who were randomized to NI plus PDC received nivolumab (360 mg administered intravenously every three weeks) and ipilimumab (1mg/kg every six weeks) administered concurrently with two cycles of PDC that was determined by the histology of their cancer:[3]

- Patients with squamous NSCLC received carboplatin area under the concentration time curve (AUC) six plus paclitaxel at 200 mg/m^2, or 175 mg/m^2 as per local institutional practice.[3]
- Patients with non-squamous NSCLC received carboplatin AUC five or six plus pemetrexed at 500 mg/m^2, or cisplatin at 75 mg/m2 plus pemetrexed at 500 mg/m^2. The decision to treat with cisplatin was made by the investigator prior to randomization.[3]

Treatment with NI could be continued up to a maximum of 24 months or until disease progression per RECIST v1.1 criteria, unacceptable toxicity, or other reasons specified in the protocol. Patients in the NI plus PDC treatment group who experienced disease progression (based on investigator assessment) were permitted to continue receiving NI (up to month 24) provided they had no rapid disease progression, had stable performance status, and were considered by the investigator to be clinical benefiting from and tolerating the treatment. In addition, treatment given beyond progression must not have been thought to delay an imminent intervention to prevent serious complications of disease progression such as CNS metastasis.[3] Patients treated beyond disease progression continued to have tumour assessments until further progression per RECIST v1.1 criteria and subsequent tumour assessment.

Patients randomized to chemotherapy alone received PDC based on histology (squamous or non-squamous), as described above. The chemotherapy treatment administered on day 1 of every three-week cycle for a total of four cycles. After completion of the four cycles, patients with non-squamous histology had the option of receiving maintenance therapy with pemetrexed (500 mg/m^2) on day 1 of each three-week treatment cycle until disease progression or unacceptable toxicity.[3]

Treatment crossover was not permitted during the trial; although, patients could receive subsequent treatment once they were off study treatment per their treating physician.[62]

Table 13: Treatments Administered in the CheckMate 9LA Trial

	Week 1, Cycle 1 Day 1 ± 3 Days	Week 4, Cycle 2 Day 1 ± 3 days	Week 7, Cycle 3 Day 1 ± 3 Days
Nivolumab + ipilimumab + platinum-doublet chemotherapy q 3wk x 2 cycles followed by nivolumab (360 mg q 3weeks) + ipilimumab (1mg/kg q 6weeks)	Cycle 1 Nivolumab + Ipilimumab + Histology-based chemotherapy	Cycle 2 Nivolumab + Histology-based chemotherapy	Cycle 3 Nivolumab + Ipilimumab
Platinum doublet chemotherapy q 3wk x 4 followed by optional maintenance Pemetrexed for non-squamous histology	Cycle 1 Histology-based chemotherapy	Cycle 2 Histology-based chemotherapy	Cycle 3 Histology-based chemotherapy

Source: Study Protocol[59]

Alternative Infusion Times for Nivolumab and Ipilimumab

Nivolumab and ipilimumab monotherapies have infusion times of 60 minutes and 90 minutes (1 to 3 mg/kg dosing for both), respectively.[59] Infusion times for both nivolumab and ipilimumab were shortened in the CheckMate 9LA trial to 30 minutes. However, if a patient developed an infusion reaction, nivolumab or ipilimumab could be administered over 60 minutes at the investigator's discretion.[8] The sponsor considered shorter infusion times to be safe based on prior clinical studies of nivolumab (renal cell cancer and NSCLC[64,65]) and ipilimumab (prostate cancer[66] and melanoma[67,68]).

The sponsor stated within the study protocol that a change to a 30-minute infusion time was not expected to change the safety profile of the NI combination.[59]

Treatment Exposure

The median duration of treatment was 6.1 months (range, 0-23.5) for patients in the NI plus PDC group and 2.4 months (range, 0-24.0) in the PDC group. Within the NI plus PDC group, [redacted]% of patients received greater than six months of therapy and [redacted]% received greater than 12 months of therapy, which was greater than the chemotherapy group where [redacted]% and [redacted]% of patients received greater than six months and greater than 12 months of therapy, respectively (Table 14).[4] This difference in treatment exposure between the two treatment groups was expected due to the difference in planned duration of therapy. Of 238 non-squamous patients in the PDC group, [redacted] ([redacted]%) received pemetrexed maintenance therapy.[4] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed)*

Table 14: Duration of Therapy for All Treated in the CheckMate 9LA Trial

Source: Clinical Study Report[4]

(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed)

Dose Intensity

Data on the dose intensity of study drugs received by patients in the NI plus PDC and PDC treatment groups are summarized in Table 15 and Table 16, respectively. [redacted].[4]*(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed)*

At the March 9, 2020 DBL, in the NI plus PDC group, the median number of doses of nivolumab and ipilimumab were nine (range, 1-34) and four (range, 1-17), respectively. The median number of doses of chemotherapy agents received was two (range, 1-2) for each of cisplatin, carboplatin, paclitaxel, and pemetrexed in the NI plus PDC group, which was the maximum number of cycles of chemotherapy allowed in this treatment group. Most patients (93%, n=333) in the NI plus PDC group received the planned two cycles of chemotherapy.

In the PDC group, chemotherapy was given for a maximum of four cycles, or 12 weeks, followed by optional maintenance therapy with pemetrexed for patients with non-squamous histology. Patients in this group received a median of four cycles of assigned treatment (cisplatin, caraboplatin and paclitaxel). Patients in the PDC group received a median of six cycles of pemetrexed as maintenance therapy.[4]

Table 15: Dose Intensity for All Treated Patients in the NI plus PDC Group of the CheckMate 9LA Trial

Source: Clinical Study Report[4]

(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed)

Table 16: Dose Intensity for All Treated Patients in the PDC Group of the CheckMate 9LA Trial

Source: Clinical Study Report[4]

(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed)

Dose Delay

[redacted].[59] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed)*

[redacted] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed)*

[redacted].[59] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed)*

[redacted].[59] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed)*

AEs were the most common reason for dose delay in both treatment groups. The most common drug-related AEs resulting in dose delay or reduction are reported in the safety analysis section of this report. Overall, drug-related AEs resulting in dose delay or reduction occurred in a higher proportion of patients in the PDC group.[4]

Infusion interruptions and infusion rate interruptions were infrequent in both treatment groups.[4] In the NI plus PDC group, infusion interruptions occurred more frequently during administration of nivolumab (5.9%, n=21) than ipilimumab (1.1%, n=4). In the PDC group, infusion interruptions occurred mostly with paclitaxel (6.3%, n=7) than with carboplatin and pemetrexed (0.4%, n=1 for each) and cisplatin (n=0). Similarly, infusion rate reductions in the NI plus PDC group occurred more frequently during nivolumab administration (2.8%, n=10) than with ipilimumab (1.1%, n=4); and in the PDC group, infusion rate reductions were more frequent during administration of paclitaxel (5.4%, n=6) than carboplatin and pemetrexed (0.4%, n=1 for each) and cisplatin (n=0).

Dose Reductions

Dose reductions were not permitted for nivolumab or ipilimumab.

The dose reductions permitted for chemotherapy agents are outlined in Table 17. [redacted].[59] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed)*

Table 17: Dose Modification of Chemotherapy Agents in the CheckMate 9LA Trial

Source: Study Protocol[59]

(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed)

In cases of hematologic toxicity (as per CTCAE version 4), specific dose modifications were outlined based on nadir blood counts since the preceding administration of chemotherapy, as assessed per local standards. In general, both chemotherapy drugs in the platinum doublet had to be reduced together and adjustments should have been relative to the preceding administration of treatment.

A summary of the dose reductions occurring in the trial for both treatment groups is provided in Table 18. The number of patients with at least one dose reduction for chemotherapy agents was similar between the treatment groups, which occurred more frequently with carboplatin compared to pemetrexed, cisplatin, and paclitaxel. [redacted].[4]

(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed)

Table 18: Dose Reductions in the CheckMate 9LA Trial

	Nivo+Ipi+Chemo: Cisplatin N = 74	Nivo+Ipi+Chemo: Carboplatin N = 284	Nivo+Ipi+Chemo: Paclitaxel N = 115	Nivo+Ipi+Chemo: Pemetrexed N = 244
SUBJECTS WITH AT LEAST ONE DOSE REDUCTION (%)	8 (10.8)	72 (25.4)	19 (16.5)	22 (9.0)
NUMBER OF DOSE REDUCTIONS PER SUBJECT (%)				
0	66 (89.2)	212 (74.6)	96 (83.5)	222 (91.0)
1	7 (9.5)	51 (18.0)	14 (12.2)	19 (7.8)
2	1 (1.4)	21 (7.4)	5 (4.3)	3 (1.2)
TOTAL NUMBER OF DOSE REDUCTIONS / TOTAL NUMBER OF DOSES RECEIVED (%)	9/143 (6.3)	93/546 (17.0)	24/221 (10.9)	25/470 (5.3)
REASON FOR DOSE REDUCTION (%) (A)				
ADVERSE EVENT	6 (66.7)	13 (14.0)	9 (37.5)	10 (40.0)
NOT REPORTED (B)	3 (33.3)	80 (86.0)	15 (62.5)	15 (60.0)
	Chemo: Cisplatin N = 75	**Chemo: Carboplatin N = 280**	**Chemo: Paclitaxel N = 111**	**Chemo: Pemetrexed N = 239**
SUBJECTS WITH AT LEAST ONE DOSE REDUCTION (%)	9 (12.0)	78 (27.9)	25 (22.5)	39 (16.3)
NUMBER OF DOSE REDUCTIONS PER SUBJECT (%)				
0	66 (88.0)	202 (72.1)	86 (77.5)	200 (83.7)
1	6 (8.0)	36 (12.9)	13 (11.7)	17 (7.1)
2	0	15 (5.4)	4 (3.6)	1 (0.4)
3	3 (4.0)	16 (5.7)	4 (3.6)	4 (1.7)
>= 4	0	11 (3.9)	4 (3.6)	17 (7.1)
TOTAL NUMBER OF DOSE REDUCTIONS / TOTAL NUMBER OF DOSES RECEIVED (%)	15/249 (6.0)	158/960 (16.5)	49/374 (13.1)	219/2190 (10.0)
REASON FOR DOSE REDUCTION (%) (A)				
ADVERSE EVENT	8 (53.3)	29 (18.4)	19 (38.8)	36 (16.4)
OTHER	0	1 (0.6)	0	0
NOT REPORTED (B)	7 (46.7)	128 (81.0)	30 (61.2)	183 (83.6)

Database lock: 09-Mar-2020
(A) Percentages are computed out of the total number of dose reductions.
(B) Dose modifications based on local clinical practice standards (for example, some sites routinely gave carboplatin AUC 5 (instead of AUC 6) per local standards when given in combination with paclitaxel)) are derived as dose reductions with reason=not reported.

Source: Clinical Study Report[4]

Concomitant Therapies

[redacted].[59] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed)* The use of the following medications was permitted during the trial:

- [redacted]. *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed)*
- [redacted]. *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed)*
- [redacted]. *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed)*
- [redacted]. *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines*

for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed)

- [redacted]. *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed)*

[redacted].[8] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed)* Data on the use concomitant medications were not reported for the updated analysis (DBL: March 9, 2020).

Discontinuation

For patients in the NI plus PDC treatment group, if patients discontinued treatment with ipilimumab they were permitted to continue treatment with nivolumab. However, if nivolumab was discontinued, then ipilimumab was not permitted to continue as monotherapy. Within the NI plus PDC group, ipilimumab was discontinued for [redacted] ([redacted]%) patients; among these patients, the median number of doses of nivolumab received after discontinuation of ipilimumab was [redacted] (range, [redacted]) with a median treatment duration of [redacted] days (range, [redacted]).[4] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed)*

Subsequent Anticancer Therapies

[redacted] (Table 19).[7] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed)* [redacted]. *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed)*

Table 19: Subsequent Anticancer Therapies Received by All Randomized Patients and Patients with a PFS Event in the CheckMate 9LA Trial

Data are n (%). Patients may have received more than one type of subsequent therapy.

In the NI plus PDC, subsequent therapies received by one patient each included ALT-803, ABBV-181, ABBV-927, and investigational IL-15. In the PDC group, these included durvalumab, REGN2810, AMG 510, investigational anti-CD44, ADXS-503, JNJ-757, TQB2450, and an unspecified immunotherapy (in all randomized patients only).

*Includes patients that had an event of progression or death as well as being censored for subsequent systemic therapy.

BICR = blinded independent central review; PFS = progression-free survival.

Source: CADTH Submission[7]

(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed)

Treatment Beyond Progression

[redacted].[5] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed)*

d) Patient Disposition

The disposition of patients through the CheckMate 9LA trial as of the updated analysis (DBL: March 9, 2020) is outlined in Figure 4. Overall, the trial enrolled 1,150 patients between August 24, 2017 and January 30, 2019 but only 719 were randomized and assigned to either NI plus PDC (n=361) or PDC (n=358).[3,4] There were 431 patients who were not randomized, mainly due to no longer meeting study eligibility criteria (85.4%).[3] Among the 368 patients who no longer met study criteria the main reasons were due to being untreated for their CNS metastases (n=79), having a known EGFR mutation (n=59), having an ECOG PS ≤1 at screening that was not confirmed prior to randomization (n=46), or due to patient tumour tissue samples being unavailable at a central laboratory for PD-L1 testing during the screening period (n=45). Patients with non-squamous NSCLC with unknown or indeterminate EGFR status were also excluded.[3,62] [redacted].[4,62] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed)*

Figure 4: Patient Flow in the CheckMate 9LA Trial

Source: CADTH Submission[7]

(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed)

A summary of patient disposition based on the primary and updated analyses is provided in Table 20. Patients were randomized between October 3, 2017 and January 30, 2019.[4] Of the 719 patients randomized, 707 (98%) received their allocated treatment, with 358 patients receiving NI plus PDC and 349 patients receiving PDC. At the time of the updated analysis (DBL: March 9, 2020), 0.8% of patients in the NI plus PDC group and 28.7% of patients in the PDC group had completed treatment, and 20.7% and 8.0% of patients were still on treatment, respectively. The proportions of patients completing treatment and still in treatment for both treatment groups is reflective of the planned duration of therapy in each treatment group. In both treatment groups the primary reasons for discontinuing treatment were disease progression (48.9% in the NI plus PDC group versus 45.8% in the PDC group), study drug toxicity (18.2% in the NI plus PDC group versus 6.0% in the PDC group), and AEs unrelated to study treatment (7.5% in the NI plus PDC group versus 6.9% in the PDC group). It should be noted that discontinuations due to study drug toxicity were greater in the NI plus PDC group (18.2%) compared to the PDC group (6.0%). Other reasons for discontinuation were similar between the treatment groups.[4]

Table 20: Summary of Patient Disposition in the CheckMate 9LA Trial

	Primary Analysis (DBL: October 3, 2019)		Updated Analysis (DBL: March 9, 2020)	
	NI plus PDC N=358	PDC N=349	NI plus PDC N=358	PDC N=349
Patients enrolled	361	358		
Patients randomized	361	358		
Patients treated	358 (99.2)	349 (97.5)	-	-

	Primary Analysis (DBL: October 3, 2019)		Updated Analysis (DBL: March 9, 2020)	
	NI plus PDC N=358	PDC N=349	NI plus PDC N=358	PDC N=349
Patients not treated	3 (0.8)	9 (2.5)	-	-
Reasons for not being treated				
AE unrelated to study drug	1 (0.3)	0	-	-
Patient withdrew consent	1 (0.3)	3 (0.8)	-	-
Patient no longer meets study criteria	1 (0.3)	4 (1.1)	-	-
Other	0	2 (0.6)	-	-
Ongoing in the treatment period	105 (29.3)	43 (12.3)	74 (20.7)	28 (8.0)
Completing the treatment period	16 (4.5)	103 (29.5)	3 (0.8)	100 (28.7)
Not completing the treatment period	237 (66.2)	203 (58.2)	281 (78.5)	221 (63.3)
Reason for not completing the treatment period				
Disease progression	150 (41.9)	142 (40.7)	175 (48.9)	160 (45.8)
Study drug toxicity	53 (14.8)	21 (6.0)	65 (18.2)	21 (6.0)
Death	2 (0.6)	1 (0.3)	3 (0.8)	1 (0.3)
AE unrelated to study drug	24 (6.7)	23 (6.6)	27 (7.5)	24 (6.9)
Patient request to discontinue study treatment	1 (0.3)	6 (1.7)	2 (0.6)	7 (2.0)
Patient withdrew consent	3 (0.8)	4 (1.1)	4 (1.1)	4 (1.1)
Lost to follow-up	0	1 (0.3)	0	1 (0.3)
Other	4 (1.1)	5 (1.4)	5 (1.4)	3 (0.9)
Continuing in the study	301 (84.1)	303 (86.8)	298 (83.2)	302 (86.5)
Not continuing in the study	57 (15.9)	46 (13.2)	60 (16.8)	47 (13.5)
Reason for not continuing in the study				
Death	54 (15.1)	40 (11.5)	56 (15.6)	41 (11.7)
Withdrew consent	3 (0.8)	4 (1.1)	3 (0.8)	4 (1.1)
Lost to follow-up	0	1 (0.3)	0	1 (0.3)
Other	0	1 (0.3)	1 (0.3)	1 (0.3)

Source: Clinical Study Report[4,8]

Protocol Deviations

The sponsor reported significant and relevant protocol deviations that occurred in the CheckMate 9LA trial. Significant protocol deviations were defined as those related to study conduct that differed significantly from the study protocol, including good clinical practice (GCP) non-compliance. Significant protocol deviations were reported for 136 patients (77 in the NI plus PDC group and 59 in the PDC group). Significant protocol deviations were most commonly due to inclusion and exclusion deviations (n=29 in the NI plus PDC group and n=26 in the PDC group) and are summarized in Table 21 (DBL: October 3, 2020).[3,62]

Relevant protocol deviations are summarized in Table 22, and were defined as those related to inclusion/exclusion criteria, study conduct, study management, or subject assessment that were programmable and could potentially affect the interpretability of study results.[3] Overall, there were few relevant protocol deviations in each treatment group [redacted]

[redacted].[4] [redacted]. *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed)*

Table 21: Summary of Significant Protocol Deviations in the CheckMate 9LA Trial

	Nivo+Ipi+Chemo	Chemo	Total
Failure to obtain written informed consent prior to each subject's participation in the study	**8**	**3**	**11**
Failure to obtain written informed consent on the correct approved version	7	3	10
Failure to consent on treatment beyond progression	1	0	1
Failure to report all SAEs in accordance with the time period required by GCP, the protocol, BMS and applicable regulations	**10**	**17**	**27**
Implementation of protocol changes prior to review by IRB/IEC (except when necessary to eliminate an immediate hazard(s) to trial subjects)	**6**	**2**	**8**
Use of prohibited concomitant medications	**4**	**1**	**5**
Inclusion or exclusion deviations	**29**	**26**	**55**
Safety Labs Not Performed	11	5	16
Baseline Tumor Assessment	11	12	23
Adequate Tumor Slides	2	1	3
Prior Therapy	0	4	4
EGFR Testing for Non Squamous NSCLC	1	3	4
Other	4	1	5
Incorrect dosing or study treatment assignment	**9**	**0**	**9**

Table 4.3.1-1: Summary of Significant Protocol Deviations

	Nivo+Ipi+Chemo	Chemo	Total
Other	**11**	**10**	**21**
ECOG not done at screening and/or on D1 prior to dosing	1	2	3
D1 dose given >6 days post randomization	4	1	5
Misclassified PD-L1 stratification level [IRT vs. Clinical database]	2	1	3
No baseline disease as per Investigator assessment	1	2	3
PRO not collected per protocol	2	4	6
Baseline ECG not performed	1	0	1
Grand Total	**77**	**59**	**136**

Abbreviations: BMS - Bristol-Myers Squibb, Chemo - chemotherapy, D1 - day 1, ECG - electrocardiogram, ECOG - Eastern Cooperative Oncology Group, EGFR - epidermal growth factor receptor, GCP - Good Clinical Practice, ICF - informed consent form, IEC - independent ethics committee, Ipi - ipilimumab, IRB - institutional review board, IRT - interactive response technology, Nivo - nivolumab, NSCLC - non-small cell lung cancer, PD-L1 - programmed death ligand 1, PRO - patient reported outcome, SAEs - serious adverse events

Source: EMA Assessment Report[3]

Table 22: Summary of Relevant Protocol Deviations in All Randomized Population in the CheckMate 9LA Trial

Source: Clinical Study Report[4]

(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed)

Issues related to the COVID-19 Public Health Emergency: Since the updated analysis (March 9, 2020) was performed prior to COVID-19 becoming widespread, the sponsor indicated that the pandemic had no impacts on trial conduct including patient visits or medication schedule. After the DBL, the FDA and EMA released guidelines on the management of clinical trials during the COVID-19 pandemic; in response, the sponsor developed overarching principles and guidance for the conduct of clinical research during the public health emergency. The sponsor stated that they are continuing to monitor the impact of COVID-19 on the CheckMate 9LA trial.[4]

e) Limitations/Sources of Bias

At the time of writing this report, the CheckMate 9LA trial was unpublished. Therefore, CADTH's critical appraisal of the trial was based on the sponsor's CADTH submission and published trial data available from conference proceedings and other sources, which included reports from the EMA[3] and FDA.[58] The CADTH Methods Team identified limitations or potential sources of bias that should be considered when interpreting the trial results, and these have been summarized below:

Study design

- The study protocol of CheckMate 9LA was amended several times. The nature of some amendments impacted the sample size, statistical analyses, interim analysis, and endpoints of the trial, which raise concern about the integrity of the results. The EMA Assessment report[3] indicated that changes made to the protocol were unlikely influenced by the sponsor staff having access to preliminary unaggregated data (i.e., safety and mortality data) for the following reasons:
  - No interim analysis was conducted prior to the prespecified interim analysis
  - The sponsor reviewed safety and mortality data at the patient level
  - A third party prepared and communicated safety and mortality data to the IDMC
  - The sponsor was able to demonstrate that protocol amendments 2 and 4, which were related to the increase in sample size and changes to the statistical analysis, were informed by external trial data; and ad hoc analyses requested by the EMA to compare the trial results before and after the implementation of amendments aligned.
  - The updated trial results (DBL: March 9, 2020) confirm the primary analysis efficacy results.
- The open-label study design of the CheckMate 9LA trial allowed for both investigators and patients to be aware of the assigned treatment of patients. The choice of an open-label design is considered appropriate given the differences in treatment administration (i.e., schedule, optional maintenance therapy), mechanisms of action resulting in distinct AE profiles (i.e., chemotherapy versus immunotherapy), and planned duration of therapy in the two treatment groups. In a blinded trial design, these differences could have resulted in unintended unblinding. Lack of blinding is associated with different types of bias that can affect the performance, measurement, and reporting of clinical outcomes (i.e., efficacy and safety) by both patients and investigators, which has the potential to influence trial results in favour of the investigational therapy (i.e., NI plus PDC). OS was the primary endpoint of the trial and is an objective measure that is unlikely to be biased by the open-label study design; and BICR was implemented for the assessment of secondary efficacy endpoints (i.e., PFS, ORR) to mitigate the potential for bias. However, bias is a concern for subjective outcomes assessed in the trial, including HRQoL and safety, as patient or investigator knowledge of treatment assignment could have influenced the assessment and reporting of these outcomes.

- The CheckMate 9LA trial compared NI plus PDC to PDC. However, pembrolizumab with or without PDC has become the standard of care in Canada for the treatment of patients with metastatic or recurrent NSCLC with no EGFR or ALK genomic tumour aberrations. Therefore, while PDC was considered the standard of care when the CheckMate 9LA trial was designed in 2017, it is not currently considered the most clinically relevant treatment comparator. Accordingly, the sponsor provided an ITC comparing NI plus PDC to other relevant first-line treatments, which is summarized and critically appraised in Section 7 of this report.

Statistical analyses and assessment of outcomes

- The testing of some secondary efficacy endpoints (i.e., PFS and ORR) was adjusted to control for multiplicity and the risk of type 1 error, while the results of other endpoints (i.e., TTR, DOR, efficacy by PD-LI expression) were not included in the statistical testing hierarchy. There were also many prespecified subgroup analyses preformed for multiple endpoints. These analyses should be considered exploratory in nature as the trial was not powered to test specific hypotheses in these outcomes and subgroups. Overall, the results of all efficacy outcomes and most subgroup analyses showed a consistent treatment benefit in favour of NI plus PDC when compared to PDC alone. For some subgroups, however, including patients older than 75, never smokers, and those with unquantifiable PD-L1 expression, treatment effect estimates favoured PDC. The results obtained for these subgroups are particularly uncertain given the smaller sample size in these groups.

- Similarly, given the short duration of follow-up in the trial at the primary analysis (minimum follow-up of 8.1 months for OS), the updated analysis was conducted to further characterize the clinical benefit of NI plus PDC compared to PDC alone, providing an additional 4.6 months of follow-up.[3] This unplanned analysis was not prespecified; therefore, no statistical considerations were employed to account for multiplicity.

- In the analysis of OS, censoring occurred for patients on the last date a patient was known to be alive. Censoring for OS did not take into consideration the use of subsequent therapies that patients received after completion of assigned study treatment. [redacted].[7] [redacted].[7] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed)* It is expected that patients in the PDC group who received subsequent immunotherapy would experience additional clinical benefit from immunotherapy, which confounds the analysis of OS and likely underestimates the treatment effect associated with NI plus PDC compared to PDC alone.

- The analysis of OS and corresponding treatment effect estimates were based on a stratified Cox proportional hazard model that assumes proportional hazards. At the primary analysis, the results for OS indicated statistical significance and thus the superiority of NI plus PDC over PDC was demonstrated (HR=0.69; 95% CI 0.55 to 0.87; P=0.0006).[3] However, the graphical representation of OS clearly showed crossing of the KM curves at approximately 15 months. The sponsor did not report whether the validity of the proportional hazards assumption was tested, and that, combined with the large amount of patient censoring in the analysis makes the primary analysis OS data challenging to interpret. The updated OS analysis confirmed the primary analysis results and showed a clear separation of the KM curves at approximately four months. Although the updated analysis was not prespecified, it is consistent with the shape of the curves at the primary analysis and supports the conclusion of improved efficacy of NI plus PDC over PDC.

- In the analysis of PFS using the primary definition, patients who received palliative local therapy or subsequent anticancer therapy without a reported progression were censored in the analysis. This type of censoring is considered biased per FDA guidelines, and patients who receive another anti-cancer therapy before progression should be considered a PFS event in the analysis. The sponsor conducted two additional analyses of PFS, one using a secondary definition that did not consider the receipt of subsequent therapy, and PFS2, which assessed progression after the next line of treatment. At the primary analysis the results for PFS based on the primary definition were statistically significantly favoured treatment with NI plus PDC over PDC alone (HR=0.70; 95% CI, 0.57 to 0.86; P=0.0001)[3]. Both of these additional analyses of PFS, using the secondary definition

(HR=0.67; 97.48% CI, 0.55 to 0.8)[8] and PFS2 (HR=0.62, 95% CI 0.51 to 0.76),[3] supported the primary results for PFS using the primary definition. Similar results were obtained at the updated analysis (DBL: March 9, 2020 DBL). Therefore, results for PFS which favour treatment with NI plus PDC over PDC alone, may be considered reliable.

- PRO questionnaires required a compliance rate of ≥10% of patients to be deemed sufficient for analyses. While compliance was stated to be over 90% at baseline and over 80% at subsequent assessments, compliance rates dropped to a low of 60% over the course of the trial. While this is above the required 10% threshold of patient compliance, the number of patients included in the analyses of PROs at later assessment timepoints was reduced and the patients left in the trial who completed PRO assessments are likely not representative (i.e., have better HRQoL) of all patients randomized in each treatment group. In this scenario, data are not missing at random since patients who have left the trial are likely sicker or have died, and therefore, the HRQoL results at later timepoints are likely biased. TTD analysis of HRQoL outcomes mitigates some of the bias associated with analyses based on mean changes in scores from baseline because all available data are used in the analysis. In the CheckMate 9LA trial, the TTD analysis of all subscales of the LCSS and EQ-5D-3L demonstrated a longer TTD in the NI plus PDC group compared to the PDC group, and a greater probability of worsening for patients in the PDC group.
- The MID used for the LCSS ABSI instrument has not been validated among NSCLC patients. The sponsor provided supporting literature that demonstrates the measurement properties of the instrument based on its use in multicentre trials. However, currently, there is no established MID to guide the analysis and interpretation of PRO data using the LCSS ABSI in patients with metastatic NSCLC. Consequently, it is unclear if the threshold used in the trial (i.e., MID of 10 points) is appropriate and reflective of a clinically meaningful change in outcome in patients with NSCLC.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

Efficacy Outcomes

CheckMate 9LA

The efficacy results of the trial based on the primary (DBL: October 3, 2019) and updated analyses (DBL: March 9, 2020) with a minimum follow-up of 8.1 months and 12.7 months, respectively, are reported in Table 23. The updated efficacy outcomes were based on an additional 4.6 months of follow-up.

Table 23: Summary of Primary and Secondary Endpoints in the CheckMate 9LA Trial

Efficacy Outcomes	Primary Analysis (DBL: October 3, 2019)[a]		Updated Analysis (DBL: March 9, 2020)[b]	
	NI plus PDC N=361	PDC N=358	NI plus PDC N=361	PDC N=358
Median Follow-up (months)	10.35	9.07	14.19	10.89
OS				
Events, n (%)	156 (43.2)	195 (54.5)	190 (52.6)	242 (67.6)
Median, months (95% CI)	14.13 (13.24, 16.16)	10.74 (9.46, 12.45)	15.64 (13.93, 19.98)	10.91 (9.46, 12.55)
HR (95% CI) P value	0.69 (0.55-0.87) 0.0006		0.66 (0.55-0.80) NR	
6-month OS rate (95% CI)	80.9 (76.4-84.6)	72.3 (67.4-76.7)	NR	NR
12-month OS rate (95% CI)	NR	NR	62.9 (57.7, 67.6)	46.9 (41.6, 51.9)
PFS				
Events, n (%)	232 (64.3)	249 (69.6)	249 (69.0)	265 (74.0)
Median, months (95% CI)	6.83 (5.55-7.66)	4.96 (4.27-5.55)	6.74 (5.55, 7.75)	4.96 (4.27, 5.55)
HR (95%CI) P value	0.70 (0.57-0.86) 0.0001		0.68 (0.57-0.82) NR	
6-month PFS rate (95% CI)	51.7 (46.2-56.8)	35.9 (30.5-41.3)	NR	NR
12-month PFS rate (95% CI)	NR	NR	32.9 (27.8, 38.0)	17.6 (13.4, 22.2)
ORR				
N responders (%)	136 (37.7)	90 (25.1)	138 (38.2)	89 (24.9)
95% CI	32.7-42.9	20.7-30.0	33.2-43.5	20.5-29.7[c]
Difference in ORR (95% CI) P value	12.4 (4.8-20.0) P=0.0003		13.3 (6.6, 19.9) NR	
Confirmed BOR, n (%)				
CR	7 (1.9)	3 (0.8)	8 (2.2)	4 (1.1)
PR	129 (35.7)	87 (24.3)	130 (36.0)	85 (23.7)
SD	166 (46.0)	184 (51.4)	164 (45.4)	185 (51.7)
PD	32 (8.9)	45 (12.6)	32 (8.9)	45 (12.6)
UTD	24 (6.6)	30 (8.4)	27 (7.5)	36 (10.1)
NR	3 (0.8)	9 (2.5)	0	3 (0.8)
TTR				
Median, months (min, max)	2.51 (1.1, 10.6)	1.56 (1.2, 8.3)	[redacted]	[redacted]
DCR				
N responders (%)	302 (83.7)	274 (76.5)	302 (83.7)	274 (76.5)

Efficacy Outcomes	Primary Analysis (DBL: October 3, 2019)[a]		Updated Analysis (DBL: March 9, 2020)[b]	
	NI plus PDC N=361	PDC N=358	NI plus PDC N=361	PDC N=358
(95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
DOR				
N events/N responders (%)	57/136 (41.9)	54/90 (60.0)	67/138 (48.6)	64/89 (71.9)
Median, months (95%CI	10.02 (8.21-13.01)	5.09 (4.34-7.00)	11.30 (8.51, NA)	5.59 (4.37, 7.46)
Min, max	1.0+, 16.5+	1.4+, 15.2+	1.0+, 22.0+	1.6, 20.9+
% of subjects with DOR (95%CI) ≥6 months	74 (66-81)	41 (30-52)	73 (65-80)	45 (34-55)
% of subjects with DOR (95%CI) ≥12 months	NR	NR	[redacted]	[redacted]

BOR = best overall response; CI = confidence interval; CR = confirmed complete response; DOR = duration of response; max = maximum; min = minimum, NI plus PDC = nivolumab plus ipilimumab and 2 cycles of chemotherapy; NR = not reported; ORR = objective response rate; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PR = confirmed partial response; SD = stable disease; TTR = time to response; UTD = unable to determine.

[a] Based on a minimum follow-up of 8.1 months for OS and 6.5 months for all other endpoints.

[b] Based on a minimum follow-up of 12.7 months for OS and 12.2 months for all other endpoints.

[c] At the updated analysis, two patients in the PDC group had their responses changed from SD due to re-adjudication by BICR and one patient had their response changed from SD to PR.

Source: FDA,[58] Clinical Study Report 2020,[4,8] EMA Assessment Report[3]

(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed)

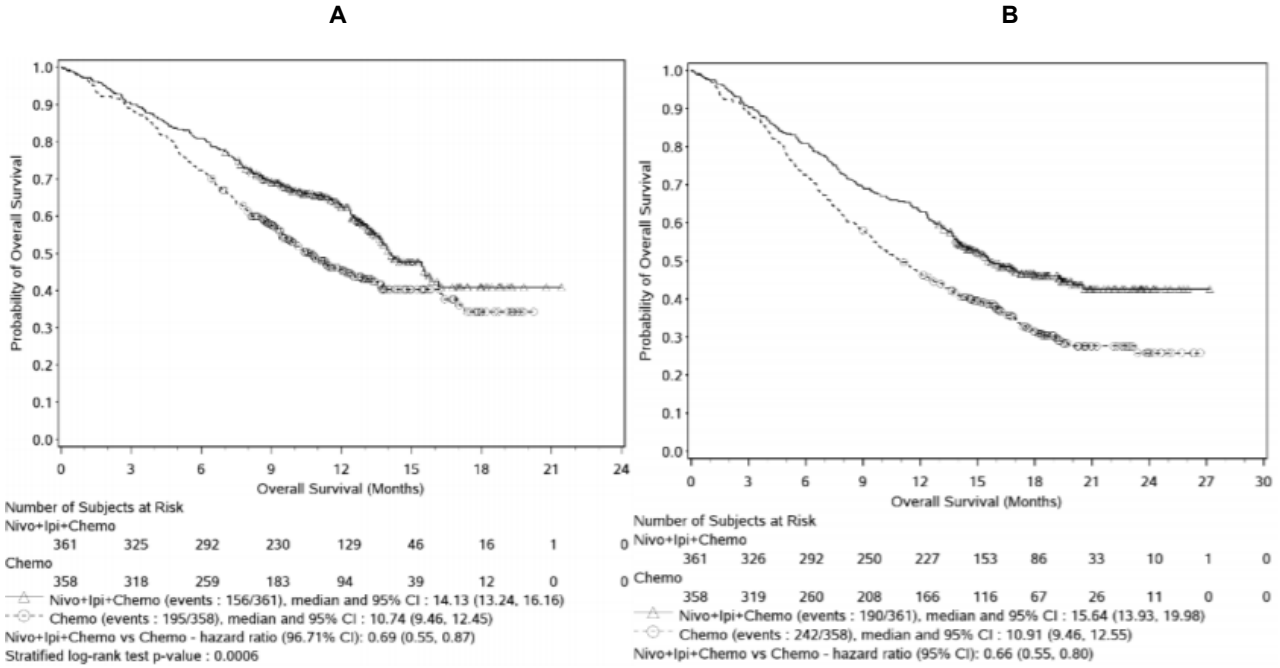
Primary Endpoint – Overall Survival

Primary Analysis (DBL: October 3, 2019): At the interim analysis of OS, the CheckMate 9LA trial met its primary endpoint by exceeding the prespecified threshold for superiority. Therefore, the interim analysis is considered the primary analysis of the trial. A total of 156 OS events (43%) had occurred in the NI plus PDC group compared to 195 events (54%) in the PDC group. Median OS was longer in the NI plus PDC treatment group at 14.13 months (95% CI, 13.24 to 16.16) compared to 10.74 months (95% CI, 9.46 to 12.45) in the PDC group , demonstrating a statistically significant prolongation in OS (HR=0.69, 95% CI 0.55-0.87; P=0.0006; Figure 5 – A) (.[3]

There were 56.8% and 45.5% patients censored in the primary analysis of OS in the NI plus PDC and PDC groups, respectively.[3] The status of censored patients is reported in Table 24.

[redacted].[4] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed)*

Figure 5: Kaplan-Meier Plot of OS in All Randomized Patients in CheckMate 9LA at the (A) Primary (DBL: October 3, 2019) and (B) Updated (DBL: March 9, 2020) Analyses



Source: EMA Assessment Report[3]

Table 24: Status of Censored Patients for OS at Primary Analysis (DBL: October 3, 2019)

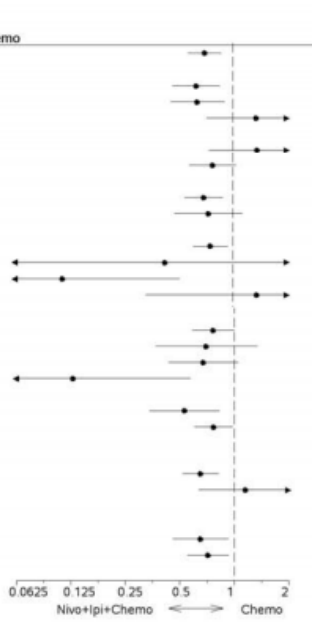
Source: Clinical Study Report[8]

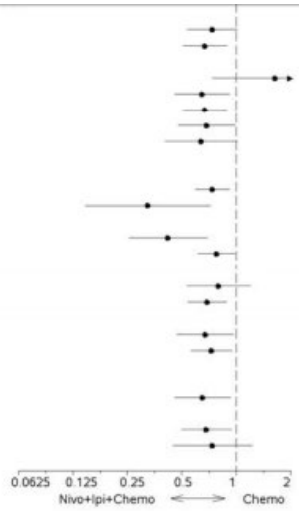
(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed)

The results of subgroup analyses of OS are presented in Figure 6. In almost all subgroups, OS favoured treatment with NI plus PDC except for patients aged 75 or older, of other race, who had never smoked, and had non-quantifiable PD-L1 status. However, the interpretation of results in these subgroups is limited by smaller sample sizes and therefore uncertain. The clinical benefit of treatment with NI plus PDC over PDC was observed regardless of histology or PD-L1 status.[3] The KM graphs of OS by histology are presented in Figure 6.

Figure 6: Subgroup Analyses of OS in the CheckMate 9LA Trial (DBL: October 3, 2019)

		Nivo+Ipi+Chemo		Chemo		Unstratified
	N	N of Events (N of Subjects)	mOS (95% CI)	N of Events (N of Subjects)	mOS (95% CI)	Hazard Ratio (95% CI) Nivo+Ipi+Chemo vs. Chemo
Overall	719	156 (361)	14.13 (13.24, 16.16)	195 (358)	10.74 (9.46, 12.45)	0.70 (0.57, 0.86)
Age Categorization						
<65	354	74 (176)	13.96 (12.62, N.A.)	100 (178)	10.25 (8.80, 13.73)	0.63 (0.46, 0.85)
>=65 and <75	295	56 (148)	15.80 (14.23, N.A.)	78 (147)	11.86 (9.03, 16.23)	0.64 (0.45, 0.90)
>=75 and <85	68	26 (37)	8.51 (5.59, 13.34)	16 (31)	10.91 (4.96, N.A.)	1.35 (0.72, 2.51)
>=85	2	0 (0)	N.A.	1 (2)	N.A. (5.75, N.A.)	N.A.
>=75	70	26 (37)	8.51 (5.59, 13.34)	17 (33)	10.91 (5.75, N.A.)	1.36 (0.74, 2.52)
>=65	365	82 (185)	14.46 (13.11, N.A.)	95 (180)	11.50 (9.49, 13.54)	0.77 (0.58, 1.04)
Sex						
Male	504	119 (252)	13.77 (12.45, 15.44)	150 (252)	9.69 (8.15, 11.37)	0.69 (0.54, 0.88)
Female	215	37 (109)	15.80 (13.11, N.A.)	45 (106)	N.A. (10.87, N.A.)	0.73 (0.47, 1.13)
Race						
White	638	149 (322)	13.93 (12.91, 15.57)	174 (316)	10.58 (9.43, 12.55)	0.75 (0.61, 0.94)
Black or African American	9	1 (5)	N.A. (2.96, N.A.)	2 (4)	N.A. (6.21, N.A.)	0.42 (0.04, 4.66)
Asian	60	3 (30)	15.44 (11.93, N.A.)	13 (30)	12.22 (7.33, N.A.)	0.11 (0.03, 0.51)
Other	12	3 (4)	3.79 (3.58, N.A.)	6 (8)	4.96 (1.48, N.A.)	1.36 (0.33, 5.61)
Region						
Europe	425	101 (212)	13.93 (12.75, 16.16)	116 (213)	10.58 (9.26, 13.73)	0.76 (0.58, 1.00)
North America	64	19 (36)	13.24 (7.43, N.A.)	18 (28)	8.90 (4.96, N.A.)	0.70 (0.37, 1.34)
Rest of The World	172	33 (85)	N.A. (10.25, N.A.)	48 (87)	10.78 (8.77, 12.45)	0.68 (0.43, 1.05)
Asia	58	3 (28)	15.44 (11.93, 15.44)	13 (30)	12.22 (7.33, N.A.)	0.13 (0.03, 0.57)
Baseline ECOG PS						
0	225	32 (113)	N.A. (15.44, N.A.)	50 (112)	13.31 (10.78, N.A.)	0.53 (0.34, 0.83)
>=1	492	123 (247)	13.11 (11.93, 14.03)	144 (245)	9.46 (7.98, 11.01)	0.77 (0.60, 0.98)
Not Reported	2	1 (1)	9.03 (N.A., N.A.)	1 (1)	4.01 (N.A., N.A.)	
Smoking Status						
Current/Former	620	134 (315)	14.13 (13.34, 16.16)	173 (305)	10.02 (8.97, 12.06)	0.65 (0.52, 0.82)
Never Smoked	99	22 (46)	11.99 (8.02, N.A.)	22 (53)	12.55 (9.46, N.A.)	1.15 (0.64, 2.08)
Unknown	0	0 (0)	N.A.	0 (0)	N.A.	
Histology - per IRT						
Squamous	227	56 (115)	13.67 (12.39, 15.57)	69 (112)	8.97 (7.16, 12.22)	0.65 (0.46, 0.93)
Non-Squamous	492	100 (246)	15.80 (13.08, N.A.)	126 (246)	11.40 (9.69, 16.33)	0.72 (0.55, 0.93)
PD-L1 Status - per IRT						
<1%/Not Quantifiable	311	69 (157)	13.77 (12.32, 16.16)	84 (154)	11.01 (8.57, 16.23)	0.74 (0.54, 1.02)
>=1%	408	87 (204)	14.23 (13.08, N.A.)	111 (204)	10.58 (9.43, 12.91)	0.67 (0.51, 0.89)
PD-L1 Subgroups						
Not Quantifiable	46	14 (21)	10.84 (7.16, 15.57)	12 (25)	17.05 (8.64, N.A.)	1.64 (0.74, 3.63)
<1%	264	55 (135)	14.03 (13.24, N.A.)	72 (129)	9.95 (7.69, 13.73)	0.65 (0.46, 0.92)
>=1%	406	87 (203)	14.23 (13.08, N.A.)	111 (203)	10.58 (9.36, 12.55)	0.67 (0.51, 0.89)
1-49%	233	58 (127)	14.46 (12.45, N.A.)	61 (106)	10.25 (8.67, 12.22)	0.69 (0.48, 0.98)
>=50%	173	29 (76)	14.13 (12.39, N.A.)	50 (97)	11.86 (9.26, N.A.)	0.64 (0.41, 1.02)
Not Reported	3	0 (2)	N.A.	0 (1)	N.A.	
Disease Stage						
Stage IV	668	145 (330)	14.03 (13.11, 16.16)	181 (338)	10.87 (9.46, 13.31)	0.74 (0.59, 0.92)
Recurrent to Metastatic Disease	51	11 (31)	15.57 (12.45, N.A.)	14 (20)	9.05 (6.60, 12.91)	0.32 (0.15, 0.72)
CNS Metastasis						
Yes	121	25 (63)	13.63 (12.32, N.A.)	41 (58)	7.36 (4.99, 10.02)	0.42 (0.26, 0.69)
No	598	131 (298)	14.03 (13.24, 16.16)	154 (300)	11.37 (9.79, 13.73)	0.78 (0.62, 0.98)
Liver Metastasis						
Yes	155	40 (68)	9.89 (7.43, 13.77)	57 (87)	8.02 (6.60, 10.02)	0.80 (0.53, 1.20)
No	564	116 (293)	15.54 (13.67, N.A.)	138 (271)	11.86 (10.25, 16.23)	0.69 (0.54, 0.88)
Bone Metastasis						
Yes	206	51 (96)	11.93 (8.61, 15.80)	72 (110)	8.02 (6.60, 9.46)	0.67 (0.47, 0.97)
No	513	105 (265)	15.44 (13.34, N.A.)	123 (248)	12.06 (10.35, 17.05)	0.73 (0.56, 0.95)
Actual Investigator's Choice Therapy						
Carboplatin/Cisplatin/Pemetrexed	7	1 (1)	4.34 (N.A., N.A.)	4 (6)	10.02 (1.48, N.A.)	
Carboplatin/Paclitaxel	224	55 (114)	13.67 (12.39, 15.57)	67 (110)	8.97 (7.16, 12.22)	0.65 (0.45, 0.93)
Carboplatin/Paclitaxel/Pemetrexed	2	0 (1)	N.A.	1 (1)	10.25 (N.A., N.A.)	
Carboplatin/Pemetrexed	331	68 (168)	15.80 (13.24, N.A.)	86 (163)	10.74 (9.13, 16.33)	0.68 (0.50, 0.94)
Cisplatin/Pemetrexed	142	28 (73)	N.A. (12.32, N.A.)	33 (69)	12.55 (9.46, N.A.)	0.74 (0.45, 1.22)
Paclitaxel/Pemetrexed	1	1 (1)	6.24 (N.A., N.A.)	0 (0)	N.A.	
Not Reported	12	3 (3)	1.74 (0.03, 9.03)	4 (9)	N.A. (1.58, N.A.)	

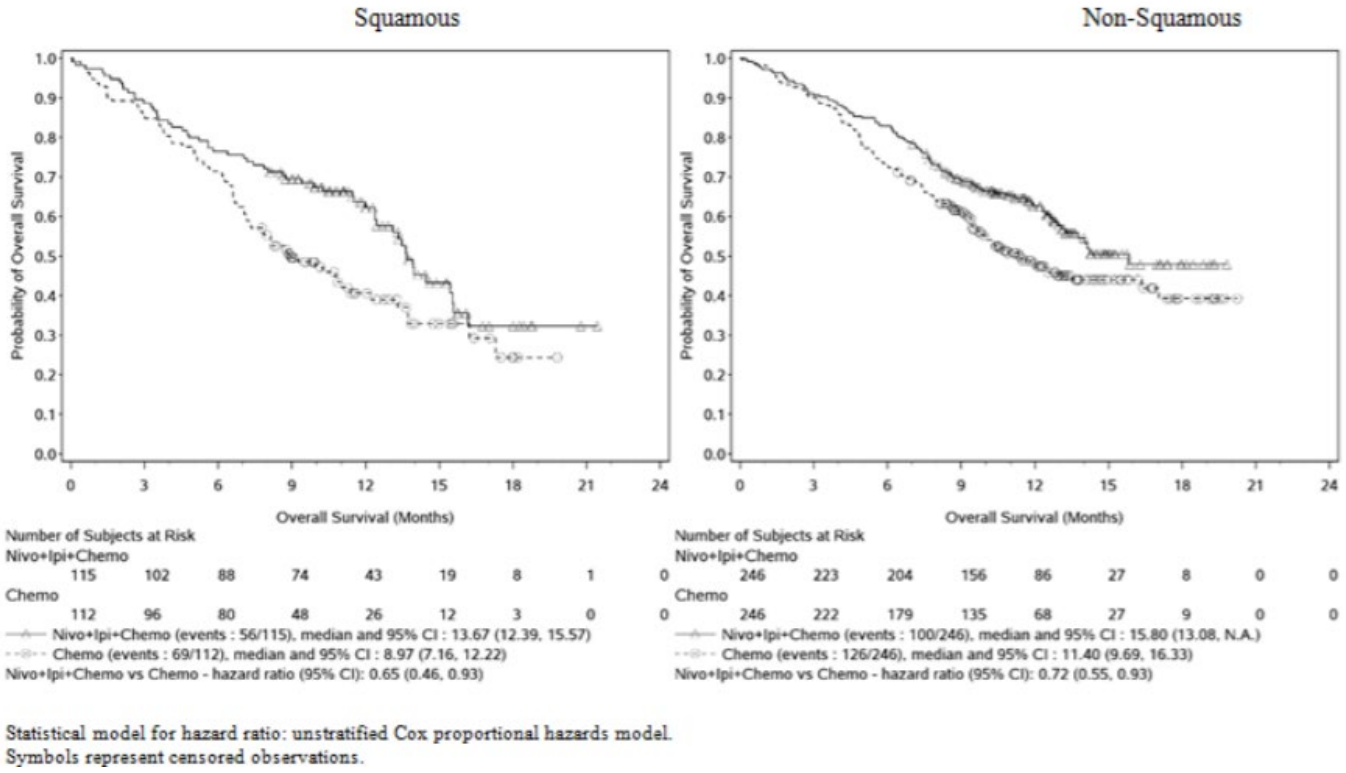




HR is not computed for subsets (except age, race, region, and sex) category with less than 10 subjects per treatment group.

Source: EMA Assessment Report[3]

Figure 7: Analysis OS by Histology in the CheckMate 9LA Trial (DBL: October 3, 2019)



Source: EMA Assessment Report[3]

Updated Analysis (DBL: March 9, 2020): At the time of the updated analysis, the trial was reported to have reached 60% maturity in terms of the primary endpoint of OS. After a minimum follow-up of 12.7 months, median OS was longer in the NI plus PDC group at 15.64 months (95% CI, 13.93 to 19.98) compared to the PDC group at 10.91 months (95% CI, 9.46 to 12.55).[3] OS rates were higher in the NI plus PDC group at both six- and 12-months, compared to the PDC group (*(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed)* [redacted]).[4] The updated analysis showed results that were consistent with the primary analysis and the magnitude of OS benefit associated with NI plus PDC was maintained at longer follow-up (HR=0.66; 95% CI,0.55 to 0.80; Figure 5-B) .

[redacted][4] [redacted].[4] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed)*

Subgroup analyses for OS favoured treatment with NI plus PDC in most subgroups except for patients aged 75 or older and who had never smoked (Table 25). As previously noted, the interpretation of results in these subgroups is limited by small sample size and

therefore uncertain. The clinical benefit associated with NI plus PDC over PDC continued to be observed regardless of histology or PD-L1 status (Figure 8 and Figure 9).

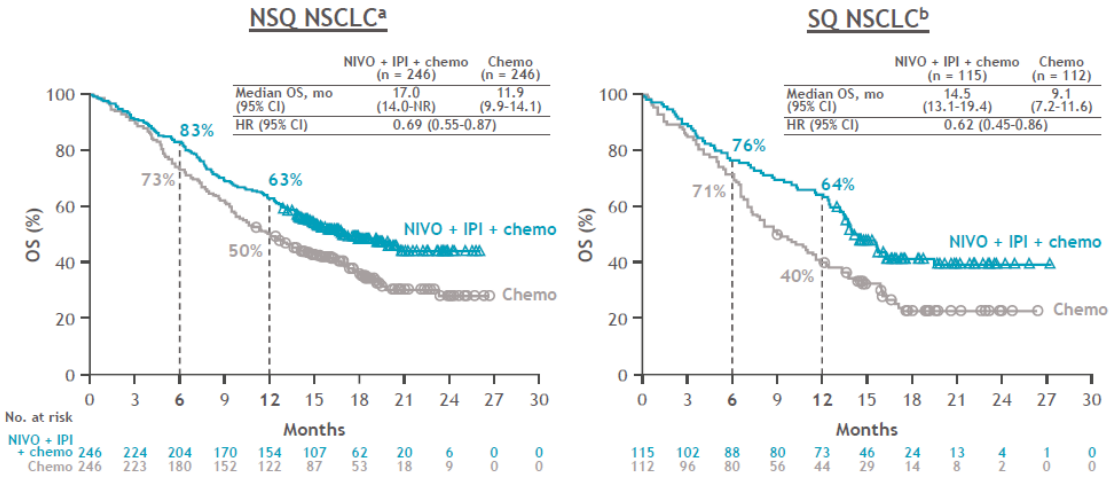
Table 25: Subgroup Analyses of OS in the CheckMate 9LA Trial (DBL: March 9, 2020)

Subgroup	Median OS, mo		Unstratified HR
	NIVO + IPI + chemo n = 361	Chemo n = 358	
All randomized (N = 719)	15.6	10.9	0.66[a]
< 65 years (n = 354)	15.6	10.7	0.61
65 to < 75 years (n = 295)	19.4	11.9	0.62
≥ 75 years (n = 70)	8.5	11.5	1.21
Male (n = 504)	14.1	9.8	0.66
Female (n = 215)	19.4	15.8	0.68
ECOG PS 0 (n = 225)	NR	15.4	0.48
ECOG PS 1 (n = 492)	13.6	9.7	0.75
Never smoker (n = 98)	14.1	17.8	1.14
Smoker (n = 621)	15.6	10.4	0.62
Squamous (n = 227)	14.5	9.1	0.62
Non-squamous (n = 492)	17.0	11.9	0.69
Liver metastases (n = 154)	10.2	8.1	0.83
No liver metastases (n = 565)	19.4	12.4	0.64
Bone metastases (n = 207)	11.9	8.3	0.74
No bone metastases (n = 512)	20.5	12.4	0.65
CNS metastases (n = 122)	NR	7.9	0.38
No CNS metastases (n = 597)	15.4	11.8	0.75
PD-L1 < 1% (n = 264)	16.8	9.8	0.62
PD-L1 ≥ 1% (n = 407)	15.8	10.9	0.64
PD-L1 1-49% (n = 233)	15.4	10.4	0.61
PD-L1 ≥ 50% (n = 174)	18.0	12.6	0.66

Minimum follow-up: 12.7 months.
[a]Stratified HR; unstratified HR was 0.67 (95% CI, 0.55-0.81).

Source: Reck et al., 2020[2]

Figure 8: Subgroup of Analysis of OS by Histology in the CheckMate 9LA Trial (DBL: March 9, 2020)



Minimum follow-up: 12.7 months.
[a]Subsequent systemic therapy was received by 30% of patients in the NIVO + IPI + chemo arm and 39% of patients in the chemo arm; subsequent immunotherapy was received by 6% and 28%, and subsequent chemotherapy by 29% and 22%, respectively; [b]Subsequent systemic therapy was received by 31% of patients in the NIVO + IPI + chemo arm and 44% of patients in the chemo arm; subsequent immunotherapy was received by 4% and 35%, and subsequent chemotherapy by 30% and 24% of patients, respectively

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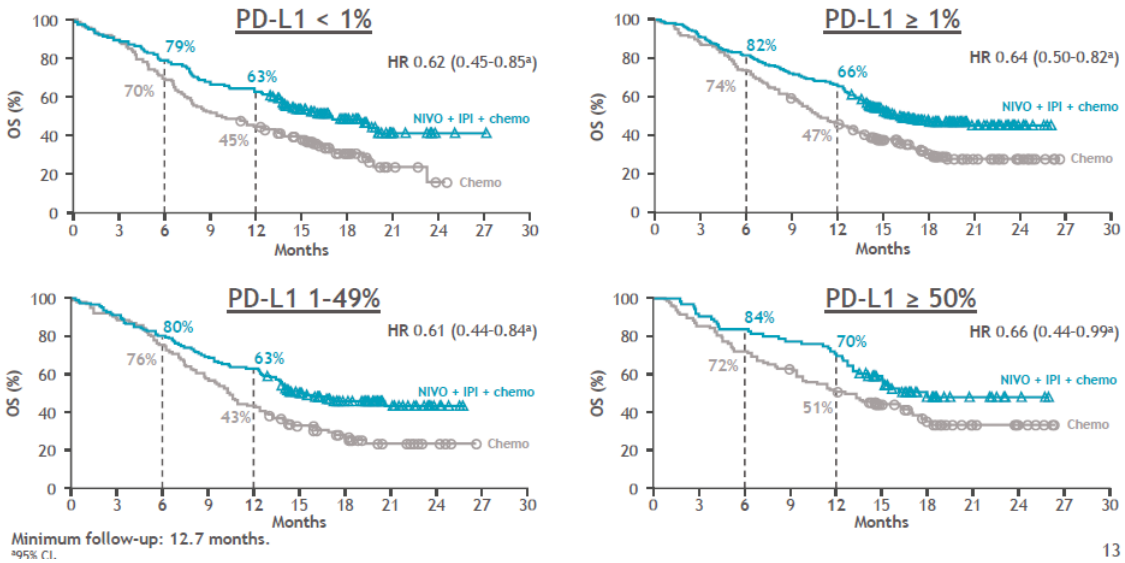
Source: Reck et al., 2020[2]

Figure 9: Subgroup of Analysis of OS by PD-L1 Status in the CheckMate 9LA Trial (DBL: March 9, 2020)



Source: Reck et al., 2020[2]

Secondary Endpoints

As previously noted, testing of secondary endpoints was based on a prespecified statistical hierarchy; whereby, analyses of PFS and ORR were conducted only if the primary endpoint of OS demonstrated statistical significance. Since statistically significant superiority of NI plus PDC was demonstrated over PDC at the primary analysis, the hierarchical testing of secondary endpoints was conducted and the results of anayses are summarized below.[3]

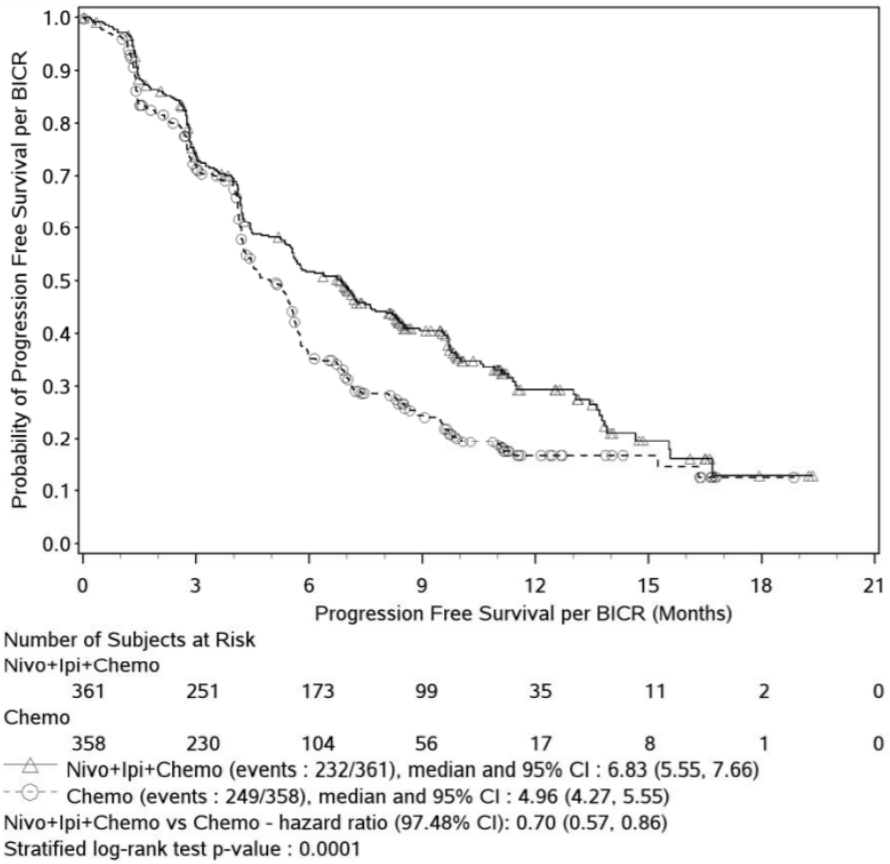
Progression-free Survival: The PFS results presented below are based on the primary definition of PFS, which censored patients who received subsequent anti-cancer therapy.

Primary Analysis (DBL: October 3, 2019): The median PFS, as assessed by BICR, was longer in the NI plus PDC group at 6.83 months (95% CI, 5.55 to 7.66) compared to the PDC group at 4.96 months (95% CI, 4.27 to 5.55). The KM curves for PFS are presented in Figure 10 and show a clear separation of the curves starting at approximately four months and the statistically significant improvement in PFS with NI plus PDC versus PDC (HR=0.70; 95% CI, 0.57 to 0.86; P=0.0001).[3] The PFS rates at six months was 51.7% in the NI plus PDC group (compared to 35.9% in the PDC group.[8]

The results of subgroup analyses for PFS by BICR are presented in Figure 11. Most subgroups showed a PFS benefit among patients treated with NI plus PDC compared to PDC except for patients aged 75 or older, those who never smoked, had presence of liver metastasis, and who were of Black or African American race. However, the interpretation of results in these subgroups is limited by small sample size and therefore uncertain. The clinical benefit of NI plus PDC was independent of patients' histology or PD-L1 status.[3,8]

[redacted].[8] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed)*

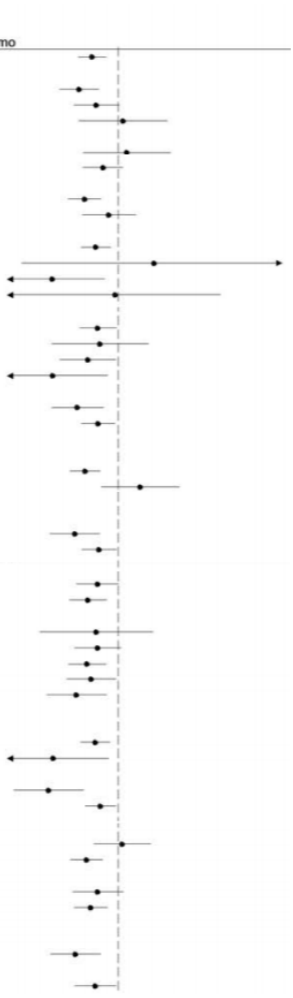
Figure 10: PFS Results per BICR for CheckMate 9LA Trial, Primary Definition (DBL: October 3, 2019)



Source: EMA Assessment Report[3]

Figure 11: Subgroup Analyses of PFS per BICR for CheckMate 9LA Trial, Primary Definition (DBL: October 3, 2019)

	N	Nivo+Ipi+Chemo N of Events (N of Subjects)	Nivo+Ipi+Chemo mPFS (95% CI)	Chemo N of Events (N of Subjects)	Chemo mPFS (95% CI)	Unstratified Hazard Ratio (95% CI) Nivo+Ipi+Chemo vs. Chemo
Overall	719	232 (361)	6.83 (5.55, 7.66)	249 (358)	4.96 (4.27, 5.55)	0.72 (0.60, 0.86)
Age Categorization						
<65	354	114 (176)	6.37 (4.44, 7.49)	131 (178)	4.21 (4.11, 4.50)	0.61 (0.47, 0.78)
>=65 and <75	295	89 (148)	7.62 (5.59, 10.02)	96 (147)	5.59 (4.99, 6.93)	0.76 (0.57, 1.01)
>=75 and <85	68	29 (37)	5.08 (2.92, 8.51)	21 (31)	5.78 (4.14, 7.13)	1.06 (0.60, 1.88)
>=85	2	0 (0)	N.A.	1 (2)	N.A. (5.75, N.A.)	N.A.
>=75	70	29 (37)	5.08 (2.92, 8.51)	22 (33)	5.78 (4.21, 7.13)	1.12 (0.64, 1.96)
>=65	365	118 (185)	7.20 (5.39, 9.69)	118 (180)	5.62 (5.26, 6.05)	0.82 (0.64, 1.06)
Sex						
Male	504	165 (252)	5.75 (4.93, 7.62)	185 (252)	4.50 (4.21, 5.42)	0.65 (0.53, 0.80)
Female	215	67 (109)	7.20 (5.55, 9.89)	64 (106)	5.82 (4.24, 7.20)	0.89 (0.63, 1.25)
Race						
White	638	209 (322)	6.37 (5.49, 7.49)	216 (316)	4.99 (4.27, 5.59)	0.75 (0.62, 0.91)
Black or African American	9	4 (5)	6.97 (2.96, N.A.)	4 (4)	6.83 (1.25, 11.07)	1.59 (0.29, 8.72)
Asian	60	16 (30)	9.69 (4.24, 13.70)	21 (30)	5.39 (2.76, 6.93)	0.43 (0.22, 0.84)
Other	12	3 (4)	3.60 (1.31, N.A.)	8 (8)	4.53 (1.35, 5.45)	0.96 (0.25, 3.73)
Region						
Europe	425	143 (212)	5.91 (5.22, 7.26)	139 (213)	4.63 (4.17, 5.55)	0.77 (0.61, 0.97)
North America	64	23 (36)	5.85 (3.61, 9.72)	18 (28)	5.45 (2.66, 6.70)	0.79 (0.43, 1.48)
Rest of The World	172	52 (85)	6.97 (4.47, 9.53)	71 (87)	4.96 (4.21, 5.75)	0.68 (0.47, 0.97)
Asia	58	14 (28)	8.38 (4.21, 13.70)	21 (30)	5.39 (2.76, 6.93)	0.43 (0.21, 0.87)
Baseline ECOG PS						
0	225	65 (113)	8.48 (6.74, 9.92)	79 (112)	5.45 (4.21, 6.70)	0.59 (0.43, 0.82)
>=1	492	167 (247)	5.59 (4.40, 7.10)	170 (245)	4.70 (4.27, 5.55)	0.77 (0.62, 0.96)
Not Reported	2	0 (1)	N.A.	0 (1)	N.A.	
Smoking Status						
Current/Former	620	198 (315)	7.03 (5.59, 8.34)	221 (305)	4.53 (4.21, 5.39)	0.65 (0.54, 0.79)
Never Smoked	99	34 (46)	5.55 (4.21, 6.90)	28 (53)	7.13 (5.42, 9.59)	1.33 (0.80, 2.19)
Unknown	0	0 (0)	N.A.	0 (0)	N.A.	
Histology - per IRT						
Squamous	227	78 (115)	5.65 (4.44, 9.69)	82 (112)	4.30 (4.17, 4.99)	0.57 (0.42, 0.79)
Non-Squamous	492	154 (246)	6.97 (5.55, 8.05)	167 (246)	5.55 (4.47, 5.78)	0.78 (0.63, 0.97)
PD-L1 Status - per IRT						
<1%/Not Quantifiable	311	101 (157)	6.14 (4.44, 7.62)	109 (154)	5.32 (4.21, 5.68)	0.77 (0.58, 1.01)
>=1%	408	131 (204)	7.13 (5.55, 8.51)	140 (204)	4.70 (4.24, 5.55)	0.68 (0.53, 0.86)
PD-L1 Subgroups						
Not Quantifiable	46	16 (21)	6.14 (3.61, 11.47)	17 (25)	5.78 (2.83, 8.84)	0.76 (0.36, 1.57)
<1%	264	85 (135)	5.82 (4.40, 7.26)	92 (129)	4.86 (4.17, 5.65)	0.77 (0.57, 1.03)
>=1%	406	130 (203)	7.03 (5.55, 8.51)	140 (203)	4.70 (4.24, 5.55)	0.67 (0.53, 0.85)
1-49%	233	87 (127)	6.74 (5.39, 8.51)	72 (106)	5.29 (4.24, 5.68)	0.71 (0.52, 0.97)
>=50%	173	43 (76)	8.28 (4.47, 11.50)	68 (97)	4.27 (4.14, 5.45)	0.59 (0.40, 0.86)
Not Reported	3	1 (2)	N.A. (8.05, N.A.)	0 (1)	N.A.	
Disease Stage						
Stage IV	668	212 (330)	6.74 (5.49, 7.49)	233 (338)	4.99 (4.30, 5.59)	0.74 (0.62, 0.90)
Recurrent to Metastatic Disease	51	20 (31)	10.55 (2.86, 13.90)	16 (20)	4.24 (2.89, 5.95)	0.43 (0.21, 0.88)
CNS Metastasis						
Yes	121	35 (63)	9.66 (5.68, 11.40)	45 (58)	4.11 (2.79, 4.99)	0.41 (0.26, 0.64)
No	598	197 (298)	5.78 (5.36, 7.20)	204 (300)	5.32 (4.47, 5.62)	0.80 (0.66, 0.97)
Liver Metastasis						
Yes	155	52 (68)	4.11 (2.83, 4.24)	66 (87)	4.24 (4.04, 5.42)	1.06 (0.73, 1.52)
No	564	180 (293)	7.62 (6.74, 9.59)	183 (271)	5.39 (4.47, 5.62)	0.66 (0.54, 0.82)
Bone Metastasis						
Yes	206	72 (96)	4.40 (4.11, 5.78)	78 (110)	4.21 (4.11, 5.16)	0.77 (0.56, 1.07)
No	513	160 (265)	8.05 (5.91, 9.69)	171 (248)	5.49 (4.40, 5.78)	0.70 (0.57, 0.87)
Actual Investigator's Choice Therapy						
Carboplatin/Cisplatin/Pemetrexed	7	1 (1)	2.46 (N.A., N.A.)	6 (6)	4.68 (0.03, 10.02)	
Carboplatin/Paclitaxel	224	78 (114)	5.65 (4.44, 9.69)	81 (110)	4.34 (4.17, 4.99)	0.58 (0.42, 0.80)
Carboplatin/Paclitaxel/Pemetrexed	2	0 (1)	N.A.	1 (1)	1.41 (N.A., N.A.)	
Carboplatin/Pemetrexed	331	102 (168)	7.13 (5.78, 8.51)	114 (163)	5.59 (4.47, 5.82)	0.74 (0.57, 0.97)



Source: EMA Assessment Report[3]

Updated Analysis (DBL: March 9, 2020): Based on a minimum follow-up of 12.2 months, median PFS assessed by BICR was longer in the NI plus PDC group at 6.47 months (95% CI, 5.55-7.75) compared to 4.96 months (95 % CI, 4.27-5.55) in the PDC group (HR=0.70; 95% CI, 0.57 to 0.86).[3] PFS rates at both six- and 12-months were higher in the NI plus PDC group compared to the PDC group (51.3% versus 35.7% and 32.9% versus 17.6%, respectively). The KM plots (Figure 12) show early separation occurring at approximately four months, and a lack of crossing in the curves favouring treatment with NI plus PDC and suggesting sustained treatment effects at all time points. [redacted] (Table 26).[4] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed)*

The results of subgroup analyses for PFS based on the primary definition favoured treatment with NI plus PDC in most subgroups including histology and PD-L1 status (Figure 13).[2]

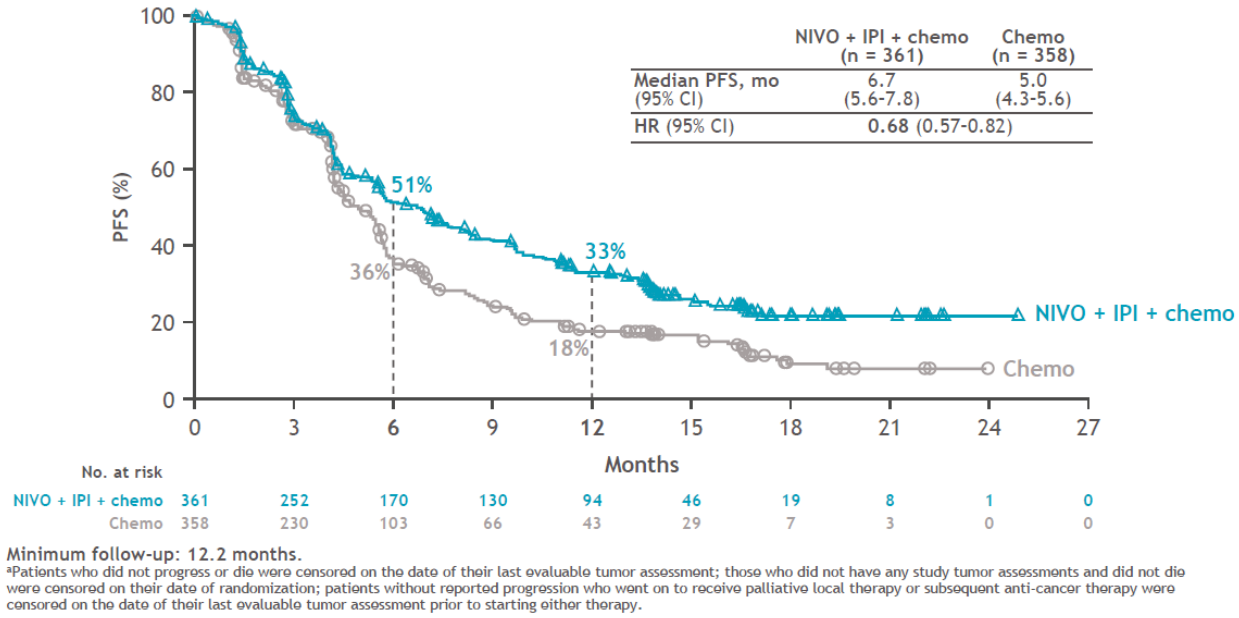
The analysis of PFS by BICR using the secondary definition of PFS, which included the tumour scans of patients after receiving subsequent therapies, also showed treatment effect estimates that favoured NI plus PDC versus PDC ([redacted]) that were consistent with the results of PFS using the primary definition.[4] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed)*

Table 26: Censoring of PFS per BICR

Source: Clinical Study Report[4]

(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed)

Figure 12: PFS Results per BICR for CheckMate 9LA Trial, Primary Definition (DBL: March 9, 2020)



Source: Reck et al., 2020[2]

Figure 13: Subgroup Analyses of PFS in the CheckMate 9LA Trial (DBL: March 9, 2020)

Source: Clinical Study Report[4]

(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed)

Objective Response Rate

Primary Analysis (DBL: October 3, 2019): Response outcomes from the CheckMate 9LA trial are summarized in Table 27 and Table 28. ORR per BICR assessment was statistically significantly higher in the NI plus PDC group (37.7%; 95% CI, 32.7 to 42.9) compared to the PDC group (25.1%; 95% CI 20.7 to 30.0; stratified CMH test P-=0.0003).[3] A greater proportion of patients in the NI plus PDC group had a BOR of CR or PR compared to patients in the PDC group (1.9% versus 0.8% or 35.7% versus 24.3%, respectively); as well, patients in the NI plus PDC group had a lower proportion of patients with a BOR of PD than patients in the PDC group (8.9% versus 12.6%, respectively).[3]

Table 27: Confirmed BOR per BICR in All Randomized Patients in CheckMate 9LA Trial (DBL: October 3, 2019)

	Number of Subjects (%)	
	Nivo+Ipi+Chemo N = 361	Chemo N = 358
CONFIRMED BEST OVERALL RESPONSE		
COMPLETE RESPONSE (CR)	7 (1.9)	3 (0.8)
PARTIAL RESPONSE (PR)	129 (35.7)	87 (24.3)
STABLE DISEASE (SD)	166 (46.0)	184 (51.4)
PROGRESSIVE DISEASE (PD)	32 (8.9)	45 (12.6)
UNABLE TO DETERMINE (UTD)	24 (6.6)	30 (8.4)
NOT REPORTED	3 (0.8)	9 (2.5)
OBJECTIVE RESPONSE RATE (1)	136/361 (37.7%)	90/358 (25.1%)
(95% CI)	(32.7, 42.9)	(20.7, 30.0)
DIFFERENCE OF OBJECTIVE RESPONSE RATES (2, 3)	12.4%	
(97.5% CI)	(4.8, 20.0)	
(95% CI)	(5.7, 19.1)	
ESTIMATE OF ODDS RATIO (3, 4)	1.81	
(97.5% CI)	(1.25, 2.62)	
(95% CI)	(1.31, 2.50)	
P-VALUE (5)	0.0003	
DISEASE CONTROL RATE (6)	302/361 (83.7%)	274/358 (76.5%)
(95% CI)	(79.4, 87.3)	(71.8, 80.8)

Per RECIST 1.1, confirmation of response required.
(1) CR+PR, confidence interval based on the Clopper and Pearson method.
(2) Strata adjusted difference in objective response rate (Nivo+Ipi+Chemo - Chemo) based on CMH method of weighting.
(3) Stratified by Histology (squamous vs non-squamous), PD-L1(>= 1% vs < 1%/not quantifiable), Sex (male vs female) as entered into the IRT.
(4) Strata adjusted odds ratio (Nivo+Ipi+Chemo over Chemo) using CMH method.
(5) Two-sided p-value from stratified CMH Test.
(6) CR+PR+SD, confidence interval based on the Clopper and Pearson method.

Source: EMA Assessment Report[3]

Considering the confirmed responders in each treatment group, the median TTR was shorter in the PDC group at 1.56 months (range, 1.2 to 8.3) compared to 2.51 months (range, 1.1 to 10.6) in the NI plus PDC group. Conversely, the median DOR was longer in the NI plus PDC group at 10.02 months (95% CI, 8.21 to 13.01) compared to 5.09 months (95% CI, 4.34 to 7.00) in the PDC group; based on the non-overlapping CIs, the median DOR was significantly longer in the NI plus PDC group. The proportion of patients showing a DOR of at least three and six months was also greater in the NI plus PDC group versus the PDC group (Table 28).[3]

Table 28: TTR and DOR per BICR among All Randomized Patients in CheckMate 9LA Trial (DBL: October 3, 2019)

	Nivo+Ipi+Chemo N = 136	Chemo N = 90
TIME TO OBJECTIVE RESPONSE (MONTHS)		
MEAN	2.81	2.55
MEDIAN	2.51	1.56
MIN, MAX	1.1, 10.6	1.2, 8.3
Q1, Q3	1.41, 3.01	1.41, 2.86
STANDARD DEVIATION	1.99	1.72
DURATION OF RESPONSE (MONTHS)		
MIN, MAX (A)	1.0+, 16.5+	1.4+, 15.2+
MEDIAN (95% CI) (B)	10.02 (8.21, 13.01)	5.09 (4.34, 7.00)
N EVENT/N RESP (%)	57/136 (41.9)	54/90 (60.0)
PROPORTION OF SUBJECTS WITH DURATION OF RESPONSE OF AT LEAST (95% CI) (C)		
3 MONTHS	0.88 (0.81, 0.92)	0.76 (0.66, 0.84)
6 MONTHS	0.74 (0.66, 0.81)	0.41 (0.30, 0.52)

(A) Symbol + indicates a censored value.
(B) Median computed using Kaplan-Meier method.
(C) Based on Kaplan-Meier estimates of duration of response.

Source: EMA Assessment Report[3]

Unweighted subgroup analyses of ORR favoured treatment with NI plus PDC compared to PDC in most subgroups. ORR also significantly improved in the NI plus PDC group for the histology and PD-L1 subgroups except for patients with PD-L1 <1% (unweighted ORR difference=10.2, 95% CI -0.4 to 20.5).[3]

Updated Analysis (DBL: March 9, 2020): The ORR results at the updated analysis were consistent and very similar to the primary analysis results. ORR was higher in patients receiving NI plus PDC (38.2%; 95% CI 33.2 to 43.5) than PDC (24.9%; 95%CI 20.5 to 29.7) favouring treatment with NI plus PDC.[3] Patients in the NI plus PDC group had greater odds of experiencing a CR or PR compared to patients in the chemo group (OR=1.88, 95% CI 1.36 to 2.60).[4] More patients in the NI plus PDC group experienced a BOR of CR (2%) compared to the PDC group (1%). Patients in the NI plus PDC group also experienced less PD than patients in the PDC group (9% versus 13%, respectively). Most prespecified subgroup analyses of this outcome, including histology and PD-L1 status, favoured treatment with NI plus PDC.[4]

The median TTR per BICR assessment was longer for patients in the NI plus PDC group (2.56 months) compared to patients in the PDC group (1.54 months), which was consistent with the results of the primary analysis (DBL: October 3, 2019). Similarly, results of DOR at the updated analysis were also consistent with the primary analysis; the median DOR was longer for all confirmed responders in the NI plus PDC group compared to the PDC group.[3]

Exploratory Endpoint – PFS2

Primary Analysis (DBL: October 3, 2019): Median PFS2 per investigator assessment was longer in the NI plus PDC group at 13.34 months (95% CI, 11.86-14.46) compared to 8.71 months in the PDC group (95% CI, 7.43-9.79), which is a treatment benefit (HR=0.62; 95% CI 0.51-0.76) consistent with the results of the primary and secondary efficacy endpoints in the trial. Censoring occurred for 175 patients (48.5%) in the NI plus PDC group and 226 patients (63.1%) in the PDC group.[3]

Updated Analysis (DBL: March 9, 2020): [redacted].[4] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed)*

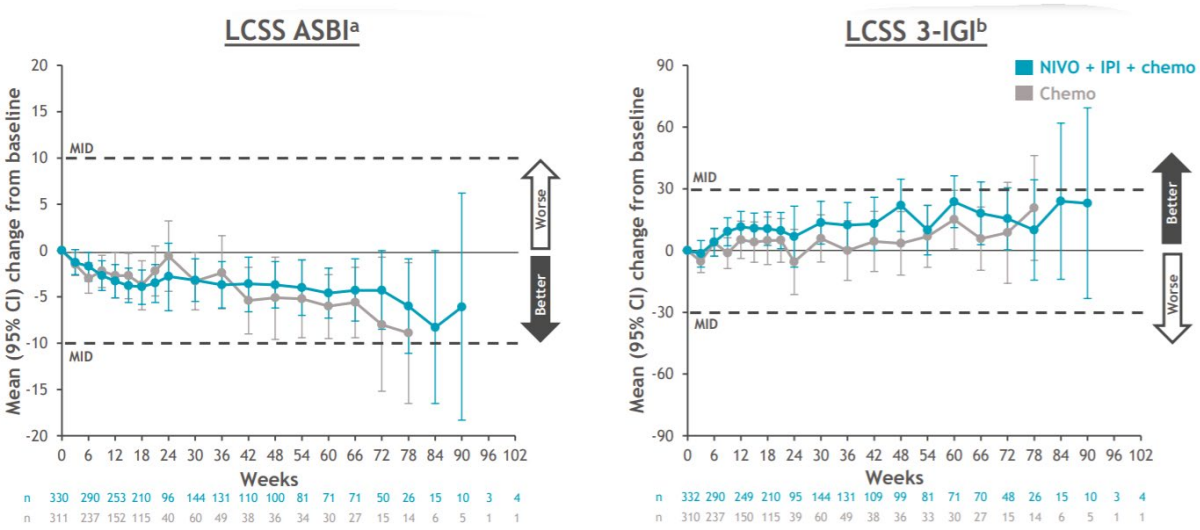
Health-related Quality of Life

Patient reported outcomes were assessed in the All Randomized Population. In general, the results of all assessment instruments at both the primary and updated analyses (LCSS, EQ-5D VAS, and EQ-5D-3L UI) showed improvements over time in patient reported HRQoL outcomes in both treatment groups based on changes from baseline, but these improvements did not meet prespecified MID thresholds in either group. The degree of improvement in outcomes from baseline appeared similar between the treatment groups at all assessment time points.[4,6] The HRQoL data presented below are based on the updated analysis (DBL: March 9, 2020).

Compliance: Completion rates for the LCSS questionnaire were greater than 90% at baseline and declined over time but remained at a rate of ≥80% at most on-treatment assessments with sufficient data (≥10% patients). Compliance was lower during the follow-up period, with compliance rates ranging from 60 to 72% in both treatment groups. Similar compliance rates were observed for the EQ-5D (VAS and UI).[4]

Lung Cancer Symptom Scale: Figure 14 displays the mean change in LCSS score from baseline over time in each treatment group of the CheckMate 9LA trial. At baseline, the mean LCSS ABSI score was slightly lower (i.e. less symptom burden) among patients in the NI plus PDC treatment group (21.28; 95% CI, 19.67 to 22.89) compared to patients in the PDC group (24.39, 95% CI, 22.75 to 26.03). At on-treatment assessment timepoints with sufficient data (≥10% through to week 90 for the NI plus PDC group, and through to week 78 for the PDC group), LCSS ABSI scores decreased in both treatment groups, indicative of improved lung cancer symptoms and HRQoL. However, the MID of 10 points was not reached in either treatment group at any time point where there was sufficient data (N ≥10%).[4] The 3-IGI showed trends of improvement in both treatment groups, as the mean change from baseline over time increased; however, the MID of 30 was not reached in either treatment group.[6]

Figure 14: Mean Change in Lung Cancer Symptom Scale Average Symptom Burden Index Score and 3-Item Global Index from Baseline



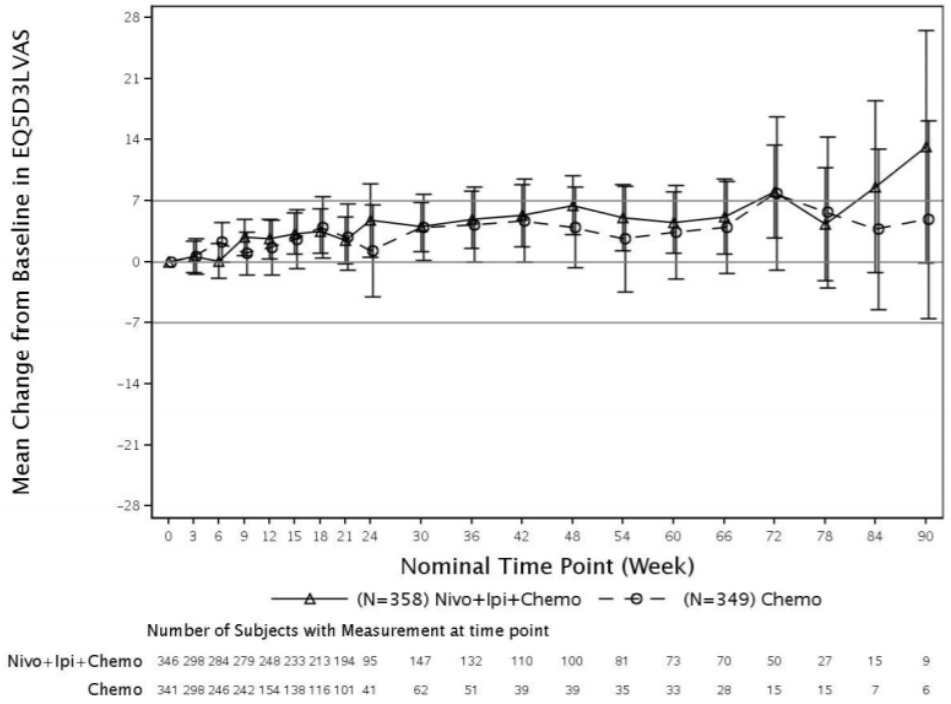
Completion rates out of expected patients were mostly comparable between treatment arms and above 80%. Only on-treatment time points with data for ≥ 10 patients in either treatment group are shown. No assessment was scheduled at Week 24, thus data at Week 24 represents delay of an earlier scheduled assessment.
[a]LCSS ASBI is the average of 6 disease-related symptom scores on a 100-mm VAS; range: 0 (best) to 100 (worst); MID = 10 points; [b]LCSS 3-IGI is the sum of 3 items on a 100-mm VAS; range of total score: 0 (worst) to 300 (best); MID = 30 points.

Source: Reck et al., 2020[6]

EQ-5D Visual Analogue Score: Figure 15 displays the mean change from baseline in the self-rated health of patients over time, based on the EQ-5D VAS, in each treatment group of the CheckMate 9LA trial. At baseline, the mean EQ-5D VAS scores were slightly higher (i.e. better overall self-rated health) among patients in the NI plus PDC group (73.47; 95% CI, 71.63 to 75.31) compared to patients in the PDC group (69.50; 95% CI, 67.34 to 71.67). At on-treatment assessments with sufficient data (N≥10%), mean VAS scores increased in both treatment groups through to week 84 in the NI plus PDC group and through week to 78 in the PDC group, indicating patients' self-rated health improved in both groups. The improvements from baseline were considered clinically meaningful based on meeting or exceeding the prespecified MID of ≥7 points at weeks 72 and 84 in the NI plus PDC group,

and at week 72 in the PDC group. However, during follow-up visits, there were numerical decreases in patients' questionnaire scores in both treatment groups indicating worsening of patient's health status.[4]

Figure 15: Mean Changes in Overall Self-rated Health Status EQ-5D Visual Analogue Scale from Baseline



Error bars represent 95% CI for the mean. Horizontal reference indicates minimum important difference (MID), considered a change of ≥ 7 points from baseline. Only time points where data available for >=5 subjects in each treatment group are plotted. Database lock: 09-Mar-2020

Source: Clinical Study Report[4]

EQ-5D-3L Utility Index: Figure 21 displays the mean change from baseline in mean UI score (i.e. overall health status) over time, based on the EQ-5D-3L, in each treatment group of the CheckMate 9LA trial. At baseline, mean UI scores were similar in the treatment groups (NI plus PDC: [redacted] versus PDC: [redacted]). At on-treatment assessments with sufficient data (N≥10), [redacted], EQ-5D UI scores improved in both groups. These mean changes from baseline did not exceed the MID of 0.08 in either treatment group, [redacted].[4] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until June 30, 2021 or until notification by the sponsor that it can be publicly disclosed)*

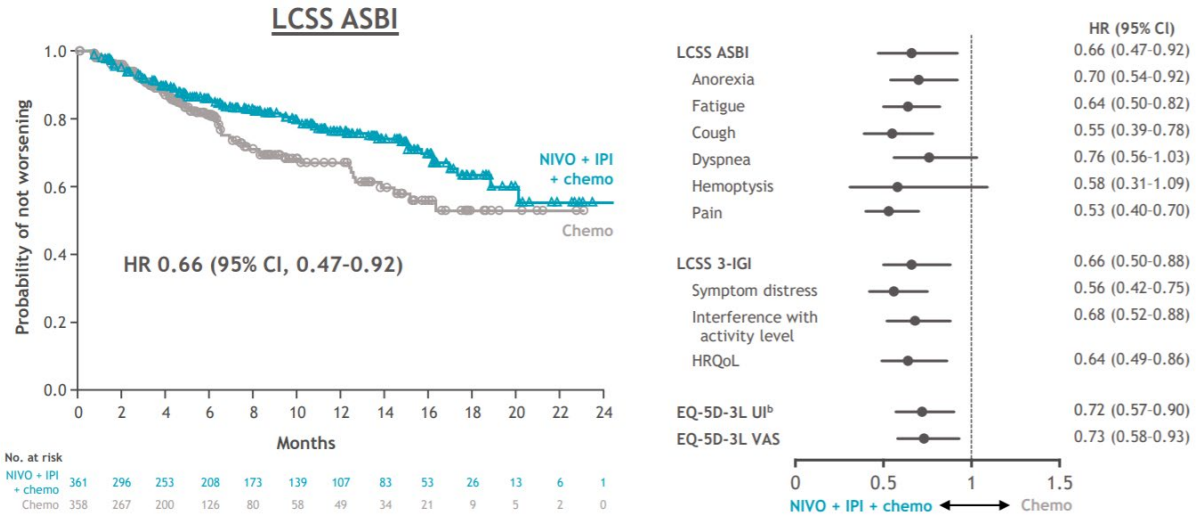
Figure 16: Mean Changes in EQ-5D Utility Index Scores from Baseline

Source: Clinical Study Report[4]

(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until June 30, 2021 or until notification by the sponsor that it can be publicly disclosed)

TTD Analyses: A TTD analysis was conducted for the ABSI and 3-IGI subscales of the LCSS, and the EQ-5D-3L UI and VAS (Figure 17). All subscales of the LCSS and EQ-5D demonstrated a longer time to deterioration in the NI plus PDC group compared to the PDC group, and a greater probability of worsening for patients in the PDC group.[6]

Figure 17: Analyses of TTD (on treatment and follow-up)



[a]Defined as time from randomization to the first deterioration that met or exceeded the MID, provided that all subsequent assessments also met or exceeded the MID; MID = 10 points (LCSS ASBI), 30 points (LCSS 3-IGI), 0.08 points (EQ-5D-3L UI), and 7 points (EQ-5D-3L VAS); [b]Scoring derived from UK weights.
Time to first deterioration HR (95% CI): LCSS ASBI, 1.16 (0.91-1.48); LCSS 3-IGI, 1.10 (0.89-1.36); EQ-5D-3L VAS, 1.07 (0.88-1.30); EQ-5D-3L UI, 0.88 (0.72-1.07).

Source: Reck et al., 2020[6]

Harms Outcomes

CheckMate 9LA: The safety data from the CheckMate 9LA trial based on the primary (DBL: October 3, 2019) and updated analyses (DBL: March 9, 2020) are summarized in Table 29 and are presented for the All Treated Population (N=707). The reporting of safety results in the proceeding section is focused on the updated analysis which were consistent with the primary analysis and showed no new safety signals for NI plus PDC. Overall, NI plus PDC was associated with an increased incidence of AEs when compared to PDC alone: grade 3 or 4 AEs ([redacted]), SAEs of any grade ([redacted]), drug-related SAEs of any grade ([redacted]), drug-related AEs of any grade ([redacted]), and grade 3 or 4 drug-related AEs ([redacted]).[4]
(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this safety information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed)

Table 29: Summary of AEs in the CheckMate 9LA Trial

AEs	Primary Analysis (DBL: October 3, 2019)				Updated Analysis (DBL: March 9, 2020)			
	NI plus PDC N=358		PDC N=349		NI plus PDC N=358		PDC N=349	
Grade	Any grade	Grade 3-4	Any grade	Grade 3-4	Any grade	Grade 3-4	Any grade	Grade 3-4
All AEs (regardless of causality), %	355 (99.2)	228 (63.7)	341 (97.7)	184 (52.7)	[redacted]			
≥10% of patients in any treatment group:								
Anemia	115 (32.1)	28 (7.8)	157 (45.0)	59 (16.9)	[redacted]			
Nausea	114 (31.8)	6 (1.7)	144 (41.3)	3 (0.9)	[redacted]			
Diarrhea	105 (29.3)	15 (4.2)	64 (18.3)	6 (1.7)	[redacted]			
Asthenia	102 (28.5)	10 (2.8)	88 (25.2)	14 (4.0)	[redacted]			
Decreased appetite	101 (28.2)	7 (2.0)	76 (21.8)	6 (1.7)	[redacted]			
Pruritus	72 (20.1)	3 (0.8)	8 (2.3)	0	[redacted]			
Fatigue	77 (21.5)	9 (2.5)	55 (15.8)	3 (0.9)	[redacted]			
Constipation	76 (21.2)	2 (0.6)	79 (22.6)	2 (0.6)	[redacted]			
Drug-related AEs, %	322 (89.9)	159 (44.4)	304 (87.1)	129 (37.0)	[redacted]			
≥15% of patients in any treatment group:								
Nausea	94 (26.3)	5 (1.4)	126 (36.1)	3 (0.9)	[redacted]			
Anemia	80 (22.3)	20 (5.6)	130 (37.2)	48 (13.8)	[redacted]			
Asthenia	73 (20.4)	3 (0.8)	61 (17.5)	8 (2.3)	[redacted]			
Diarrhea	73 (20.4)	14 (3.9)	42 (12.0)	4 (1.1)	[redacted]			
Pruritus	66 (18.4)	3 (0.8)	4 (1.1)	0	[redacted]			
Rash	64 (17.9)	5 (1.4)	10 (2.9)	0	[redacted]			
Fatigue	59 (16.5)	8 (2.2)	37 (10.6)	2 (0.6)	[redacted]			
Decreased appetite	56 (15.6)	4 (1.1)	53 (15.2)	4 (1.1)	[redacted]			
Neutropenia	35 (9.8)	22 (6.1)	58 (16.6)	31 (8.9)	[redacted]			
All AEs leading to drug discontinuation, %	100 (27.9)	77 (21.5)	59 (16.9)	38 (10.9)	[redacted]			
Drug-related AEs leading to drug discontinuation*, %	68 (19.0)	54 (15.1)	26 (7.4)	14 (4.0)	[redacted]			
All SAEs, %	203 (56.7)	157 (43.9)	144 (41.3)	111 (31.8)	[redacted]			
Drug-related SAEs, %	104 (29.1)	90 (25.1)	61 (17.5)	51 (14.6)	[redacted]			

AE = adverse event; DBL = database lock; NI plus PDC = nivolumab plus ipilimumab and two cycles of platinum doublet chemotherapy; PDC = platinum doublet chemotherapy; SAE = serious adverse event.

* Includes discontinuations due to any component of the regimen. If criteria for nivolumab discontinuation were met, ipilimumab was also discontinued.

Source: Clinical Study Report 2019,[4,8] EMA Assessment Report[3]

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Adverse Events: Almost all patients in each treatment group experienced AEs of any grade ([redacted]), with most AEs being of low grade (i.e. grade 1-2). The most common AEs in the NI plus PDC group included [redacted]. In the PDC group,

the most common AEs were [redacted].[4] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this safety information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed)* The specific AEs occurring in greater than 10% or 15% of patients in any treatment group are presented in Table 29.

Drug-related AEs of any grade occurred in most patients in both treatment groups ([redacted]% in the NI plus PDC group and [redacted]% in the PDC group).[59] Nausea and anemia were the most common drug-related AEs in each treatment group but they occurred at a lower frequency in the NI plus PDC group compared to the PDC group ([redacted]% versus [redacted]% and [redacted]% versus [redacted]%, respectively).[7] The incidence of all grade drug-related AEs was greater in the NI plus PDC group except for neutropenia, which occurred in more patients in the PDC group ([redacted]% versus [redacted]% the NI plus PDC group).[7] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this safety information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed)*

The incidence of grade 3 or 4 drug-related AEs was higher in the NI plus PDC group ([redacted]) compared to the PDC group ([redacted]).[7] [redacted].[7] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this safety information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed)*

Serious Adverse Events: The incidence of SAEs (any grade) was higher in the NI plus PDC group ([redacted]) compared to the PDC group ([redacted]). [redacted].[4] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this safety information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed)*

The most common drug-related SAEs of any grade in the NI plus PDC group were [redacted]. The most common drug-related SAEs of any grade in the PDC group were [redacted].[4] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this safety information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed)*

Adverse Events leading to Discontinuation: [redacted].[4] [redacted]. Specifically, [redacted]% of patients in the NI plus PDC group experienced AEs of any grade resulting in drug discontinuation, of which [redacted]% were of grade 3 or 4. In the PDC group, [redacted]% of patients experienced AEs that lead to drug discontinuation, of which [redacted]% were grade 3 or 4.[4] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this safety information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed)*

The most common AEs in the NI plus PDC group that led to drug discontinuation were [redacted]; and in the PDC group, the most common AEs leading to drug discontinuation were [redacted]. AEs resulting in treatment discontinuation specifically related to treatment were reported in [redacted] and [redacted] of patients in the NI plus PDC and PDC groups, respectively; of these, [redacted] and [redacted] were grade 3 or 4 in the NI plus PDC and PDC groups, respectively. The most common drug related AEs resulting in treatment discontinuation were [redacted] in the NI plus

PDC group and [redacted] in the PDC group.[4] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this safety information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed)*

Select and Immune Mediated Adverse Events: Select AEs included events with potential immunologic aetiology associated with the use of nivolumab and ipilimumab in combination as well as nivolumab. AEs including endocrinopathies, diarrhea/colitis, hepatitis, pneumonitis, interstitial nephritis, and rash were classified as select AEs; events that described the listed AEs were grouped into endocrine, gastrointestinal, hepatic, pulmonary, renal, and skin select AE categories, respectively.[3] Select AEs were mostly grade 1-2 and were deemed drug-related by the investigator (Table 30).[3] Select AEs as well as drug-related select AEs were more common in the NI plus PDC group compared to the PDC group. In the NI plus PDC group, the most common grade 3-4 select AEs were gastrointestinal ([redacted]%) and skin and hepatic ([redacted]% each);[7] [redacted] (Table 31).[7] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this safety information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed)*

Table 30: Summary of Select AEs in the CheckMate 9LA Trial

AE=adverse event, chemo=chemotherapy, CTC=Common Toxicity Criteria, DC=discontinuation, IMAEs=immune-mediated adverse events, ipi=ipilimumab, MedDRA=Medical Dictionary for Regulatory Activities, nivo=nivolumab, OESI=other events of special interest, SAEs=serious adverse events

a The causes of death per investigator were as follows: in the NI plus PDC group: two deaths were due to NI (pneumonitis, hepatitis), one death was due to ipilimumab (diarrhea), one death was due to ipilimumab plus chemotherapy (sepsis), one death was due to NI plus PDC (hepatic toxicity), and two deaths were due to PDC (acute renal failure, thrombocytopenia); and in the PDC group: sepsis (two subjects), anemia, pancytopenia, respiratory failure, and neutropenia.

b The verbatim terms reported for the 'other' reasons for death were consistent with events expected in the study population. MedDRA version 22.1 CTCAE version 4.0. All events are within 30 days of the last dose of study drug, unless otherwise indicated.

Source: Clinical Study Report[4]

(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this safety information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed)

Table 31: Time to Onset and Resolution of Drug-related Select AEs

Source: CADTH Submission[7]

(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this safety information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed)

Immune-related Adverse Events: [redacted] (Table 32). [redacted].[4] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this safety information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed)*

Table 32: Summary of irAEs

Source: Clinical Study Report[4]

(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this safety information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed)

Adverse Events of Special Interest: [redacted].[4] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this safety information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed)*

Deaths: A summary of the deaths occurring in the CheckMate 9LA trial is provided in Table 33. [redacted].[4] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this safety information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed)*

[redacted].[4] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this safety information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed)*

[redacted].[4] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this safety information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed)*

[redacted] (Table 33). [redacted].[4] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this safety information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed)*

Table 33: Summary of Deaths Occurring in the CheckMate 9LA Trial in the All Treated Population

Source: Clinical Study Report[4]

(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this safety information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed)

6.4 Ongoing Trials

Checkmate 9LA is an ongoing trial, no other ongoing trials meeting the selection criteria of the review were identified.

7 Supplemental Questions

There is currently no direct trial evidence that compares NI plus PDC to current standards of care, specifically immunotherapy-based (IO) treatments, for the first-line treatment of patients with metastatic or recurrent NSCLC without EGFR mutations or ALK translocations. In the absence of head-to-head comparisons, the objective of this section is to critically appraise the indirect treatment comparison (ITC) submitted by the sponsor that assess the comparative efficacy of NI plus PDC to other first-line treatments where results were used as inputs in the submitted pharmacoeconomic model.[69]

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

7.1 Sponsor-submitted ITC for the Treatment of Patients with Advanced or Recurrent NSCLC

7.1.1 Objective

The primary objective of the sponsor's ITC was to compare the clinical efficacy, in terms of OS and PFS, associated with NI plus PDC relative to other first-line treatments for metastatic or recurrent NSCLC. Secondary, the ITC also sought to compare response endpoints between NI plus PDC and other first-line treatments.[69]

The ITC was provided to CADTH in the form of an unpublished report.[69] At the request of CADTH, the sponsor provided the systematic literature review (SLR) that was performed and informed the ITC.[9] The CADTH Methods Team summarized and appraised the quality of the SLR and ITC in the sections below.

Methods of the Sponsor's Submitted ITC

Systematic Literature Review

The SLR conducted by the sponsor aimed to identify all existing RCTs that evaluated nivolumab, with or without ipilimumab, and relevant comparators for the first-line treatment of advanced NSCLC. The search strategy included disease, study design, and intervention-specific search terms and was not limited by language. Relevant studies were identified through searches of EMBASE, MEDLINE and the Cochrane Central Register of Controlled Trials. Comparators were identified by reviewing international treatment guidelines and included potentially emerging therapies. The initial search was conducted in June 2016 and was extended multiple times up to April 2020. Major oncology conference abstracts and trial registries (Clinicaltrials.gov and WHO Clinical trials registry) were searched in 2018 and 2019 to identify unpublished studies.[9]

Eligibility Criteria and Study Selection: Studies were eligible for inclusion in the SLR based on the population, interventions, comparators, outcomes, and study design (i.e. PICOS) criteria outlined in Table 34. All eligibility criteria were defined a priori. These criteria were broadly aligned with the inclusion criteria of the CheckMate trials of nivolumab conducted in NSCLC. Eligible studies were published or unpublished RCTs that included one of the interventions of interest, irrespective of other RCT characteristics such as blinding status. Studies were screened based on titles and abstracts, and eligibility was confirmed based on full-text review. Full text articles were screened by two independent reviewers.[9]

Table 34: Population, Interventions, Comparisons, Outcomes and Study Design Criteria for SLR Study Inclusion

Population	• Adults aged 18 years or older • Advanced, metastatic (stage IV), or recurrent NSCLC • No prior systemic anticancer therapy (including chemotherapy, targeted therapy, and IO)
Interventions	• Nivolumab monotherapy • Nivolumab plus ipilimumab • Nivolumab plus platinum doublet
Comparators	• Pembrolizumab monotherapy (200 mg every 3 weeks) • Pembrolizumab plus pemetrexed-based platinum doublet combination • Pembrolizumab plus platinum doublet • Atezolizumab combination therapy • Durvalumab monotherapy • Durvalumab plus tremelumab • Other durvalumab combination with chemotherapy • Camrelizumab • Tislelizumab • Carboplatin or cisplatin-based platinum doublet combinations with 3rd generation chemotherapies (excluding pemetrexed and nab-paclitaxel): ○ carboplatin/paclitaxel ○ carboplatin/docetaxel ○ carboplatin/gemcitabine ○ carboplatin/vinorelbine ○ carboplatin/irinotecan ○ cisplatin/docetaxel ○ cisplatin/paclitaxel ○ cisplatin/vinorelbine ○ cisplatin/gemcitabine ○ cisplatin /irinotecan • Pemetrexed-based platinum-doublet combinations: ○ cisplatin/pemetrexed ○ carboplatin/pemetrexed • Etoposide-based platinum-doublet combinations: ○ cisplatin/etoposide ○ carboplatin/etoposide • Nab-paclitaxel plus carboplatin • Necitumumab plus cisplatin plus gemcitabine • Bevacizumab with platinum doublet combination (7.5-15 mg per kilogram body weight every two or three weeks) • Bevacizumab with pemetrexed-based platinum doublet • Gemcitabine plus docetaxel or gemcitabine plus vinorelbine • S-1 plus platinum Additional comparators (expansion of core comparators): • Single agent chemotherapy ○ gemcitabine ○ vinorelbine ○ docetaxel • paclitaxel • best supportive care

Outcomes	• Efficacy: ○ Overall survival ○ Progression-free survival ○ Time to progression ○ Objective response rate ○ Complete response ○ Partial response ○ Stable disease ○ Progressive disease ○ Disease control rate ○ Duration of response ○ Time to treatment failure • Safety ○ Overall discontinuation during treatment phase ○ Discontinuation due to AEs ○ Treatment-related death (Grade 5 AEs) ○ Overall incidence of Grade 3 or 4 AEs ○ Overall incidence of serious AEs ○ Individual AEs (i.e. hematologic and non-hematologic)
Study design	RCTs
Inclusion Criteria	Broadly adopted from CheckMate 227 and CheckMate 026 Trials: • Adults aged ≥ 18 years, with stage IV or recurrent NSCLC • No known EGFR mutations which are sensitive to available targeted inhibitor therapy • No known ALK translocations which are sensitive to available targeted inhibitor therapy • No untreated central nervous system metastasis • ECOG performance status of 1 or less • No prior systemic anticancer therapy given as primary therapy for advanced or metastatic disease.
Language	No language limits
Search Period	Initial search in June 2016 and refreshed in April 2020

AEs = adverse events; ALK = anaplastic lymphoma kinase; ECOG = eastern cooperative oncology group; EGFR = epidermal growth factor receptor; IO = immunotherapies; IV = Intravenous; NSCLC = non-small-cell lung carcinoma; RCT = randomized controlled trial

Source: Adopted from sponsor's submitted ITC Report[69]

Data Extraction: Two independent reviewers carried out the data extraction process; one conducted the data extraction and the second verified and validated the extraction results. Data were extracted in duplicate for study characteristics, interventions, patient characteristics, and outcomes for the final list of included studies.[9]

Outcomes: The primary efficacy endpoints of interest were OS, PFS, and ORR. Treatment group-specific estimates were extracted from the primary source with relative scale estimates. If data on PFS were not available, data for other similar endpoints (i.e., event-free survival, failure-free survival, or time-to-progression) were extracted. HRs (point estimate and 95% CI) were recorded. Additionally, data from KM curves were extracted when available, such as median time to an event, and information related to PH assumptions. If endpoints were not reported in trial publications, the author was contacted for the necessary data. If required data could not be obtained, imputation methods were used to calculate an estimate where the number of patients experiencing an event was derived by using the percentage of patients with an event and the total number at risk.[69]

Quality Assessment of Included Studies: The risk of bias associated with included studies was assessed using the NICE "Guide to the methods of technology appraisal", and the results of these assessments were presented.[69] The NICE guide covers potential biases associated with different aspects of trial conduct including the sequence generation and allocation concealment (selection of bias), baseline similarity, blinding, dropout between groups, outcomes reported, as well as the financial relationship with the trial sponsor reported by the trial authors. The risk of bias assessment was restricted to peer-reviewed publications of the included RCTs and not unpublished studies identified.[69] No sensitivity analyses were conducted to investigate the impact of the quality assessment results.

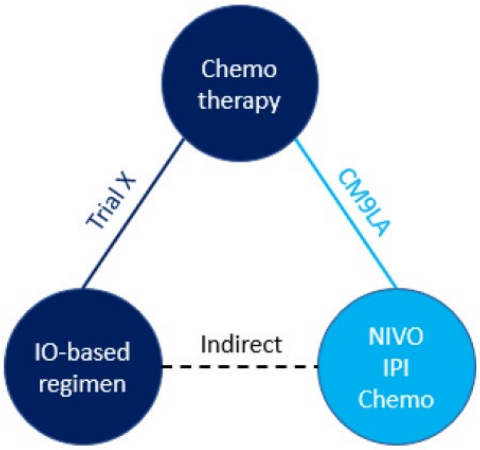
Indirect Comparison Methods

Eligibility Criteria for Selection of Studies Included in ITC: The eligibility criteria used for the selection of studies included in the ITC restricted the ITC to trials that compared IO-based regimens as first-line treatment for patients with advanced or recurrent NSCLC without EGFR mutations or ALK translocations. The eligibility criteria for the ITC were restricted to studies that evaluated IO-based therapies that had regulatory approval in one or more regions in Canada, and those in which the control group was a PDC.[69]

Data Preparation and Statistical Analyses: Three node ITC networks were constructed using the CheckMate 9LA trial[6] of NI plus PDC and comparator RCTs involving other IO-based regimens. The three nodes in each network included chemotherapy, NI plus PDC, and other IO-based regimens (refer to Figure 18).[69]

Frequentist methods were used to derive relative treatment effect estimates between NI plus PDC and IO-based regimens. Data preparation was conducted that converted HRs to Log HRs, and numerators were calculated for all binary outcomes. Proportional hazards assumptions were tested through visual inspection of KM curves, hazard plots and Schoenfeld residual plots. For trials that shared a common comparator in the same patient population, pairwise meta-analysis was performed using the R package "meta". This software uses the inverse variance approach for pooling and the DerSimonian-Laird method for estimating variance. Fixed-effects models were used when the number of RCTs (i.e. at most two) in any given meta-analysis was insufficient for estimating a value for the between studies standard deviation. The ITCs were based on a frequentist approach using the Bucher method. Inputs were based on the pooled pairwise meta-analysis estimates when there was more than one RCT comparing the same treatment. Statistical heterogeneity was not calculated due to the small number of studies. No assessment of consistency was conducted as it was not possible in the three-node networks, which often only included two studies. No sensitivity analyses were conducted by the sponsor.[69]

Figure 18: Three-node ITC Network



Source: From sponsor's submitted ITC Report[69]

Assessment of Clinical Heterogeneity: The characteristics of patients in the RCTs of any given ITC were summarized to highlight any differences across trials. Treatment effect modifiers were identified by reviewing endpoint-specific plots showing treatment effect size by subgroup, as presented in the RCT. The subgroup estimates from each trial were summarized in tabular format and p-values were calculated; however, the sponsor did not report the results of these effect modification analyses. The sponsor cited the current immaturity of the CheckMate 9LA trial data and that the analyses would be updated when mature data become available.

At the request of CADTH, sensitivity analyses were performed by the sponsor to explore the impact of limiting analyses to patients with different levels of PD-L1 expression in trials that included all-comers, and by histology (i.e., squamous versus non-squamous).[69] The sponsor indicated that the full ITT population from the CheckMate 9LA trial was used as the main data input for the ITC in order

to preserve the trial design and power of the statistical analysis, noting the trial was not powered to detect treatment effects within PD-L1-based or histology subgroups. Further, they noted that the trial results support this approach as the subgroup analysis results for PD-L1 expression level and histology demonstrated the treatment effect is independent of these patient factors.

Assessment of Outcome Heterogeneity: Since the PDC treatment groups of individual RCTs were combined into a common chemotherapy group in the ITC, treatment effect estimates in the PDC groups of each RCT were evaluated to assess outcome heterogeneity. Tabular summaries were prepared that included the median and landmark OS and PFS, as well as KM curve overlays, for each RCT. Heterogeneity in outcome was assessed from a clinical perspective and considered multiple factors that included the prevalence of subsequent IO use, delay in the receipt of subsequent IO, characteristics of enrolled patients, and the duration of follow-up and maturity of the data in each trial.

7.1.2 Findings

Summary of included studies

Results of SLR

The SLR identified a total of 1,722 unique publications. Overall, 67 trials met the criteria for inclusion based on the comparators outlined in Table 34, with 14 trials involving IO-based regimens that included nivolumab, pembrolizumab, atezolizumab and durvalumab.[9] The majority of trials were limited to treatment naïve patients or at minimum had a treatment washout prior to initiation of study treatment.[9]

Study Selection for ITC

The 14 RCTs[14,15,19,24,27,36-40,42,70,71] of IO-based treatments that were identified by the SLR[9] were further restricted to RCTs of funded comparators in Canada, which could have included any regimen that received an initial or final pERC recommendation, or were undergoing negotiations through the pan-Canadian Pharmaceutical Alliance. These criteria limited the evidence base to the following four comparator trials that were included in the ITC:

- KEYNOTE 024 of pembrolizumab monotherapy;[15]
- KEYNOTE 042 of pembrolizumab monotherapy;[36]
- KEYNOTE 189 of pembrolizumab plus platinum and pemetrexed;[19]
- KEYNOTE 407 of pembrolizumab plus platinum plus (nab) paclitaxel;[14]

The characteristics of the trials included in the ITC are summarized in Table 35.[69] Altogether, the five trials included a total of 3,473 patients.[9] All the studies, with the exception of the CheckMate 9LA trial, restricted enrollment to patients with advanced NSCLC; CheckMate 9LA[6] also included patients with recurrent NSCLC.[6] All of the studies were conducted in the last five years and evaluated the three efficacy outcomes of interest. The median follow-up time in each study was not reported in the ITC report. Three of the five trials (CheckMate 9LA, KEYNOTE024, and KEYNOTE042) included all-comers for PD-L1 status and mixed histology. Two of the five trials (KEYNOTE407 and KEYNOTE189) were double-blinded.

As previously mentioned, the included RCTs were assessed for clinical heterogeneity in terms of patient characteristics, with a focus on differences across trials that could potentially modify treatment effect. Considering the information on baseline characteristics presented by the sponsor in Table 36, there were notable differences in the distribution of baseline characteristics (i.e., sex, ECOG PS, presence of metastases) among the trials reporting this information. Specifically, there was evidence of imbalance within the studies related to the proportions of male patients, ECOG PS, and the presence of CNS and liver metastases.[69] Treatment crossover upon disease progression was permitted in four of the trials, where the use of subsequent IO treatments either during or after each trial varied across the trials (Table 37).

The sponsor did not comment on the results of the risk of bias assessment for the trials included in the ITC.

The results of the individual RCTs for OS, PFS, and ORR are provided in Table 38. Overall, the individual trial results were consistent and show that, all efficacy endpoint estimates favour treatment with IO-based regimens over PDC.

Table 35: Key Characteristics of Studies Included in ITC

Trials	Study Design	Population	Study Groups (n)	
Intervention Trial				
CheckMate 9LA[6]	• Randomization stratified by PD-L1, histology, gender. • Open-label, international, phase III RCT • Enrolment period: 2017 – 2019	• Mixed Histology • Advanced or recurrent NSCLC • PD-L1 all-comers	• NI plus PDC (361)	• PDC (358)
Comparator Trials				
KEYNOTE189[19]	• Randomization stratified by PD-L1, choice of platinum, smoking status. • Double-blind, international, phase III RCT • Enrolment period: February 2016 - March 2017	• Non-squamous • Advanced NSCLC • PD-L1 all-comers	• Pembrolizumab plus PDC (410)	• PDC (206)
KEYNOTE407[14]	• Randomization stratified by PD-L1, (nab)-paclitaxel vs. paclitaxel, geographic region • Double-blind, international, phase III RCT • Enrollment period: August 2016 – December 2017	• Squamous • Advanced NSCLC • PD-L1 all-comers	• Pembrolizumab plus PDC (278)	• PDC (281)
KEYNOTE024[15]	• Randomization stratified by ECOG PS, histology, geographic region. • Open-Label, International Phase III trial • Enrollment period: September 2014 - October 2015	• Mixed Histology • Advanced NSCLC • PD-L1 ≥ 50%	• Pembrolizumab (154) •	• PDC (151)
KEYNOTE042[36]	• Randomization stratified by: ECOG PS, histology, geographic region, PD-L1 expression (≥50% vs. 1-49%). • Open-label, international, phase III RCT • Enrollment period: December 2014 - March 2017	• Mixed Histology • Advanced or locally advanced NSCLC • PD-L1 ≥ 1% (with pre-defined subgroup analysis by PD-L1 ≥ 20% and PD-L1 ≥ 50%)	• Pembrolizumab (637)	• PDC (637)

Chemo = chemotherapy; ECOG = Eastern Cooperative Oncology Group; NI = nivolumab plus ipilimumab; Nab =nanoparticle albumin bound; NSCLC = non-small-cell lung carcinoma; PDC = Platinum doublet chemotherapy; PD-L1 = programmed cell death protein ligands 1; RCT = randomized controlled trial

Source: Adopted from sponsor's submitted ITC Report[69]

Table 36: Baseline Characteristics of Studies Included in ITC

Trial	Median age in years	Male, %	ECOG PS 0, %	Liver metastasis, %	CNS metastasis, %
CheckMate 9LA[6]	65	70.1	31.2	21.6	17.0
KEYNOTE189[19]	64.5	59.3	43.5	18.7	17.5
KEYNOTE407[14]	65	81.4	29.2	NR	7.9
KEYNOTE024[15]	NR	NR	NR	NR	NR
KEYNOTE042[36]	NR	NR	NR	NR	NR

CNS = central nervous system; ECOG = Eastern Cooperative Oncology Group; NR = not reported; PS = performance status

Source: Adopted from sponsor's submitted ITC Report. NR status was based on reporting in the sponsor's ITC report.[69]

Table 37: Treatment Details of Studies Included in ITC

Trials	Chemotherapy Regimens		Treatment Crossover	Crossover and Subsequent Therapy
	Non-squamous	Squamous		
CheckMate 9LA[6]	4 cycles of carboplatin or cisplatin plus pemetrexed with optional pemetrexed maintenance	4 cycles of carboplatin + paclitaxel	Yes	• Subsequent systemic therapy: 30.7% in NI plus PDC group; 40.2% in PDC group. • Subsequent IO: 5.3% in NI plus PDC group; 30.2% in PDC group. • Subsequent chemotherapy: 29.1% in NI plus PDC; 22.3% in the PDC group.
KEYNOTE189[19]	4 cycles of pemetrexed plus cisplatin or carboplatin, followed by pemetrexed q3w.	N/A	Yes	• Crossover to pembrolizumab monotherapy permitted at progression following BICR (40.8%). • Overall use of subsequent IO (within or outside of trial): 53.9%. The most frequent second-line IO was pembrolizumab (33.5%) and nivolumab (6.8%).
KEYNOTE407[14]	N/A	Paclitaxel or nab-paclitaxel plus carboplatin q3w	Yes	• Crossover to pembrolizumab monotherapy permitted at progression following BICR (40.1%). • Overall use of subsequent IO (within or outside of trial): 49.1%. The most frequent second-line IO was not reported.
KEYNOTE024[15]	Investigators Choice - 4 to 6 cycles of:		Yes	• The effective crossover rate was 65% (55% while on-study). Patients in the chemotherapy group who had disease progression, which was verified by means of BICR, could crossover to receive pembrolizumab, if safety criteria were met.
	Gemcitabine plus carboplatin or cisplatin			
	Paclitaxel plus carboplatin followed by optional pemetrexed maintenance therapy maintenance only for non-squamous patients			
	Pemetrexed plus carboplatin or cisplatin followed by optional pemetrexed			
KEYNOTE042[36]	Investigators Choice - 4 to 6 cycles of:		No	• Subsequent IO: 20% of patients in the PDC group (13% received nivolumab). • Patients with radiographic disease progression who were clinically stable could continue study treatment until progression was confirmed on a scan obtained at least four weeks later.
	Paclitaxel plus carboplatin			
	Pemetrexed plus carboplatin followed by optional pemetrexed q3w			

BICR = blinded independent central review; Chemo = chemotherapy; NI = nivolumab plus ipilimumab; IO = immunotherapy; N/A = not applicable; Nab =nanoparticle albumin bound; PDC = platinum doublet chemotherapy; q3w = every three weeks

Source: Adopted from sponsor's submitted ITC Report[69]

Table 38: Individual Results of Studies Included in ITC

Trial	Study Groups (n)	Median OS in months (95% CI)	OS HR (95% CI)	Median PFS in months (95% CI)	PFS HR (95% CI)	ORR, %	OR (95% CI)
CheckMate 9LA[6]	NI plus PDC (361)	15.6 (13.9 – 20.0)	0.66 (0.55-0.80)	6.7 (5.6 – 7.8)	0.68 (0.57-0.82)	38.2	1.87 (1.36-2.58)
	PDC (358)	10.9 (9.5 – 12.6)		5.0 (4.3 – 5.6)		24.8	
KEYNOTE189[19]	Pembrolizumab plus PDC (410)	22.0 (19.5 – 25.2)	0.56 (0.45-0.70)	9.0 (8.1 – 9.9)	0.48 (0.40-0.58)	48.1	3.84 (2.58-5.70)
	PDC (206)	10.7 (8.7 – 13.6)		4.9 (4.7 – 5.5)		19.4	
KEYNOTE407[14]	Pembrolizumab plus PDC (278)	17.1 (14.4 – 19.9)	0.71 (0.58-0.88)	8.0 (6.3 – 8.4)	0.57 (0.47-0.69)	57.9	2.68 (1.90-3.77)
	PDC (281)	11.6 (10.1 – 13.7)		5.1 (4.3 – 6.0)		38.4	
KEYNOTE024[15]	Pembrolizumab (154)	26.3 (18.3 – 40.4)	0.65 (0.50-0.86)	10.3 (6.7 – NA)	0.50 (0.37-0.68)	44.8	2.11 (1.31-3.39)
	PDC (151)	14.2 (9.8 – 18.3)		6.0 (4.2 – 6.2)		27.8	
KEYNOTE042[36]	Pembrolizumab (299)*	20.0 (15.4 – 24.2)	0.70 (0.58-0.86)	6.5 (5.9 – 8.5)	0.83 (0.69-1.00)	39.5	1.39 (0.99-1.94)
	PDC (300)*	12.2 (10.4 – 14.6)		6.4 (6.2 – 7.2)		32.0	

NA = not applicable; NI = nivolumab plus ipilimumab; ORR = objective response rate; OS = overall survival; PDC = Platinum doublet chemotherapy; PFS = progression-free survival

*Patients with PD-L1 ≥ 50%

Source: Adopted from sponsor's submitted ITC Report.[69] NA status was based on the reporting in the sponsor's ITC report.

Results

The sponsor performed four independent ITCs based on a comparison of NI plus PDC to the following three comparator regimens: pembrolizumab plus platinum and pemetrexed, pembrolizumab plus platinum and (Nab) paclitaxel, and pembrolizumab monotherapy. All analyses were based on a three-node network that included the CheckMate 9LA trial and one comparator trial except for the ITC to pembrolizumab monotherapy, which included two comparator trials (KEYNOTE024[15] and KEYNOTE042[36]). The results of the ITCs for OS, PFS, and ORR are presented in Table 39.[69] The results showed no statistically significant differences in OS between NI plus PDC and each comparator treatment. Similarly, the results showed no statistically significant differences in PFS between NI plus PDC and each comparator treatment, with the exception of pembrolizumab plus platinum and pemetrexed where PFS was statistically significantly longer in favour of pembrolizumab plus platinum and pemetrexed ([redacted]). *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed)* Similar results were obtained for the outcome of ORR.[69] The assessment of PH assumptions showed that three of the included trials had a PH assumption violation (Table 40). The sensitivity analyses performed that assessed the results according to PD-L1 expression level and histology (Table 41and Table 42) indicated that the treatment effect was independent of either of these factors.

Table 39: Summary of ITC Results

ITC of NI plus PDC versus:	OS HR (95% CI)	PFS HR (95% CI)	ORR OR (95% CI)
Pembrolizumab plus platinum and pemetrexed (KEYNOTE 189)			
Pembrolizumab plus platinum and (nab)paclitaxel (KEYNOTE 407)			
Pembrolizumab monotherapy (KEYNOTE 024and KEYNOTE 042)			

CI = confidence interval; HR = hazards ratio; NI = nivolumab plus ipilimumab; nab =nanoparticle albumin bound OR = odds ratio; ORR = overall response rate; OS = overall survival; PFS = progression-free survival
Source: Adopted from sponsor's submitted ITC Report[69]

(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until June 30, 2021 or until notification by the sponsor that it can be publicly disclosed)

Table 40: Assessment of Proportional Hazards Assumption Across Studies Included in ITC

Trial	Endpoint	P value	Evidence of PH violation
CheckMate 9LA	OS		
	PFS		
KEYNOTE189	OS		
	PFS		
KEYNOTE407	OS		
	PFS		
KEYNOTE024	OS		
	PFS		
KEYNOTE042	OS		
	PFS		

OS = overall survival; PFS = progression-free survival; PH = proportional hazards
Source: Adopted from sponsor's submitted ITC Report[69]

(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until June 30, 2021 or until notification by the sponsor that it can be publicly disclosed)

Table 41: Summary of ITC Sensitivity Analyses - Non-squamous NSCLC

Source: Adopted from sponsor's submitted ITC[69]

(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until June 30, 2021 or until notification by the sponsor that it can be publicly disclosed)

Table 42: Summary of ITC Sensitivity Analyses – Squamous NSCLC

Source: Adopted from sponsor's submitted ITC[69]

(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until June 30, 2021 or until notification by the sponsor that it can be publicly disclosed)

Conclusion of ITC

The sponsor concluded that the ITCs estimated the effect of NI plus PDC over the first year of treatment relative to chemotherapy and other IO-based regimens. The sponsor cautioned the interpretation of the results based on the heterogeneity of the treatment regimens compared (i.e. different dynamics in terms of short- and long-term benefit), and differences across trials with respect to study design and conduct.[69]

Critical Appraisal of the Sponsor-Submitted ITC

The objective of the sponsor-submitted ITC was to assess the comparative efficacy (as measured by OS, PFS and ORR) between NI plus PDC and alternative immunotherapy-based regimens as first-line treatment in adult patients (≥18 years old) with advanced NSCLC. The eligibility criteria for studies included in the ITC were set up according to this objective, where the target population consisted of treatment-naïve patients with advanced or recurrent NSCLC, without EGFR mutations or ALK translocations and an ECOG PS of 0 or 1. The trial populations of included studies were varied by including patients with different histologies (mixed, squamous or non-squamous) and PD-L1 expression levels, (i.e., all-comer populations, high PD-L1 expression of PD-L1 ≥ 50%). The ITC assumed that histology and PD-L1 expression level do not modify treatment effect. In addition, there was variation in treatments; comparator trials evaluated pembrolizumab monotherapy and combination regimens of pembrolizumab and chemotherapy; for the purpose of performing the ITCs, all platinum-based chemotherapy doublets were lumped together into a common chemotherapy comparator.[69]

Table 43 summarizes the critical appraisal of the ITCs using the International Society for Pharmacoeconomics and Outcomes (ISPOR) criteria. Overall, the design and statistical analysis of the ITC were deemed appropriate by the CADTH Methods Team in terms of addressing the study objective. No sensitivity analyses were performed, except those requested by CADTH, to assess the assumptions related to histology and PD-L1 expression. The comparative treatment efficacy estimates from the ITC, as measured by OS and PFS, showed a consistent, statistically non-significant difference between NI plus PDC and pembrolizumab-based combination therapies. However, there are several limitations in interpreting the ITC results. The major concerns with the submitted ITCs are related to the heterogeneity of study populations, differential treatment effects in the common comparator of chemotherapies, varied trial designs and lengths of follow-up, as well as proportion hazard assumption violations. Additionally, the insufficiency of evidence, in terms of outcomes assessed, limits the utility of these ITC results in evaluating the comparative efficacy, safety and QoL of NI plus PDC both within class and within indication.

One of the main limitations with the submitted ITC is the approach taken for the primary analysis of outcomes. Although the sponsor acknowledged the ITC was limited by a small number of included studies, this issue was made worse by further limiting the evidence base included in the network of evidence by only including trials with chemotherapy as the control. Further, as noted above, because all PDC control treatments were grouped as a common comparator, the analysis assumes treatment equivalence of the individual PDC regimens used in each trial, which ignores differential treatment effects. The efficacy results (i.e. OS) of the individual trials show that the PDC control groups performed differently, although as the sponsor acknowledged, this is likely attributed to a multitude of factors (i.e., study period, specific chemotherapy regimens and dosing, timing and extent of the use of subsequent therapies).

Significant differences in inclusion criteria and the distribution of baseline characteristics of patients, in terms of ECOG PS, metastases, and the sex of patients, were apparent across the trials. There were missing data for some characteristics (i.e. CNS and liver metastases) which precludes an assessment of heterogeneity of these other potential treatment effect modifiers. The sponsor performed sensitivity analyses at the request of CADTH to explore the impact of various PD-L1 expression levels in trials that included all-comers; these results exhibited little change to the primary analysis results. However, additional sensitivity analyses and alternative methodologies could have been performed to account for heterogeneity and to compare expanded and limited networks. Such analyses may be limited by the evidence base, but it is not evident that these types of analyses were explored.

There were no data reported in the ITC report on the length of follow-up in each trial included in the ITC. However, the sponsor acknowledged the CheckMate 9LA data are immature (based on approximately one year of follow-up) when compared to the data from comparator trials. The ITC results need to be interpreted considering the differences in follow-up duration given the short-term and long-term effects associated with chemotherapy and IO-based regimens, respectively.

There was evidence of a proportional hazards violation in some included studies. This led to differences in results when comparing the time-to-event analyses and ORR, although this did not greatly impact overall conclusions.

Lastly, there were three efficacy outcomes assessed in the ITCs, while other relevant response endpoints and safety were not assessed. This is surprising given that safety information was cited as being collected for the ITC. Tolerability is an important consideration when comparing agents within a drug class and indication. Inclusion of a safety outcome would greatly increase the utility of the ITCs, especially for inclusion in economic models. Further analysis could have been conducted to explore QoL, provided the trials applied the same outcome measures.

Table 43: Adapted ISPOR Questionnaire to Assess the Credibility of an ITC or NMA

ISPOR Questions	Sponsor-Provided ITC and NMA
Is the population relevant?	Yes. The study populations included in the sponsor's submitted ITC matched the indication under review, which was to evaluate the efficacy and safety of NI-chemo in the first-line treatment of advanced or recurrent NSCLC without EGFR mutations or ALK translocations
Are any critical interventions missing?	No. All relevant immunotherapies were included. A more robust network including trials with control treatments other than PDC may have helped expand the evidence base.
Are any relevant outcomes missing?	Yes. A robust SLR was conducted and outcomes related to efficacy (OS, PFS, ORR) were evaluated; safety and QoL were not assessed.
Is the context (e.g., settings and circumstances) applicable to your population?	Yes. The clinical setting is appliciable to Canadian populations. It is unknown the extent to which any of the trials included Canadian patients.
Did the researchers attempt to identify and include all relevant randomized controlled trials?	A large SLR was conducted to inform the ITC and the ITC included a small subset of identified trials.
Do the trials for the interventions of interest form one connected network of RCTs?	No. Four small, independent ITCs were performed. This approach limits the ability to draw from other information. A more robust analysis would have been to conduct a larger network and conduct the submitted analysis as secondary analyses.
Is it apparent that poor quality studies were included thereby leading to bias?	Unclear. They conducted a risk of bias assessment but this information was not well reported and it is unclear how it was used for the ITCs performed.
Is it likely that bias was induced by selective reporting of outcomes in the studies?	No. The majority of trials reported major outcomes of interest.
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. There are some important differences between trials. There were noteable differences with respect to PD-L1 expression, CNS metastases, ECOG PS, and sex.
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. Differences between trials was discussed but no analysis was conducted to account for these differences. Sensitivity analyses were conducted at the request of CADTH to explore the impact of PD-L1 status and histology.
Were statistical methods used that preserve within study randomization? (No naïve comparisons)	Yes. All analyses were based on RCTs (i.e., no naïve comparisons).
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?	N/A
In the presence of consistency between direct and indirect comparisons, were both direct and indirect evidence included in the NMA?	N/A

ISPOR Questions	Sponsor-Provided ITC and NMA
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?	N/A
Was a valid rationale provided for the use of random effects or fixed effect models?	Yes – this was based on the use of smaller networks.
If a random effects model was used, were assumptions about heterogeneity explored or discussed?	N/A
If there are indications of heterogeneity, were subgroup analyses or meta-regression analysis with pre-specified covariates performed?	No. There was observable heterogeneity based on baseline patient and disease characteristics but no subgroup analyses were performed aside from those requested by CADTH.
Is a graphical or tabular representation of the evidence network provided with information on the number of RCTs per direct comparison?	Yes.
Are the individual study results reported?	Yes. Individual study results were reported for the endpoints of interest.
Are results of direct comparisons reported separately from results of the indirect comparisons or NMA?	Yes.
Are all pairwise contrasts between interventions as obtained with the network meta-analysis reported along with measures of uncertainty?	Yes. Measures of uncertainty were reported for the indirect treatment effect estimates (95% confidence intervals)
Is a ranking of interventions provided given the reported treatment effects and its uncertainty by outcome?	No.
Is the impact of important patient characteristics on treatment effects reported?	Not reported.
Are the conclusions fair and balanced?	Yes.
Were there any potential conflicts of interest? If yes, were steps taken to address these	This was a sponsor-submitted ITC. No external validation or peer-reviewed evaluations of the ITC were conducted.

7.1.3 Summary

In the absence of direct trial evidence, the sponsor submitted ITCs that compared the efficacy of NI plus PDC to standard of care IO-based treatments currently funded in Canada. The ITCs that were performed were based on the pivotal CheckMate 9LA trial of NI plus PDC and four comparators trials contributing to three comparisons: 1) pembrolizumab plus PDC in patients with non-squamous NSCLC (KEYNOTE189), 2) pembrolizumab plus PDC in squamous NSCLC patients (KEYNOTE 407), and 3) pembrolizumab monotherapy in high PD-L1 expression (≥50%) and mixed histology NSCLC patients (KEYNOTE 024 and KEYNOTE 042). The data from the full intent-to-treat population from CheckMate 9LA trial were used in the ITCs despite patient population differences compared with the comparator trials with respect to PD-L1 expression level and histology; this was based on the assumption that histology and PD-L1 expression levels do not modify treatment effect. The primary ITC results showed comparable, statistically non-significant differences in OS, PFS and ORR when NI plus PDC was compared to IO-based treatment for each comparison. In sensitivity analyses, the results did not change significantly when data from the CheckMate 9LA based on PD-L1 expression (≥1%, >1%) and histology were used (non-squamous and squamous). The ITCs represent quantitative estimates of treatment effect over the first year of treatment with NI plus PDC relative to other IO-based regimens. Given the identified limitations of the ITC, which include heterogeneity of study populations, differential treatment effects in the common comparator of chemotherapies, varied trial designs, and lengths of follow-up, the findings of the ITC should be interpreted with caution.

8 Comparison with Other Literature

Data from the CheckMate 227 trial were included in the sponsor's submission to CADTH for the reimbursement of NI plus PDC for the first-line treatment of patients with metastatic or recurrent NSCLC without EGFR or ALK tumour aberrations. Since the pivotal trial supporting the submission, CheckMate 9LA, provided efficacy data based on 12.7 months of follow-up, the CheckMate 227 trial data were used to inform the sponsor's submitted pharmacoeconomic model on the long-term efficacy of NI compared to PDC. Published data from the CheckMate 227 trial provided efficacy data for NI based on a minimum follow-up of 29.3 months at the final analysis (DBL: July 2, 2019)[21], and a median follow-up of 43.1 months at an updated analysis.[25] Further, it also provided additional safety data on the NI combination. The sponsors submitted model incorporates data based on 37.7 months of trial follow-up.[10] The CheckMate 227 trial did not meet the selection criteria of the CADTH systematic review, which is summarized in section 6 of this report; therefore, the trial and its results are summarized in this section. The CheckMate 227 trial was a multi-group trial that compared the efficacy of different nivolumab-based regimens to PDC. The purpose of this section is to summarize the evidence from this trial, with a focus on the comparison of NI to PDC.

Methods

CheckMate 227 was an open-label, multi-part phase III trial conducted in previously untreated adult patients with stage IV metastatic or recurrent NSCLC. Eligible patients had measurable disease by CT or MRI per RECIST version 1.1 criteria, an ECOG PS of 0 or 1, and were naïve to prior systemic anticancer therapy (including EGFR and ALK inhibitors) for advanced or metastatic disease. Patients with known EGFR mutations or ALK translocations, untreated or symptomatic CNS metastases, or autoimmune disease were excluded. The trial was conducted in two parts:

- Part 1a: conducted in patients with PD-L1 expressing tumours
- Part 1b: conducted in patients with PD-L1 non-expressing tumours
- Part 2: conducted in patients regardless of PD-L1 expression

Part 1

A schematic of Part 1 of the CheckMate 227 trial is provided in Figure 19. In Part 1, patients were randomly assigned in a 1:1:1 ratio to treatment and were stratified based on tumour histology (squamous versus non-squamous) and PD-L1 status):[3]

- In Part 1a, patients with PD-L1 expression ≥1% were assigned to either NI (nivolumab 3 mg/kg of body weight every two weeks and ipilimumab 1 mg/kilogram every six weeks), nivolumab monotherapy (240 mg every two weeks) or PDC alone.
- In Part 1b, patients with PD-L1 <1% were assigned to either NI, nivolumab (360 mg every three weeks) plus PDC, or PDC alone.

The dosing and schedule details for the nivolumab-based treatment groups are provided in Figure 19 and Table 44. PDC regimens based on histology were administered to patients every three weeks for up to four cycles:

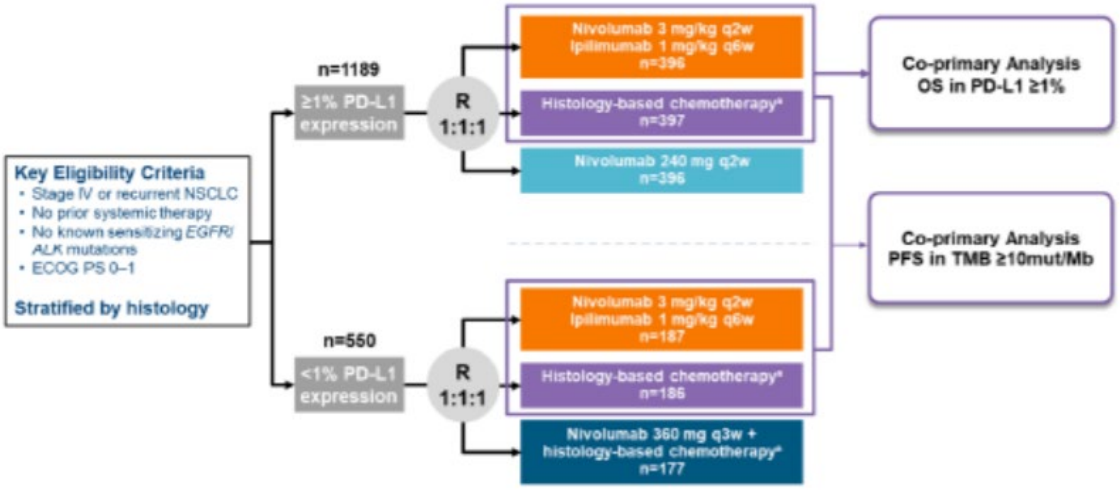
- Patients with squamous NSCLC:
  - Gemcitabine (1,000 or 1,250 mg/m^2) plus cisplatin (75 mg/m^2),
  - Gemcitabine (1,000 mg/m^2) plus carboplatin (AUC 5).[21]
- Patients with non-squamous NSCLC:
  - Pemetrexed (500 mg/m^2 BSA) plus cisplatin (75 mg/m^2),
  - Pemetrexed (500 mg/m^2 BSA) plus carboplatin (AUC 5 or 6).

Patients with non-squamous histology who achieved a response or stable disease after four cycles were also provided with the option of receiving pemetrexed maintenance therapy (500 mg/m^2) until disease progression or unacceptable toxicity.[21]

Patients with non-squamous NSCLC who had stable disease or a response after four cycles of PDC or nivolumab plus PDC could have also received maintenance therapy with pemetrexed or pemetrexed plus nivolumab.

All patients received treatment until disease progression, unacceptable toxicity or completion per protocol (≤ two years for immunotherapy). Treatment beyond disease progression was permitted for patients receiving nivolumab or NI for up to two years if, based on investigator assessment, they showed clinical benefit and no rapid disease progression, were tolerating study treatment, had stable PS, and treatment beyond progression would not delay an imminent intervention to prevent serious complications of disease. Based on these criteria, patients who progressed on nivolumab plus PDC were permitted to continue treatment with nivolumab. Treatment was discontinued permanently if patients further progressed, defined as an additional 10% increase in tumour burden from time of initial disease progression. Treatment beyond progression was not permitted for patients randomized to PDC. Subsequent treatment was determined at the physician's discretion. Crossover between treatment groups was not permitted.[21]

Figure 19: CheckMate 227 Part 1Trial Design



[a] Squamous (SQ) histology: gemcitabine with cisplatin or gemcitabine with carboplatin
Non-squamous (NSQ) histology: pemetrexed with cisplatin or pemetrexed with carboplatin. Subjects with stable disease or response after cycle 4 could have continued pemetrexed alone as maintenance therapy until disease progression or unacceptable toxicity.

ALK = anaplastic lymphoma kinase; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; IV = intravenous; mut/Mb = mutations per megabase; NSCLC = non-small cell lung cancer; OS = overall survival; PD-L1 = programmed cell death ligand 1; PFS = progression-free survival; PS = performance status; TMB = tumour mutational burden.

Source: EMA Assessment Report [3]

Part 2

In Part 2 of CheckMate 227, patients were randomized 1:1 to one of the following treatments:

- [redacted].[72] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed)*
- [redacted][72] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed)*

[redacted].[72] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed)*

Patients were stratified based on the following factors:

- [redacted][72] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed)*
- [redacted][72] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed)*
- [redacted][72] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed)*

A comparison of the trial characteristics of Parts 1 and 2 of the CheckMate 227 trial and the CheckMate 9LA trial is provided in Table 44.

Table 44: Summary of Trial Characteristics of CheckMate 9LA and CheckMate 227

	CheckMate 9LA	CheckMate 227 - Part 1	CheckMate 227 - Part 2
Phase	3	3	3
N randomized	719 (n=361 NI plus PDC; n=358 PDC)	1739 (n=583 NI; n=583 PDC; n=396 nivolumab; n=177 nivolumab plus PDC)	[redacted]
Population	First-line stage IV or recurrent NSCLC regardless of PD-L1 expression, ECOG 0-1, excluding patients with activating EGFR mutations or ALK genomic aberrations sensitive to targeted therapy		
Intervention	• Nivolumab 360 mg Q3W + ipilimumab 1mg/kg Q6W + 2 cycles of histology dependent PDC	• Nivolumab 3mg/kg Q2W + ipilimumab 1mg/kg Q6W • Nivolumab monotherapy 240 mg	• Nivolumab 360 mg Q3W + 4 cycles of PDC ± optional pemetrexed maintenance
Comparator	4 cycles of PDC + optional pemetrexed maintenance	4 cycles of PDC + optional pemetrexed maintenance	4 cycles of PDC + optional pemetrexed maintenance
Primary or co-primary endpoints	• OS	• OS for NI vs. PDC in patients with PD-L1 ≥1% • PFS* for NI vs. PDC in patients with TMB ≥ 10 mut/M[b] regardless of PD-L1 expression	• OS in NSQ patients
Hierarchically tested secondary endpoints	• PFS* • ORR*	• PFS* for nivolumab plus PDC vs. PDC in patients with PD-L1 <1% • OS for nivolumab plus PDC vs. PDC in patients with PD-L1 <1%	[redacted]

	CheckMate 9LA	CheckMate 227 - Part 1	CheckMate 227 - Part 2
		• OS for nivolumab monotherapy vs. PDC in patients with PD-L1 ≥50% • OS for NI vs. PDC in patients with high TMB regardless of PD-L1 expression	[redacted]
Other secondary endpoints	• Efficacy (OS, PFS*, ORR*) by PD-L1 and TMB	• ORR* for NI and PDC in all randomized patients and those with PD-L1 ≥1% and <1% • OS, PFS*, ORR*, for NI, nivolumab plus PDC, and PDC in patients with PD-L1 <1% • Overall safety and tolerability of NI, nivolumab plus PDC, and nivolumab compared with PDC • OS for NI, nivolumab plus PDC, and PDC in patients with PD-L1 <1% • OS, ORR*, and PFS* for NI and nivolumab in patients with PD-L1 ≥1% and ≥50% • OS for NI, PDC by PD-L1 subgroups • OS by a combination of PD-L1 and TMB for NI and PDC	[redacted]

*PFS and ORR were assessed by BICR

ALK = anaplastic lymphoma kinase; BICR = blinded independent central review; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; IV = intravenous; NI = nivolumab plus ipilimumab; NI plus PDC = nivolumab plus ipilimumab plus 2 cycles of platinum-based chemotherapy; pt = platinum; NSCLC = non-small cell lung cancer; NSQ = non-squamous; ORR = objective response rate; OS = overall survival; PDC = platinum doublet chemotherapy; PD-L1 = programmed death ligand 1; PFS = progression-free survival; QXW = every X weeks; TMB = tumour mutational burden.

Sources: Hellman et al., 2019[21], Reck et al., 2020[2]

(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed)

Endpoints

The primary and secondary endpoints for Part 1 and Part 2 of the CheckMate 227 trial are listed in Table 44.

In Part 1, there were two co-primary endpoints that included 1) OS in patients with PD-L1 expression ≥1%, and 2) PFS assessed by BICR in patients with TMB ≥10 mut/Mb regardless of PD-L1 expression. [redacted].[72] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed)* Definitions of OS and PFS, as well as the censoring rules used in analyses, aligned with the outcome definitions and censoring rules used in the CheckMate 9LA trial.

[redacted].[72] *(Non-disclosable*

information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed)

Statistical Analyses

Part 1

In Part 1, the co-primary endpoints of OS and PFS were tested based on a prespecified statistical significance alpha (P=0.05) split between the endpoints (P=0.025). An interim analysis was pre-specified for the primary endpoint of OS, whereby alpha values of 0.0001 and 0.007 were spent on an interim ORR and OS analysis, respectively. [redacted].[72] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed)* An alpha of 0.023 was used for the final analysis of OS.[21]

For the secondary endpoints that were included in the statistical testing hierarchy, statistical testing was conditional on the co-primary endpoints achieving statistical significance. The following secondary endpoints were tested under the same alpha as the primary endpoint:

- OS and PFS per BICR for nivolumab plus PDC versus PDC in patients with PD-L1 <1%;
- OS for nivolumab monotherapy versus PDC in patients with PD-L1 ≥50%;
- and OS for NI versus PDC in patients with high TMB regardless of PD-L1 expression.[21,72]

The secondary outcomes that were not included in statistical testing hierarchy are listed in Table 44. Analyses of these endpoints were considered descriptive. Exploratory endpoints assessed in the trial included ORR, DOR, and safety. AEs were investigator assessed and graded according to NCI CTCAE version 4 criteria.[21]

In the event the proportional hazard assumption was violated for any time-to-event endpoint, HRs were still reported to provide conventional estimates of overall average effects, supplemented by median and landmark estimates.[21]

Part 2

[redacted].[72] [redacted].[72] [redacted].[72] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed)*

Results

Part 1

Between August 2015 and November 2016, a total of 2,876 patients were enrolled in Part 1 of the CheckMate 227 and 1,739 patients underwent randomization. Of the patients randomized, 1,189 had a PD-L1 expression of ≥1% and 550 had PD-L1 expression of <1%. The baseline characteristics of patients in Part 1 are summarized in Table 45, and were balanced across the treatment groups for patients with PD-L1 ≥1% and PD-L1 <1%. The median duration of therapy was 4.2 months (range, 0.03 to 25.5) in the NI group and 2.7 months (range, 0.03-37.6+) in the PDC group. The median number of doses of nivolumab and ipilimumab received by patients in the NI group was nine (range, 1-55) and three (range, 1-19), respectively.

Among all patients with a PFS event per BICR, subsequent systemic therapy was received by 43.6% of patients in the NI group and 55.8% in the PDC group. In the NI group, chemotherapy was the most common subsequent systemic therapy (40.4%), followed by targeted therapy (6.6%), immunotherapy (6.4%), and experimental drugs (1.2%). In the PDC group, immunotherapy was the most common subsequent systemic therapy (42.4%), followed by chemotherapy (30.6%), targeted therapy (5.9%), and experimental drugs (1.8%). The proportion of patients who received subsequent radiotherapy and surgery were similar between the NI versus PDC groups (20.4% versus 22.8% and 2.8% versus 3.8%, respectively).[21]

Table 45: Baseline Characteristics of Patients in Part 1 of the CheckMate 227 Trial

	PD-L1 ≥1%		PD-L1 <1%		All Patients	
	NI N=396	PDC N=397	NI N=187	PDC N=186	NI N=583	PDC N=583
Age (year)						
Median (range)	64.0 (26–84)	64.0 (29–87)	63.0 (34–87)	64.0 (30–80)	64.0 (26–87)	64.0 (29–87)
Age category, n (%)						
<65 years	199 (50.3)	207 (52.1)	107 (57.2)	98 (52.7)	306 (52.5)	305 (52.3)
≥65 to <75 years	157 (39.6)	149 (37.5)	62 (33.2)	74 (39.8)	219 (37.6)	223 (38.3)
≥75 years	40 (10.1)	41 (10.3)	18 (9.6)	14 (7.5)	58 (9.9)	55 (9.4)
Sex, %						
Male	255 (64.4)	260 (65.5)	138 (73.8)	125 (67.2)	393 (67.4)	385 (66.0)
Region, n (%)						
North America	40 (10.1)	55 (13.9)	16 (8.6)	15 (8.1)	56 (9.6)	70 (12.0)
Europe	199 (50.3)	201 (50.6)	103 (55.1)	92 (49.5)	302 (51.8)	293 (50.3)
Asia	81 (20.5)	81 (20.4)	40 (21.4)	43 (23.1)	121 (20.8)	124 (21.3)
Rest of world[a]	76 (19.2)	60 (15.1)	28 (15.0)	36 (19.4)	104 (17.8)	96 (16.5)
ECOG PS, n (%)						
0	135 (34.1)	134 (33.8)	69 (36.9)	57 (30.6)	204 (35.0)	191 (32.8)
1	260 (65.7)	259 (65.2)	117 (62.6)	127 (68.3)	377 (64.7)	386 (66.2)
≥2	1 (0.3)	3 (0.8)	1 (0.5)	1 (0.5)	2 (0.3)	4 (0.7)
Not reported	0	1 (0.3)	0	1 (0.5)	0	2 (0.3)
Smoking Status, n (%)						
Never smoked	56 (14.1)	51 (12.8)	23 (12.3)	27 (14.5)	79 (13.6)	78 (13.4)
Current or former smoker	334 (84.3)	340 (85.6)	163 (87.2)	159 (85.5)	497 (85.2)	499 (85.6)
Unknown	6 (1.5)	6 (1.5)	1 (0.5)	0	7 (1.2)	6 (1.0)

	PD-L1 ≥1%		PD-L1 <1%		All Patients	
	NI N=396	PDC N=397	NI N=187	PDC N=186	NI N=583	PDC N=583
Tumour Histology, n (%)						
Squamous	117 (29.5)	116 (29.2)	46 (24.6)	46 (24.7)	163 (28.0)	162 (27.8)
Non-squamous	279 (70.5)	281 (70.8)	140 (74.9)	140 (75.3)	419 (71.9)	421 (72.2)
Not reported	0	0	1 (0.5)	0	1 (0.2)	0
Metastasis, n (%)						
CNS	41 (10.4)	40 (10.1)	23 (12.3)	11 (5.9)	64 (11.0)	51 (8.7)
Liver	71 (17.9)	85 (21.4)	51 (27.3)	45 (24.2)	122 (20.9)	130 (22.3)
Bone	108 (27.3)	100 (25.2)	55 (29.4)	53 (28.5)	163 (28.0)	153 (26.2)
PD-L1 status, n (%)						
Quantifiable	396 (100.0)	397 (100.0)	187 (100.0)	186 (100.0)	583 (100.0)	583 (100.0)
<1%	0	0	187 (100.0)	186 (100.0)	187 (32.1)	186 (31.9)
≥1%	396 (100.0)	397 (100.0)	0	0	396 (67.9)	397 (68.1)
1–49%	191 (48.2)	205 (51.6)	NA	NA	191 (32.8)	205 (35.2)
≥50%	205 (51.8)	192 (48.4)	NA	NA	205 (35.2)	192 (32.9)

CNS = central nervous system; NI = nivolumab plus ipilimumab; PDC = platinum doublet chemotherapy; PD-L1 = programmed death-ligand 1.

[a] Includes Argentina, Australia, Brazil, Chile, Columbia, Israel, Lebanon, Mexico, Peru, and South Africa

Sources: Hellman et al., 2019[21]

Efficacy Outcomes

Part 1

A summary of the efficacy results from Part 1 of the CheckMate 227 trial is provided in Table 46.

Overall Survival

At the time of the interim analysis, the difference in OS between the treatment groups was not statistically significant and the IDSMC recommended that the trial continue. The interim OS results were not reported.[20]

Final Analysis (DBL: July 2, 2019)

At the time of the final analysis of OS the minimum follow-up was 29.3 months. At this time, the difference in OS between the treatment groups was statistically significant and favoured treatment with NI over PDC; in patients with PD-L1 expression of ≥1%, the median OS was longer in the NI group at 17.1 months (95% CI, 15.0 to 20.1) compared to 14.9 months (95% CI, 12.7 to 16.7) in the PDC group and NI was associated with a reduced risk of death compared to PDC (HR=0.79; 97.72% CI, 0.65 to 0.96; P=0.007). The KM curves for OS are presented in Figure 20. The curves show an early detriment in OS in the NI group compared to PDC; however, at approximately seven months, the curves cross (indicating a violation of the proportional hazards assumption), and thereafter, there is a clear separation of the curves and higher patient survival that is sustained in the NI group that is sustained starting at approximately nine months.

The results of prespecified subgroup analyses of OS are presented in Figure 20, and show a consistent OS benefit in all patient subgroups in favour of NI over PDC, with the exception of patients who had never smoked and patients with liver metastases, where OS favoured treatment with PDC.

The OS data for patients with PD-L1 expression <1% (HR=0.62; 95% CI, 0.48 to 0.78) and all randomized patients (HR=0.73; 95% CI, 0.64 to 0.84) showed similar results to patients with PD-L1 ≥1%.

Table 46: Summary of Efficacy Endpoints in the Part 1 of the CheckMate 227 Trial

	PD-L1 ≥1%		PD-L1 <1%		All Patients	
	NI N=396	PDC N=397	NI N=187	PDC N=177	NI N=583	PDC N=583
OS						
Median, months (95% CI)	17.1 (15.0-20.1)	14.9 (12.7-16.7)	17.2 (12.8–22.0)	12.2 (9.2–14.3)	17.1 (15.2–19.9)	13.9 (12.2–15.1)
HR (CI) P value	0.79 (97.72% CI, 0.65-0.96)* 0.007[a]		0.62 (95% CI, 0.48–0.78) NA		0.73 (95% CI, 0.64–0.84)* NA	
1-year OS rate, %	63	56	60	51	62	54
2-year OS rate, %	40	33	40	23	40	30
3-year OS rate, %	33	22	34	15	NR	NR
PFS						
Median, months (95% CI)	5.1 (4.1-6.3)	5.6 (4.6-5.8)	5.1 (3.2-6.4)	4.7 (4.2-5.6)	5.1 (4.1-5.7)	5.5 (4.6-5.6)
HR (95% CI)	0.82 (0.69–0.97)*		0.75 (0.59–0.96)*		0.79 (0.69–0.91)*	
ORR						
N responders	142	119	51	43	193	162
ORR % (95% CI)	35.9 (31.1–40.8)	30.0 (25.5–34.7)	27.3 (21.0–34.3)	23.1 (17.3–29.8)	33.1 (29.3–37.1)	27.8 (24.2–31.6)

	PD-L1 ≥1%		PD-L1 <1%		All Patients	
	NI N=396	PDC N=397	NI N=187	PDC N=177	NI N=583	PDC N=583
DOR						
Median, months (95% CI)	23.2 (15.2–32.2)	6.2 (5.6–7.4)	18.0 (12.4-28.6)	4.8 (3.7-5.8)	19.6 (16.1-28.6)	5.8 (5.4-6.9)
TTR						
Median, months (95% CI)	2.0 (NR)	1.6 (NR)	2.8 (NR)	1.5 (NR)	2.7 (NR)	1.6 (NR)
Confirmed BOR, n%						
CR	23 (5.8)	7 (1.8)	4 (2.1)	2 (1.1)	27 (4.6)	9 (1.5)
PR	119 (30.1)	112 (28.2)	47 (25.1)	41 (22.0)	166 (28.5)	153 (26.2)
SD	116 (29.3)	190 (47.9)	73 (39.0)	97 (52.2)	189 (32.4)	287 (49.2)
PD	90 (22.7)	50 (12.6)	45 (24.1)	24 (12.9)	135 (23.2)	74 (12.7)
UTD	48 (12.1)	38 (9.6)	18 (9.6)	22 (11.8)	66 (11.3)	60 (10.3)

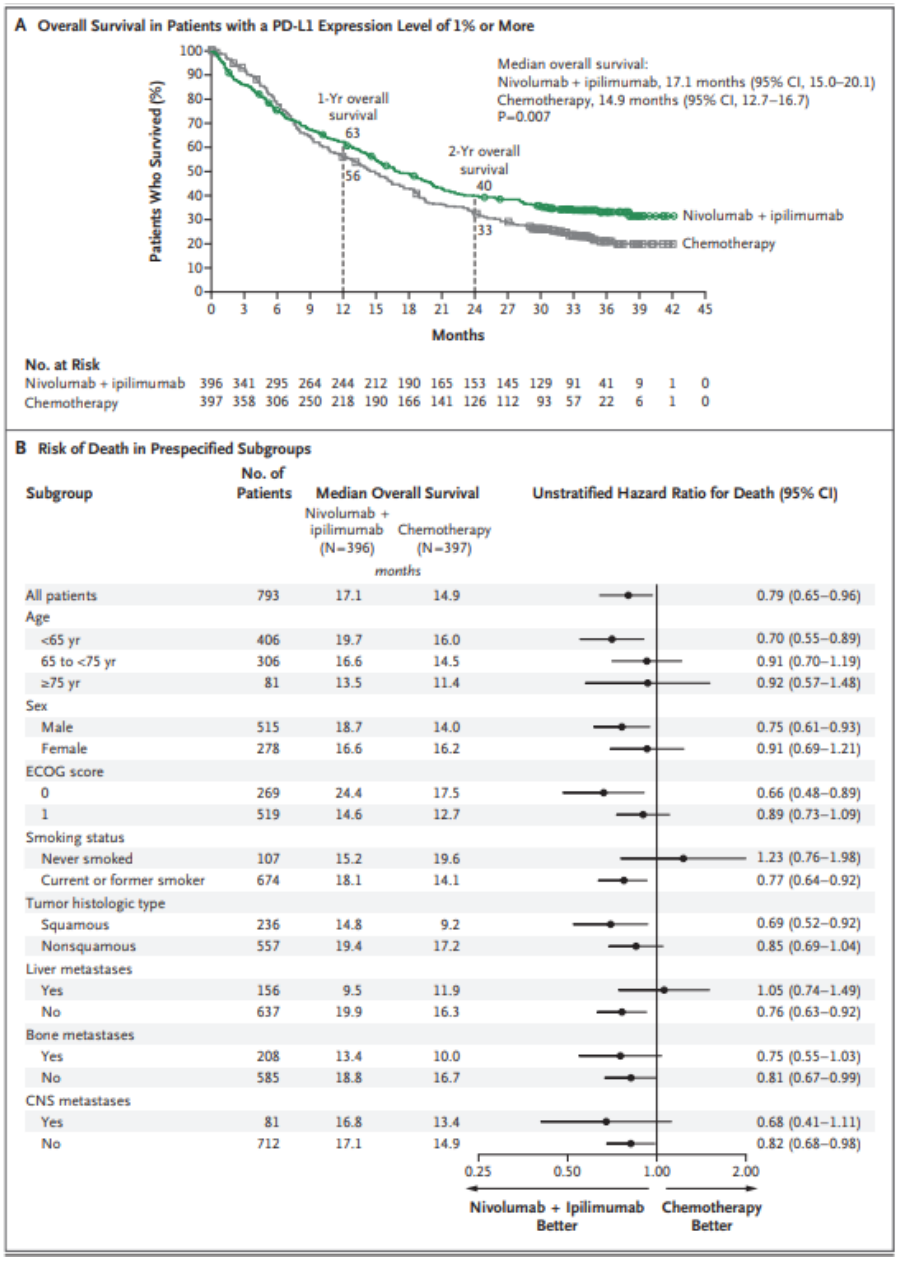
BOR = best overall response; CI = confidence interval; DOR = duration of response; CR = complete response; HR = hazard ratio; NA = not applicable; NI = nivolumab plus ipilimumab; NR = not reported; ORR = objective response rate; OS = overall survival; PD = progressive disease; PD-L1 = programmed death-ligand 1; PFS = progression-free survival PR = partial response; SD = stable disease; UTD = unable to determine; TTR = time to response.

*Hazard ratio is non-proportional. It summarizes the overall estimate of benefit but should be interpreted in the context of the shape of the curves.

[a] This is the co-primary endpoint of OS for NI versus PDC in patients with PD-L1 ≥1%.

Source: Hellman et al., 2019[21], Peters et al., 2019.[73] Ramalingam et al., 2020[25]

Figure 20: OS in Patients with PD-L1 ≥1% (Part 1)



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Updated Analysis (DBL: February 28, 2020)

An updated analysis of OS was conducted after a median follow-up of 43.1 months. For patients with PD-L1 ≥1%, the difference in OS continued to favour treatment with NI compared to PDC (HR=0.79; 95% CI, 0.67 to 0.93). Similarly, patients with PD-L1 <1% also continued to derive greater benefit from NI over PDC (HR=0.64; 95%CI, 0.51 to 0.81).[25]

Progression-free Survival

Co-Primary Endpoint

The other co-primary endpoint of the CheckMate 227 trial was PFS assessed by BICR in patients with TMB ≥10 mut/Mb regardless of PD-L1 expression. PFS results were based on a minimum follow-up of 11.2 months (DBL: January 24, 2018).[20] Among patients with high TMB (≥10 mut/MB), median PFS was longer in the NI group at 7.2 months (95% CI, 5.5 to 13.2) compared to the PDC group at 5.5 months (95% CI, 4.4 to 5.8). NI was associated with a lower risk of progression or death compared to the PDC group (HR=0.58; 95% CI, 0.41 to 0.81; P<0.001). An analysis of PFS was also conducted for all randomized patients regardless of TMB or PD-L1 status; results for all randomized patients showed a shorter median PFS for patients in the NI group at 4.9 months (95%CI, 4.1 to 5.6) compared to 5.5 months (95% CI, 4.6 to 5.6) in the PDC group (HR=0.83; 95%CI, 0.72 to 0.96).[20]

Final Analysis (DBL: July 2, 2019)

An analysis of PFS was also provided alongside the co-primary endpoint of OS at the time of the final analysis. For patients with PD-L1 <1%, the median PFS was longer in the NI group at 5.1 months (95% CI, 3.2 to 6.4) compared to 4.7 months (95% CI, 4.1 to 5.6) in the PDC group (HR=0.75; 95% CI, 0.59 to 0.96). However, for patients with PD-L1 ≥1%, median PFS was shorter in the NI group at 5.1 months (95% CI, 4.1 to 6.3) compared to 5.6 months (95% CI, 4.6 to 5.8) in the PDC group (HR=0.82; 95% CI, 0.69 to 0.97). The median PFS was also shorter when assessed among all randomized patients; the median PFS was 5.1 months (95% CI, 4.1 to 5.7) in the NI group compared to 5.5 months (95% CI, 4.6 to 5.6) in the PDC group.[21]

Updated Analysis (DBL: February 28, 2020)

At the updated analysis, similar results for PFS were observed. For patients with PD-L1 <1%, median PFS continued to be longer in the NI group at 5.1 months than the PDC group at 4.7 months (HR=0.75; 95% CI, 0.59 to 0.95). For patients with PD-L1 ≥1%, median PFS was shorter in the NI group at 5.1 months than the PDC group at 5.6 months (HR=0.81; 95% CI, 0.69 to 0.96).[25]

Secondary Endpoints: The secondary endpoints were tested hierarchically based on the statistical significance of the primary endpoint (i.e., OS for NI versus PDC in patients with PD-L1 ≥1%). The secondary endpoints tested in the hierarchy are available in Table 46, and are briefly described below:[21]

- PFS per BICR for nivolumab plus PDC versus PDC in patients with PD-L1 <1%:
  - Median PFS was longer in the NI group at 5.1 months (95% CI, 3.2 to 6.4) compared to 4.7 months (95% CI, 4.2 to 5.6) in the PDC group (HR=0.73; 97.72% CI, 0.56 to 0.95; p=0.007).[21]
- OS for nivolumab plus PDC versus PDC in patients with PD-L1 <1%:
  - Median OS was longer in the NI group at 15.2 months (95% CI, 12.3 to 19.8) compared to 12.2 months (95% CI, 9.2 to 14.3) in the PDC group (HR=0.78; 97.72% CI, 0.60 to 1.02; p=0.035).[21]
- OS for nivolumab monotherapy versus PDC in patients with PD-L1 ≥50%:
  - Since difference in OS between nivolumab plus PDC versus PDC in patients with PD-L1 <1% did not meet the nominal significance level of 0.023 (HR=0.78; 97.72% CI, 0.60-1.02; p=0.035), the sponsor did not conduct formal statistical testing of the final secondary endpoint of OS for nivolumab monotherapy versus PDC in patients with PD-L1 ≥50%.[21]

The other secondary endpoints assessed were not included in the statistical testing hierarchy and also favoured treatment with NI, with the exception of PFS for patients with PD-L1 expression ≥1%. This analysis showed longer median PFS in the PDC group at 5.6 months (95% CI, 4.6 to 5.8) compared to at 5.1 months in the NI group (95%CI, 4.1 to 6.3).[21]

Part 2

Overall Survival

[redacted][74] [redacted].[74] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed)*

Figure 21: Kaplan Meier Plot of OS for Nivolumab plus PDC and PDC in Non-Squamous Patients in CheckMate 227 Part 2

Source: Clinical Summary Figure 7[74]

(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed)

Safety

The safety data presented in this section are based on Part 1 of the CheckMate 227 trial and are summarized in Table 47.

The analysis of safety data was based on a minimum follow-up of 28.3 months; however, data on treatment-related SAEs were based on a minimum follow-up of 29.3 months. Safety analyses focused on treatment emergent AEs and SAEs reported during the time between the first dose of study drug administered in the trial to the 30 days after patients' last treatment dose.

Treatment-related AEs of any grade were similar between the treatment groups (76.7% in the NI group versus 81.9% in the PDC group). Diarrhea and rash were the most common AEs in patients treated with NI and these occurred more frequently when compared (versus) to PDC (17.0% versus 9.6% and 17.0% versus 5.3%, respectively). Conversely, compared to NI, the incidence of all grade fatigue, decreased appetite, nausea, anemia, and neutropenia were higher among patients treated with PDC. The incidence of grade 3-4 treatment-related AEs was similar in the treatment groups, except for anemia (11.6% versus 1.4%) and neutropenia (9.5% versus 0%), which were all increased in the PDC group.[21] Treatment-related SAEs of any grade (24.5% versus 13.9%) and grade 3 or 4 (18.4% versus 10.7%) were higher in the NI group compared to PDC. Updated safety data based on a median follow-up of 36.3 months (DBL: February 28, 2020) continued show similar proportions of treatment-related AEs of any grade and grade 3-4 in the NI and PDC groups (77% versus 82%, and 33% versus 36%, respectively).[25]

Treatment-related AEs leading to treatment discontinuation were more frequently reported in patients treated with NI (all grade:18.1%; grade 3 or 4: 12.3%) compared to PDC (all grade: 9.1%; grade 3 or 4: 4.9%). In the NI group, treatment discontinuations were due to treatment-related AEs that resulted in the discontinuation of either ipilimumab alone or NI, as the discontinuation of nivolumab alone was not permitted in the trial. A total of 18 patients (3.1%) experienced treatment-related AEs that led to the discontinuation of ipilimumab earlier than the discontinuation of nivolumab.[21]

Deaths were attributed to treatment in eight patients (1.4%) in the NI group and six patients (1.1%) in the PDC group; in the NI group, these deaths were from pneumonitis (n=4) and shock, myocarditis, acute tubular necrosis, and cardiac tamponade (n=1 each). Treatment-related deaths in the PDC group were from sepsis (n=2) and febrile neutropenia with sepsis, multiple brain infarctions, interstitial lung disease, and thrombocytopenia (n=1 each).[21]

Table 47: Treatment-Related AEs Among All Randomized Patients Receiving NI and PDC in the CheckMate 227 Trial Part 1

Adverse Event	Nivolumab plus Ipilimumab (N=576)		Chemotherapy (N=570)	
	Any Grade	Grade 3–4	Any Grade	Grade 3–4
	number of patients (percent)			
Treatment-related adverse events				
All events	442 (76.7)	189 (32.8)	467 (81.9)	205 (36.0)
Reported in ≥15% of patients				
Diarrhea	98 (17.0)	10 (1.7)	55 (9.6)	4 (0.7)
Rash	98 (17.0)	9 (1.6)	30 (5.3)	0
Fatigue	83 (14.4)	10 (1.7)	108 (18.9)	8 (1.4)
Decreased appetite	76 (13.2)	4 (0.7)	112 (19.6)	7 (1.2)
Nausea	57 (9.9)	3 (0.5)	206 (36.1)	12 (2.1)
Anemia	22 (3.8)	8 (1.4)	188 (33.0)	66 (11.6)
Neutropenia	1 (0.2)	0	98 (17.2)	54 (9.5)
Treatment-related serious adverse events	141 (24.5)	106 (18.4)	79 (13.9)	61 (10.7)
Treatment-related adverse events leading to discontinuation†	104 (18.1)	71 (12.3)	52 (9.1)	28 (4.9)
Treatment-related death‡	8 (1.4)	—	6 (1.1)	—

* The determination that an adverse event was related to a trial treatment was made by the investigators. The minimum follow-up for safety analyses was 28.3 months, except for treatment-related serious adverse events, which had a minimum follow-up of 29.3 months. All treatment-related adverse events and serious adverse events were reported during the time between the first dose of a trial treatment and 30 days after the last dose.

† For nivolumab plus ipilimumab, these events included treatment-related adverse events leading to the discontinuation of ipilimumab alone or the discontinuation of both nivolumab and ipilimumab; the discontinuation of nivolumab alone was not permitted. Adverse events leading to the discontinuation of ipilimumab earlier than the discontinuation of nivolumab occurred in 18 patients (3.1%).

‡ Treatment-related deaths in the group that received nivolumab plus ipilimumab were from pneumonitis (in 4 patients) and from shock, myocarditis, acute tubular necrosis, and cardiac tamponade (in 1 patient each). Deaths in the chemotherapy group were from sepsis (in 2 patients) and from febrile neutropenia with sepsis, multiple brain infarctions, interstitial lung disease, and thrombocytopenia (in 1 patient each).

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The incidence of treatment-related irAEs in patients who received NI are reported in Table 48. The most common treatment-related irAEs of any grade with a potential immunologic cause among patients in the NI group were skin reactions (34.0%), endocrine events (23.8%), gastrointestinal (18.2%), and hepatic (15.8%) AEs.[21]

Table 48: Treatment-Related irAEs Among All Randomized Patients Receiving NI and Nivolumab in the CheckMate 227 Trial

Treatment-Related Select AEs*	All Treated Patients			
	Nivolumab plus Ipilimumab† (N=576)		Nivolumab‡ (N=391)	
	Any Grade	Grade 3–4	Any Grade	Grade 3–4
	number of patients (percent)			
Skin	196 (34.0)	24 (4.2)	83 (21.2)	4 (1.0)
Endocrine	137 (23.8)	24 (4.2)	51 (13.0)	2 (0.5)
Gastrointestinal	105 (18.2)	14 (2.4)	50 (12.8)	4 (1.0)
Hepatic	91 (15.8)	47 (8.2)	42 (10.7)	15 (3.8)
Pulmonary	48 (8.3)	19 (3.3)	30 (7.7)	6 (1.5)
Renal	25 (4.3)	4 (0.7)	6 (1.5)	3 (0.8)
Hypersensitivity/Infusion reaction	23 (4.0)	0	17 (4.3)	2 (0.5)

Minimum follow-up was 28.3 months.
*Select AEs are those with potential immunologic etiology that require frequent monitoring/intervention; includes events reported between first dose and 30 days after last dose of study drug.
†Nivolumab (3 mg/kg every 2 weeks) plus ipilimumab (1 mg/kg every 6 weeks).
‡Study treatment only in PD-L1 ≥1% population; nivolumab (240 mg every 2 weeks).
AE, adverse event.

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Critical Appraisal

The CheckMate 227 trial used a complex, two-part, multi-group design to compare the efficacy of nivolumab-based regimens to PDC for the first-line treatment of patients with metastatic or recurrent NSCLC. The CADTH Methods Team's appraisal of the CheckMate 227 trial was focused on Part 1, as data from this phase were used to inform the sponsor's submitted economic model.

- The trial was open-label, and as such, patients and investigators were not blinded to treatment assignment. An independent IDSMC provided oversight of the collection of efficacy and safety data. OS was the primary endpoint of the trial and is an objective measure that is unlikely to be biased by the open-label study design. To minimize the potential biases associated with an open-label design on other endpoints, assessment of PFS and ORR were conducted by BICR. Therefore, while the efficacy outcomes assessed in the trial are unlikely to be biased by this trial design, subjective outcomes including safety may have been influenced by investigator or patient knowledge of the assigned treatment of patients in favour of the NI treatment group.
- At the final analysis of OS in patients with PD-L1 expression ≥1%, median OS estimates (17.1 months versus 14.9 months) and one- (63% versus 56%) and two-year OS rates (40% and 33%) were all higher in the NI group compared to PDC, and the reported HR indicated a significant reduction in the risk of death with NI when compared to PDC (HR=0.79; 97.72% CI, 0.65 to 0.96).[21,73] However, the OS curves crossed, and the authors reported that the proportional hazard assumption was not met.[21] Consequently, the OS benefit of NI compared to PDC was estimated by way of a descriptive analysis based on the shape of the survival curves for the two treatment groups, which suggested that patients treated with NI experienced a slight detriment during the initial months of treatment with NI but thereafter, the curves demonstrated a long-term benefit in OS over PDC. The analysis of PFS also showed non-proportional hazards and a similar pattern of clinical benefit with NI over PDC. Evidence of non-proportional hazards is common in oncology where trials often compare new therapies with different mechanisms of action to conventional treatments that may have a different course of disease progression. When the proportional hazard assumption is violated in trials demonstrating superiority, treatment effect estimates are unlikely to reflect the entire trial period and often overestimate the magnitude of clinical benefit.[75] Therefore, there is the possibility that the clinical benefit associated with NI, in terms of OS and PFS estimates, may be overestimated in the CheckMate 227 trial.
- The sponsor indicated that the trial was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice guidelines.[20,21] The EMA reported that a Good Clinical Practice inspection conducted of the trial in 2019 revealed deficiencies related to a lack of measures that would prevent dissemination of trial

information to both authorized and non-authorized personnel, and the system in place was described as a non-robust and immature risk management system.[3] The deficiencies raised concern that amendments to the study protocol may have been data-driven.[3] It is unclear how these trial conduct issues influenced the trial results, but it is possible they could have biased outcomes in favour of investigational therapy with NI.

Naïve Comparison Between CheckMate 9LA and CheckMate 227:

- Baseline characteristics - CheckMate 9LA and CheckMate 227 were designed using very similar eligibility criteria; therefore, the distributions of baseline characteristics among patients included in either trial were also very similar except for a few characteristics. Compared to 9LA, the proportions of patients with PD-L1 status of ≥1% or ≥50% were higher in the 227 trial by 11.4% and 9.9%, respectively.[21] In 9LA, the proportions of patients at baseline who presented with CNS metastases was higher at 17.5% and 16.2% in the NI plus PDC and PDC groups, respectively.[3] The corresponding proportions in the 227 trial were 11.0% and 8.7%, respectively.[21] It is unlikely that the differences in PD-L1 expression level and CNS metastases would meaningfully impact patient outcomes since the treatment effect of NI-based treatment in each trial was observed independent of PD-L1 expression and the presence of CNS metastases.
- Treatment regimens - Aside from the addition of two cycles of PDC to the combination of NI, there were some other notable differences in the treatment regimens evaluated in CheckMate 9LA and CheckMate 227. The timing and dosing of nivolumab differed, where nivolumab was administered as a flat dose (360 mg every three weeks) in the 9LA trial versus a weight-based dose (3 mg/kg every two weeks) in the 227 trial. The dosing and schedule of ipilimumab was the same in each trial. The other notable difference was in the type of PDC administered to patients with squamous NSCLC. In the 9LA trial, patients with squamous histology received carboplatin plus paclitaxel, whereas in the 227 trial they received either gemcitabine plus cisplatin or gemcitabine plus carboplatin. The doses of carboplatin used in the 9LA and 227 trials were administered at AUC 6 and AUC 5, respectively.[3] Treatment crossover was not permitted in either trial. The use of subsequent anti-cancer therapies post-progression was higher in the PDC control group of each trial, with most patients receiving immunotherapy. The overall use of subsequent therapies was higher in the CheckMate 227 trial based on a longer duration of follow-up. When the OS rates at one year (refer below) in each treatment group of the trial are compared, patients in the NI and NI plus PDC groups had similar one-year survival but the PDC control group in the 227 trial performed better, by approximately 10%, than the PDC control group in the 9LA trial. This difference in OS is likely influenced by multiple factors related to patient characteristics and trial design features that includes differential treatment effects of the PDC regimens used in each trial.
- Efficacy – Data from the CheckMate 9LA trial are considered immature (60% maturity) and are based on a minimum follow-up of 12.7 months. The CheckMate 227 trial provides insight into the longer-term efficacy associated with the NI combination based on a minimum follow-up of 29.3 months at the final analysis[3] In the 227 trial, the OS rates at one-year were 62% in the NI group and 54% in the PDC group for all randomized patients.[73] The corresponding rates in the 9LA trial were 63% and 47% in the NI plus PDC and PDC groups, respectively.[4] The two-year OS rates from CheckMate 227 trial were 40% in the NI group and 30% in the PDC group.[21,73] A visual comparison of the KM curves for OS and PFS from each trial suggests that the additional short course of PDC added to NI in the CheckMate 9LA trial addresses the early detriment in OS that was observed in the CheckMate 227 trial by providing more rapid disease control at the beginning of the treatment course. However, in the absence of a direct trial comparison of NI to NI plus PDC, equivalent long-term treatment efficacy cannot be assumed given the noted differences between the trials and the limitations associated with CheckMate 227.
- Safety - The CheckMate 227 trial provides safety data based on approximately one additional year of follow-up compared to the CheckMate 9LA trial. When considering the PDC control groups in each trial, the proportions of patients experiencing treatment-related AEs were relatively similar (227 versus 9LA) and included nausea (36.1% versus [redacted]), anemia (33.0% versus [redacted]), asthenia (12.6% versus [redacted]), neutropenia (17.2% versus [redacted]), and decreased appetite (19.6% versus [redacted]).[4,21] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this safety information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed)*When considering the NI and NI plus PDC treatment groups, respectively, treatment-related AEs of diarrhea (17.0% versus [redacted]), rash (17.0% versus [redacted]), and fatigue (14.4% vs [redacted]) were similar, but the occurrence of other treatment-related AEs were greater in the NI plus PDC group of the 9LA trial including nausea ([redacted] versus 9.9%), anemia ([redacted] versus 3.8%), asthenia ([redacted] versus 10.2%), pruritus ([redacted] versus 14.2%), and neutropenia ([redacted] versus 0.2%).[4,21] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this safety information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed)* Treatment-related AEs leading treatment discontinuation and treatment-related SAEs were also higher among patients receiving NI plus PDC in the 9LA trial compared to patients receiving NI in the 227 trial. These differences in safety data suggest that greater monitoring may be required for patients receiving NI plus PDC, and that generalizability of safety data from the 227 trial to the 9LA trial for patients in the intervention group may be limited.

Summary

Data from the CheckMate 227 trial were included to support the sponsor's submission to CADTH for the reimbursement of NI plus PDC for the first-line treatment of patients with metastatic or recurrent NSCLC without EGFR or ALK tumour aberrations. Since efficacy data from the pivotal trial, CheckMate 9LA, were considered immature based on 12.7 months of follow-up, data from the CheckMate 227 trial were used to inform the submitted pharmacoeconomic model on the long-term efficacy of NI compared to PDC, which provided data for NI based on a median of 37.7 months of follow-up.[10] The trial also provides additional safety data on the NI combination including data on patient deaths, which also informed the model. The final analysis of OS in patients with PD-L1 expression >1% demonstrated superior OS with NI compared to PDC, however, there was evidence of non-proportional hazards. Patients treated with NI experienced a slight detriment in OS during the initial months of treatment with NI but thereafter, the curves showed a sustained long-term benefit in OS over PDC. Similar findings were shown for PFS. Under the assumption of non-proportional hazards, the treatment effect estimates from the trial were interpreted as overall estimates of the average treatment effect. In a positive trial, such estimates may be biased towards overestimating the magnitude of clinical benefit. The most recent data from the trial, based on 43.1 months of follow-up, show sustained benefit from treatment with NI over PDC in patients with PD-L1 ≥1 and PD-L1 <1%.[11] The CheckMate 9LA and 227 trials used similar eligibility criteria and therefore the distributions of most baseline characteristics were also similar. Aside from the addition of two cycles of PDC to the combination of NI, there were other notable differences in the treatment regimens evaluated that included the timing and dosing of nivolumab (a flat dose of 360 mg every three weeks in CheckMate 9LA versus a weight-based dose of 3 mg/kg every two weeks in CheckMate 227) and the type of PDC administered to patients with squamous NSCLC (patients with squamous histology received carboplatin plus paclitaxel in CheckMate 9LA versus either gemcitabine plus cisplatin or gemcitabine plus carboplatin in CheckMate 227). The better survival of the PDC control group in the CheckMate 227 trial, based on one-year survival estimates, suggests differential treatment effects of the PDC regimens used in each trial. Overall, visual comparison of the KM curves of OS and PFS from each trial show that the additional short course of PDC added to NI in the CheckMate 9LA trial addresses the early OS detriment observed in CheckMate 227. However, in the absence of a direct trial comparison of NI to NI plus PDC, equivalent long-term efficacy of the NI-based regimens cannot be assumed due to noted differences between the trials and the limitations associated with CheckMate 227. In terms of safety, the data on drug-related events in the PDC control groups of each trial showed a similar safety profile. When compared to the toxicity profile of NI, NI plus PDC appeared to be associated with higher rates of drug-related AEs that included nausea, anemia, asthenia, pruritus, and neutropenia, as well as more drug-related SAEs and drug-related AEs leading to treatment discontinuation. These data suggest that greater monitoring may be required for patients receiving NI plus PDC, and generalizability of safety data from the CheckMate 227 trial to the CheckMate 9LA trial for patients in the intervention group may be limited.

9 About this Document

This Clinical Guidance Report was prepared by the CADTH Lung Clinical Guidance Panel and supported by the CADTH Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding the clinical evidence available on NI plus PDC in metastatic NSCLC with no EGFR or ALK tumour aberrations. Issues regarding resource implications are beyond the scope of this report and are addressed by the relevant CADTH Economic Guidance Report. Details of the pCODR review process can be found on the CADTH website (www.cadth.ca/pcodr).

CADTH considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Clinical Guidance Report was handled in accordance with the Procedures for the CADTH pan-Canadian Oncology Drug Review. The sponsor, 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.

Appendix 1: Literature Search Strategy and Detailed Methodology

1. Literature search via Ovid platform

Database(s): Database(s): EBM Reviews - Cochrane Central Register of Controlled Trials June 2020, Embase 1974 to 2020 July 16, Ovid MEDLINE(R) ALL 1946 to July 16, 2020.

#	Searches	Results
1	Nivolumab/	20115
2	(Opdivo* or nivolumab* or MDX 1106 or MDX1106 or BMS936558 or BMS 936558 or ONO4538 or ONO 4538 or 31YO63LBSN or HSDB8256 or HSDB 8256 or GTPL7335 or cmab819 or cmab 819).ti,ab,ot,kf,kw,hw,rn,nm.	25223
3	1 or 2	25223
4	Ipilimumab/	15889
5	(Yervoy* or ipilimumab* or strentarga* or Winglore* or anti-CTLA4 or anti-CTLA-4 or MDX-CTLA 4 or MDX-CTLA4 or MDXCTLA-4 or MDXCTLA4 or MDX-010 or MDX010 or MDX101 or MDX 101 or BMS734016 or BMS 734016 or 6T8C155666 or MOAB-CTLA-4).ti,ab,ot,kf,kw,hw,rn,nm.	23190
6	4 or 5	23190
7	3 and 6	10170
8	Carcinoma, Non-Small-Cell Lung/	81507
9	exp LUNG/ and Carcinoma, Large Cell/	447
10	(NSCLC* or LCLC*).ti,ab,kf,kw.	136082
11	((non small cell* or nonsmall cell* or large cell or undifferentiated) adj5 (lung* or bronch* or pulmonar*) adj5 (cancer* or tumor* or tumour* or carcinoma* or neoplasm*)).ti,ab,kf,kw.	187658
12	((bronchial or pulmonary or lung) adj3 (adenocarcinoma* or adeno-carcinoma*)).ti,ab,kf,kw.	54950
13	((bronchioloalveolar or bronchiolo alveolar) adj3 (carcinoma* or cancer* or neoplasm* or tumor* or tumour*)).ti,ab,kf,kw.	3670
14	or/8-13	261257
15	7 and 14	1691
16	15 use medall	199
17	limit 16 to english language	186
18	15 use cctr	129
19	17 or 18	315
20	*nivolumab/ or (Opdivo* or nivolumab* or MDX 1106 or MDX1106 or BMS936558 or BMS 936558 or ONO4538 or ONO 4538 or HSDB8256 or HSDB 8256 GTPL7335 or cmab819 or cmab 819).ti,ab,kw,dq.	18224
21	*Ipilimumab/ or (Yervoy* or ipilimumab* or strentarga* or Winglore* or anti-CTLA4 or anti-CTLA-4 or MDX-CTLA 4 or MDX-CTLA4 or MDXCTLA-4 or MDXCTLA4 or MDX-010 or MDX010 or MDX101 or MDX 101 or BMS734016 or BMS 734016 or MOAB-CTLA-4).ti,ab,kw,dq.	16134
22	20 and 21	5905
23	non small cell lung cancer/ or large cell lung carcinoma/ or lung adenocarcinoma/	156869
24	(NSCLC* or LCLC*).ti,ab,kw,dq.	135881
25	((non small* cell or nonsmall cell* or large cell or undifferentiated) adj5 (lung* or bronch* or pulmonary*) adj5 (cancer* or tumor* or tumour* or carcinoma* or neoplasm*)).ti,ab,kw,dq.	186752
26	((bronchial or pulmonary or lung) adj3 (adenocarcinoma* or adeno-carcinoma*)).ti,ab,kw,dq.	55114
27	((bronchioloalveolar or bronchiolo alveolar) adj3 (carcinoma* or cancer* or neoplasm* or tumor* or tumour*)).ti,ab,kw,dq.	3662

#	Searches	Results
28	or/23-27	275663
29	22 and 28	989
30	29 use oemezd	694
31	limit 30 to english language	681
32	31 not (conference review or conference abstract).pt.	329
33	19 or 32	644
34	remove duplicates from 33	477
35	31 and (conference review or conference abstract).pt.	352
36	limit 35 to yr="2015 -Current"	336
37	34 or 36	813

2. Literature search via PubMed

A limited PubMed search was performed to retrieve citations not found in the MEDLINE search.

Search	Query	Items Found
#12	**Search:** #10 AND #11	8
#11	**Search:** publisher[sb]	419,042
#10	**Search:** #3 AND #9	202
#9	**Search:** #4 OR #5 OR #6 OR #7 OR #8	108,255
#8	**Search:** ((bronchioloalveolar[tiab] OR bronchiolo alveolar[tiab]) AND (carcinoma*[tiab] OR cancer*[tiab] OR neoplasm*[tiab] OR tumor*[tiab] OR tumour*[tiab]))	1,805
#7	**Search:** ((bronchial[tiab] OR pulmonary[tiab] OR lung[tiab]) AND (adenocarcinoma*[tiab] OR adeno-carcinoma*[tiab]))	38,013
#6	**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]))	70,516
#5	**Search:** NSCLC[tiab] OR NSCLCs[tiab] OR LCLC[tiab] OR LCLCs[tiab]	43,716
#4	**Search:** "Carcinoma, Non-Small-Cell Lung"[Mesh]	53,161
#3	**Search:** #1 AND #2	1,615
#2	**Search:** Ipilimumab[MeSh] OR ipilimumab*[tiab] OR Yervoy*[tiab] OR Winglore*[tiab] OR anti-CTLA4[tiab] OR anti-CTLA-4[tiab] or MDX-CTLA 4[tiab] OR MDX-CTLA4[tiab] OR MDXCTLA-4[tiab] OR MDXCTLA4[tiab] OR MDX-010[tiab] OR MDX010[tiab] OR MDX101[tiab] OR MDX 101[tiab] OR BMS734016[tiab] OR BMS 734016[tiab] OR MOAB-CTLA-4	4,829
#1	**Search:** Nivolumab[MeSH] OR Opdivo*[tiab] OR nivolumab[nm] OR nivolumab[tiab] OR MDX 1106[tiab] OR MDX1106[tiab] OR BMS936558[tiab] OR BMS 936558[tiab] OR ONO4538[tiab] OR ONO 4538[tiab] OR 31YO63LBSN[rn] OR HSDB8256[tiab] OR HSDB 8256[tiab] OR cmab819[tiab] OR cmab 819[tiab]	5,145

3. Cochrane Central Register of Controlled Trials (CENTRAL)

(searched via Ovid)

4. Grey literature search via:

Clinical trial registries:

US National Library of Medicine. ClinicalTrials.gov
https://clinicaltrials.gov/

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

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

Search: Opdivo+Yervoy/nivolumab+ipilimumab, non-small cell lung cancer

Select international agencies including:

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

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

Search: Opdivo+Yervoy/nivolumab+ipilimumab, non-small cell lung cancer

Conference abstracts:
American Society of Clinical Oncology (ASCO)
https://www.asco.org/

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

Search: Opdivo+Yervoy/nivolumab+ipilimumab, non-small cell lung cancer— last five years

Detailed Methodology

The literature search for clinical studies was performed by an information specialist from the CADTH Methods Team using the abovementioned search strategy, which was peer-reviewed according to the *PRESS Peer Review of Electronic Search Strategies* checklist (https://www.cadth.ca/resources/finding-evidence/press)[76].

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946–) via Ovid, Embase (1974–) via Ovid, the Cochrane Central Register of Controlled Trials (CENTRAL) via Ovid; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Opdivo+Yervoy/nivolumab+ipilimumab and non-small cell lung cancer.

No filters were applied to limit the retrieval by study type. 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 November 19, 2020.

Grey literature (literature that is not commercially published) was identified by searching websites from relevant sections of the *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature* checklist (https://www.cadth.ca/grey-matters).[77] Included in this search were the websites of regulatory agencies (US Food and Drug Administration and European Medicines Agency), clinical trial registries (US National Institutes of Health's clinicaltrials.gov, World Health Organization's International Clinical Trials Registry, and Canadian Partnership Against Cancer Corporation's Canadian Cancer Trials), and relevant conference abstracts. Conference abstracts were retrieved through a search of the Embase database limited to the last five years. Abstracts from the American Society

of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) were searched manually for conference years not available in Embase. As well, the manufacturer of the drug was contacted for additional information, as required by the CADTH Review Team.

Study Selection

One member of the CADTH Methods Team selected studies for inclusion in the review according to the predetermined protocol. All articles considered potentially relevant were acquired from library sources. One member of the CADTH Methods Team made the final selection of studies to be included in the review.

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 CADTH Methods Team with input provided by the Clinical Guidance Panel and other members of the CADTH Review Team. Additional limitations and sources of bias were identified by the CADTH Review Team.

Data Analysis

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

Writing of the Review Report

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

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

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